No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

APPELLEES' APPENDIX
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TAB 119

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, et al.,

Plaintiffs,

v. Case No. 4:22-cv-00325-RH-MAF

JASON WEIDA, et al.,

Defendants.
_____/

PLAINTIFFS' MOTION TO EXCLUDE EXPERT TESTIMONY OF SOPHIE SCOTT, PH.D., AND SUPPORTING MEMORANDUM OF LAW

Pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403 and 702, Plaintiffs respectfully move this Court to exclude the expert report, opinions, and testimony of Defendants' proposed expert Professor Sophie Scott ***in its entirety***. Professor Scott is not a qualified expert on gender dysphoria or its treatment, and her opinions and testimony are neither relevant nor reliable under Federal Rule of Evidence 702 and the standards set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and its progeny. Her opinions and testimony are likewise inadmissible because any probative value they may have (and they have none) is substantially outweighed by the danger of unfair prejudice, confusion of the issues, waste of time, undue delay, and needless presentation of cumulative evidence. *See* Fed. R. Evid. 403.

WHEREFORE, Plaintiffs respectfully request an order excluding Professor Scott's report, expert opinions and testimony in their entirety.

MEMORANDUM OF LAW

Professor Scott is not qualified to offer the opinions stated in her report. She opines that puberty delaying medication administered to teenagers "*may have*" unknown, negative effects on brain development. Report, ¶ 15 (**Exhibit A**). She also believes without any scientific support that it is "very possible" that teenagers cannot "fully grasp the implications of puberty blocking treatment." *Id.* ¶ 16. But Professor Scott is not qualified to give these opinions because she has never treated patients with gender dysphoria (at any age) given that she is not a medical provider of any kind, nor has she administered or studied the effects of puberty delaying treatment in any clinical or academic setting. She has never written on these subjects either—except on Twitter.

Aside from her lack of qualifications, Professor Scott's opinions are inadmissible because they are entirely speculative and lack any reliable or testable foundation or methodology. There is no existing data to support her ultimate conclusions, which means her opinions are based on impermissible "leaps of faith." The data that does exist directly contradicts her conclusions, but, strikingly, she never mentions this data in her report. Her opinions moreover are based solely on her unqualified review of other studies, and they are far outside the scientific mainstream. The Court should therefore exercise its gatekeeping function under Rule 702 and exclude Professor Scott's testimony. *See Rink v Cheminova, Inc.*, 400 F.3d 1286, 1291 (11th Cir. 2005).

A. Legal Standard

Rule 702 of the Federal Rules of Evidence governs the admissibility of expert testimony. Pursuant to *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993), and Rule 702, district courts must perform a "gatekeeping" role "to ensure that speculative, unreliable expert testimony does not reach the jury under the mantle of reliability[.]" *Rink*, 400 F.3d at 1291; *Kilpatrick v. Berg, Inc.*, 613 F.3d 1329, 1335 (11th Cir. 2010) ("The trial court must make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.").

To do so, the Court must engage in a rigorous inquiry to determine whether:

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in Daubert; and (3) the testimony assists the trier of fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

E.g., *United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) (en banc), *cert. denied*, 544 U.S. 1063 (2005). The party offering the expert has the burden of satisfying each of these three elements by a preponderance of the evidence. *Rink*, 400 F.3d at 1292.

B. Professor Scott is Not Qualified To Offer An Expert Opinion on Any Issue in the Case.

A witness may be qualified as an expert by virtue of her "knowledge, skill,

experience, training, or education." Fed. R. Evid. 702. However, "[e]xpertise in one field does not qualify a witness to testify about others." *Lebron v. Secretary of Florida Dept. of Children and Families*, 772 F.3d 1352, 1368 (11th Cir. 2014) (holding that a psychiatrist was properly prevented from opining on rates of drug use because he had never conducted research on the subject, and instead relied on studies to form his opinion).

A scientist, however well credentialed, cannot be "the mouthpiece of a scientist in a different specialty." *Id*. at 1369 (quoting *Dura Automotive Systems of Indiana, Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002)); *TB Food USA, LLC v. American Mariculture, Inc*., 2021 WL 4962969, at *4 (M.D. Fla. October 26, 2021) ("[A]n expert must have at least some minimum training, education, experience, knowledge, or skill pertaining to the particular subject matter of his proposed testimony.") (cleaned up). "Merely reading literature in a scientific field does not qualify a witness—even an educated witness—as an expert." *Kadel v. Folwell*, 2022 WL 3226731, at *9, 13 (M.D.N.C. August 10, 2022) (excluding Dr. Lappert's expert opinion about puberty delaying medication because he is a surgeon, not an endocrinologist, and he never treated a patient with hormone therapies). If an expert witness does not intend to testify about matters growing directly out of "research [s]he had conducted independent of the litigation," the expert should be disqualified. *Lebron*, 772 F.3d at 1369 (quoting Fed. R. Evid. 702).

Professor Scott is the Director of University College London's Institute of Cognitive Neuroscience. Report ¶ 6.[1] Her main area of research is "speech, laughter and sound." Tr. 48:25 – 49:4 ("Q. All of these publications are about speech, laughter and sound. Isn't that right? A. There are a few other things. But yeah, that's the majority. That is my main area of research.") (**Exhibit B**). She is proffered as an expert based on her "training and experience as a neuroscientist," her reading and assessment of "the relevant neuroscientific literature on brain development, and the potential effects of [puberty delaying medication] on the developing brain." Report, ¶ 4. However, she has no experience with the provision of puberty delaying medication, gender-affirming medical care or medical treatment of gender dysphoria. She has never published any papers or studies on gender dysphoria, gender-affirming care or puberty delaying medication. Nor has she published any reviews of such studies in her entire career. Tr. 49:5-12 ("Q. Are any of [your publications] about gender-affirming care? A. No. Q. Are any of these publications specific to gender dysphoria? A. No. Q. Any about puberty blockers? No.").

Professor Scott is not a medical doctor, a psychiatrist or a clinical psychologist; she has no medical training. Tr. 34:25 – 35:4; Tr. 35:13-14. She does

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[1] According to Professor Scott, cognitive neuroscience is "a scientific field that examines the relationships between human behaviour to the human brain, and how these can be affected by age, disease and individual differences." Report, ¶ 6; Tr. 37:6-10 ("A neuroscientist is somebody who studies brains…[H]e's studying it in a purely basic science position. They're not treating people. They're not prescribing things.").

not treat patients. Tr. 44:22-23. She has never studied gender dysphoria in a clinical setting, nor has she ever administered puberty delaying medication or studied their effects, let alone in humans. Tr. 31:18-24 (Q. So you've never conducted any clinical studies yourself related to gender dysphoria? A. No. Q. What about the effects of gender-affirming care? A. Nope."). Nor has anyone at Professor Scott's place of employment, the Institute for Cognitive Neuroscience ever studied gender dysphoria or the effects of gender-affirming medical care either, meaning Professor Scott has not overseen any such study. Tr. 31:6-8 ("Q. Has anyone at the Institute ever conducted any clinical studies related to gender dysphoria? A. No, not that I'm aware of."; Tr. 31:25-32:2 (Q. Has the Institute ever studied the effects of puberty blockers? A. No.").

Without *any* qualifications, training or experience related to gender dysphoria or puberty delaying medication, Professor Scott is not qualified to give an expert opinion on these subjects. *See Kadel*, 2022 WL 3226731, at *13.[2] Nor is she

[2] *See also, e.g.*, *Fernandez v United States*, 2020 WL 3105925, at *5 (N.D. Fla. June 4, 2020) (excluding an expert because the Plaintiff offered "no information indicating that he has any experience or specialized knowledge regarding medicine generally or any of the branches of medical science which might be relevant to causation); *Doctors Licensure Group, Inc. v. Continental Casualty Company*, 2011 WL 13182969, at *4 (N.D. Fla. September 26, 2011) (excluding a proffered expert on accounting because he was "not an accountant" and had "virtually no experience in accounting"); *Webb v. Carnival Corporation*, 321 F.R.D. 420, 429 (S.D. Fla. 2017) ("Because Mr. Jaques has no experience in toxicology, responsible alcohol vending policies, nor medicine, and has never served onboard the California Dream, he is unqualified to opine on the Decedent's level of intoxication[.]").

qualified to opine on studies related to gender dysphoria or puberty delaying medication conducted by others. *See Dura Automotive*, 285 F.3d at 614 ("[A] scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty.").

This is so particularly here where Professor Scott's opinions and so-called review of literature did not "grow[] naturally and directly out of research [s]he had conducted independent of the litigation." *Lebron*, 772 F.3d at 1369 (cleaned up); *see also* Fed. R. Evid. 702, Advisory Comm. Notes (2000 Amendments). Here, Professor Scott reviewed the literature and developed her opinions in connection with litigation in the UK, namely, *Bell v. Tavistock*, and now seeks to transpose those opinions here without still having done any independent work in the area. Tr. 52:7-18 ("Q. Why did you think that you had an opinion to give in this case? A. *Because I provided an opinion before for the Keira Bell case.* And I discussed that a lot with Paul Conrathe at the time for all the reasons you said. I'm not a clinician. *I haven't worked in this area.* … And I did some reading into the literature, … ."); Tr. 53:6-9 ("Q. So you formed your opinion about puberty blockers in adolescents while you were working on the Bell case? A. Yeah.").

In *Kadel*, a case similar to this one about insurance coverage for gender-affirming medical care, the court excluded a proposed expert (Dr. Lappert) because "[h]e is not a psychiatrist, psychologist, or mental health professional, nor has he

ever diagnosed a patient with gender dysphoria,"[3] and "[h]e is not an endocrinologist, nor has he ever treated a patient with hormone therapies." *Kadel*, 2022 WL 3226731, at *13. Here, Professor Scott, who unlike the excluded expert in *Kadel*, has no medical degree and has never provided medical or mental health care, is likewise "not qualified to render opinions about the diagnosis of gender dysphoria, its possible causes, … the efficacy of puberty blocking medication or hormone treatments, the appropriate standard of informed consent for mental health professionals or endocrinologists, or any opinion on the non-surgical treatments obtained by Plaintiffs." *Id.* Her opinions should be excluded *in toto*.

C. Professor Scott's Opinions are Unreliable.

An expert's reliability concerns whether the reasoning or methodology underlying the testimony is scientifically valid and whether that reasoning or methodology properly can be applied to the facts in issue. *Kilpatrick*, 613 F.3d at 1335. When evaluating whether an expert's methodology is reliable, the Court considers, among other things:

> (1) whether the expert's theory can be and has been tested; (2) whether the theory has been subjected to peer review and publication; (3) the known or potential rate of error of the particular scientific technique; and (4) whether the technique is generally accepted in the scientific community.

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[3] While Dr. Scott has an undergraduate degree where she minored in psychology, she is not certified as psychologist, and admits she's "not clinically qualified." Tr. 35:8-17. In her words, she is "a basic scientist." *Id.*

Frazier, 387 F.3d at 1262. The court must undertake an independent analysis of each step in the logic leading to the expert's conclusions, and if any step in the logic is deemed unreliable, the expert's entire opinion must be excluded. *Hendrix v Evenflo Co., Inc.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009) (citing *McClain v. Metabolife Int'l., Inc.*, 401 F.3d 1233, 1245 (11th Cir. 2005)). Likewise, if the expert's opinions are vague or based on "leaps of faith unsupported by good science," then those opinions should be excluded as well. *Id*. at 579; *McDowell v. Brown*, 392 F.3d 1283, 1299, 1301 (11th Cir. 2004) (characterizing the experts' opinions as "too vague" and "more of a guess than a scientific theory."); *Rosen v. Ciba-Geigy Corp*., 78 F.3d 316, 319 (7th Cir. 1996) ([T]he courtroom is not the place for scientific guesswork, even of the inspired sort.").

1. Professor Scott's Opinions Lack Reliability Because They Are Based on Flawed Reasoning or Methodology.

Professor Scott's Report does not provide any basis for her "concern" about puberty delaying medication or her speculations about a teenager's ability to grasp its implications. The reason for this is simple: Professor Scott does not know what the effects of puberty delaying medication are on the brain, and she does not know whether teenagers can fully grasp its implications. She does not know what these implications are herself, and accordingly, all her opinions are hypothetical and unmoored from facts or data.

a. Puberty Delaying Medication

Her report is full of statements about the alleged lack of studies pertinent to the effects of puberty delaying medication. Report, ¶ 7 ("My concern is that we do not yet have enough evidence about the best ways to identify the individuals for whom [puberty delaying medication] are appropriate."); Report, ¶ 15 ("All the papers I can find suggest that we need much more data on the long-term brain effects of [puberty delaying medication] when administered around puberty, [and] the effects this can have on behaviour[.]"). Without any evidence (and with no experience or training in the subject), Professor Scott can only guess the effects of these treatments. Report, ¶ 15 ("As puberty is associated with very marked changes in the structure of the brain…the use of puberty blockers *may* have serious consequences for the development of the human brain.") (emphasis added); Report, ¶ 16 ("We need more research to be able to determine the *potential* for puberty blockers to be effective in alleviating some aspects of gender dysphoria[.]") (emphasis added). Guessing is not permitted under Rule 702. *McDowell*, 392 F.3d at 1301 (noting that while an expert may "draw conclusions from existing data," drawing "conclusions where there was no existing data" amounted to a "mere guess" that "fails the tests for expert opinion"); *Magical Farms, Inc. v. Land O'Lakes, Inc.*, 2007 WL 4727225, at *2 (N.D. Ohio March 8, 2007) ("Dr. Ames' report is replete with statements like, 'suggest the possibility,' 'may have,' and 'I would be concerned,' all of which fail to rise to the level of a reasonable degree of certainty required by courts.").

To substantiate her untrained guesswork, Professor Scott briefly discusses—in a single paragraph—just five articles related to puberty delaying medication. *See* Report, ¶ 15. Only one of the articles is an original study pertaining to humans, namely, children with precocious puberty (Mul et al., 2001). *See* Report, ¶ 15; Scott Bibliography. Two other articles are not studies themselves, but rather a single commentary piece (Hayes, 2017) and a review of literature (Wojniusz et al., 2016), both pertaining to the treatment of precocious puberty. *See* Report, ¶ 15; Scott Bibliography. Finally, the other two studies pertain to sheep not people. *See* Report, ¶ 15; Scott Bibliography.[4] None of the studies pertain the use of puberty delaying medications for gender dysphoria in adolescents.

Notwithstanding the above, Professor Scott's discussion is nothing more than a recitation of findings from the above papers. She does not say anything about the methodologies behind those studies, whether they have been peer reviewed, or whether or how they are applicable to the context of using puberty delaying medications as treatment of gender dysphoria in adolescents. In fact, she disclaims them away after discussing them, saying "we cannot say if the results are due to direct effects of [puberty delaying medication] on the brain, heart and behaviour, or if they are secondary to this[.]" Report, ¶ 15. Without any qualifications or training in

[4] *But see Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 147 (1997) (offering animal studies showing one type of cancer in mice to establish causation of another type of cancer in humans is "simply too great an analytical gap between the data and the opinion offered").

these areas, her use of these articles to support her opinions about puberty delaying medication is completely unreliable and the type of hypothetical guesswork prohibited by Rule 702. *Lebron*, 772 F.3d at 1368 ("Expertise in one field does not qualify a witness to testify about others."); *Dura Automotive*, 285 F.3d at 614 ("A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty.").

Most disturbingly, however, and demonstrative of her extremely flawed methodology, is the fact that she does not discuss any of the original studies that exist pertaining to the use of puberty delaying medications on transgender adolescents. There are at least three original, peer-reviewed studies that have looked specifically into the effects of puberty delaying medications on brain structure and function in transgender adolescents. *See* Corrected Edmiston Rebuttal Report, at ¶¶ 26, 29 (**Exhibit C**) (discussing Heesewijk et al., 2022; Soleman et al., 2016; Staphorsius et al., 2015). Indeed, none of these have found any significant effects of treatment on the brain. *Id.* Plaintiffs do not refer to these studies to argue the merits, but rather to starkly illustrate the flawed nature of Professor Scott's methodology. How can Professor Scott opine of the effects of puberty delaying medications on transgender adolescents' brains when she does not discuss any of the original, peer-reviewed studies looking at that question? The answer is she cannot.

Simply put, Professor Scott's concern over puberty delaying medication as a

treatment for gender dysphoria stems from her own lack of knowledge.[5] Not only does she not cite, let alone discuss, the most relevant studies in this area, but throughout her testimony, she repeatedly used the words "we don't know," when referring to the effects of puberty delaying medication. Tr. 24:11-14 ("[W]hat evidence we do have suggests that there are effects on the brain of delaying puberty. And we don't know what that might mean further down the line. We just don't know."); Tr. 68:20-21 ("Q. But you can't say here that these puberty blockers have any harmful effects on the brain? A. But we know that they change the brain and we don't know that that's not harmful."). Her concern is completely unreliable however because it ignores what we do know about puberty delaying medication. In other

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[5] It could be argued that Professor Scott's opinions really stem not out of just concern or lack of knowledge, but rather from personal feelings and biases about transgender people. Professor Scott is an active Twitter user. She often uses this platform to comment on a wide variety of topics outside her field of expertise, including transgender issues and treatments for gender dysphoria. In one tweet about a children's book for transgender youth and their families—that she did not read—she called the book a "cheap shot" and "reductive" because it "says that girls who like bugs and wear super hero capes and who don't like pink dresses are in fact boys." [**Exhibit E**]; Tr. 163:6-10; Tr. 164:12-16 ("Q. The book is about addressing that issue with your family. You didn't read the book? A. Well, that was – I've just quoted off the bits I saw. This is – you've asked me why I said it and that's why I said it."). Her rash comments about a children's book she did not read suggest a bias against the trans community.

In another tweet, Professor Scott showed disdain for a scholarship application that allowed applicants to "self-identify" as female. She wrote "Of God" in response to a tweet about the scholarship application. **[Exhibit F]** While her explanation speaks for itself, in summary, she believes that the trans community should be sectioned off from the cis community in what she calls "positive discrimination." Tr. 166:11 – 167:10.

words, her opinion ignores the research we have done on these treatments, none of which shows any significant effects on the brain. *See* Corrected Edmiston Rebuttal Report, ¶¶ 26, 29-30. In sum, Professor Scott's overall discussion about these studies is completely unreliable and should be excluded *in toto*.

b. Decision-making

Her concerns about a teenager's ability to grasp the implications of treatment is equally unreliable because the steps in her "analysis" are disconnected. In paragraphs 8-13 of the Report, Professor Scott explains how the brain develops over childhood and adolescence. Then, at paragraph 14, she says this pattern of brain development "*suggests*" that teenagers are prone to risky decision-making more than adults. From there she somehow concludes it is "very possible" that teenagers are unable to "fully grasp the implications of puberty blocking treatment." Report, ¶ 16.

There are several problems with this "analysis." First, her conclusion about teenagers being prone to risky behavior because of brain development is a guess, just like her concerns over puberty delaying medication. She cannot say with any certainty (or authority) that the pattern of brain development during adolescence leads to more risky behavior in teenagers. The same is true for her ultimate opinion about a teenager's ability to grasp the implications of these treatments. She does not cite a single study that supports this opinion. *McDowell*, 392 F.3d at 1301 (drawing "conclusions where there was no existing data" amounted to a "mere guess" that "fails the tests for expert opinion").

Second, there is a disconnect between the two steps in her analysis. Professor Scott never explains how a tendency toward risky behavior effects a teenager's ability to understand the implications of that behavior. In other words, she never explains how her conclusion about risky behavior leads to her concern over whether teenagers can grasp the implications of puberty delaying treatment. She There is thus a large "analytical gap" in her methodology that renders her ultimate conclusion unreliable. *See Joiner*, 522 U.S. at 146.

For her opinions to be reliable, Professor Scott must have "knowledge," which requires "more than subjective belief or unsupported assumptions." *Daubert*, 509 U.S. at 590. Professor Scott does not have the requisite knowledge for either of her opinions. To assume that her opinions are correct (despite a lack of evidence and experience) would be to rely on her *ipse dixit* based on conjecture to judge the reliability of her conclusion. *See Bowers v Norfolk Southern Corp.*, 537 F.Supp.2d 1343, 1355 (M.D. Ga. 2007) (" The Court cannot rely on [the expert's] *ipse dixit* to judge the reliability of his conclusion[.]").

2. Professor Scott's Opinions are Vague and Imprecise.

Despite her "concerns" over the "potential effects" of puberty delaying medication, *see* Report, ¶¶ 4, 7, Professor Scott does not believe these treatments should be denied to all teenagers with gender dysphoria. She begins her report by saying it is "entirely possible that the use of puberty blockers is appropriate in some exceptional cases of gender dysphoria in prepubescent and adolescent individuals."

Report, ¶ 7. She repeated that sentiment in her deposition. Tr. 13:10-13 ("I think it's entirely possible that there are people, young people who this is an entirely appropriate course of treatment potentially."). When asked about whether she approves of complete bans pertaining to gender-affirming care, like the Challenged Exclusion in this case, Professor Scott could not give a straight answer. On the one hand, she acknowledged that all-inclusive bans on coverage are a bad idea. Tr. 13:22-23 ("I don't think it's a good idea to ban treatment in a blanket way."; Tr. 14:21-23 ("I think it should be something that's worked out in terms of a scientific and medical approach."). On the other hand, she understood she was offering an opinion in support of one such blanket ban. Tr. 12:21 – 13:8. When asked whether she would vote for or against the Challenged Exclusion in this case, she said she would "abstain like a coward." Tr. 16:17.

Opinions like these are too vague and imprecise to be sufficiently reliable. Professor Scott cannot identify when, or under what circumstances, puberty delaying medication may be appropriate for teenagers. She thus cannot say when the unknown risks of these treatments outweigh their benefits. Where she draws the line is completely unknown, making her opinion vague and imprecise. *See Ward v Carnival Corporation*, 2018 WL 11383459, at *6 (S.D. Fla. July 31, 2018) (excluding expert testimony because it was "unclear precisely what [the expert] was claiming.").

Her opinion about a teenager's decision-making ability is equally imprecise. Professor Scott is not certain whether all teenagers are prone to risky behavior, which

is the sole basis for her opinion. Tr. 141:9-19 (Q. Is [riskiness] common for all adolescents?" A. Well, I mean adolescence is very variable like all humans."). Her opinion is also based on research related to decision-making in a "hot context," Report, ¶ 14, which ignores the body of research and peer-reviewed literature on the contextual nature of decision-making in adolescence. Corrected Edmiston Rebuttal Report at ¶ 18 (discussing eleven (11) peer-reviewed papers on the contextual nature of adolescent decision-making). She also omits all literature on decision-making in the medical context and particularly decision-making about treatment of gender dysphoria occurring over several years. These cavernous omissions render her opinion about decision-making in the "hot" context both imprecise and misleading by leaving out the proper context.

3. Professor Scott's Opinions are Far Outside the Mainstream

General acceptance in the relevant scientific community is an important element to the reliability inquiry. See *Allison v. McGahn Medical*, 184 F.3d 1300, 1313 (11th Cir. 1999). Not only is widespread acceptance an important factor in assessing the reliability of an expert's opinions, but the fact that a known theory "has been able to attract only minimal support within the community may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Here, Professor Scott's opinions about the propriety of puberty delaying treatment is far outside the mainstream of medical and scientific opinion. In fact, her views have been explicitly rejected by every relevant scientific and medical community. Professor Scott says she is "slightly

worried" about using puberty delaying medication to treat even precocious puberty, the indication for which it was originally developed and for which it is approved by the FDA. Tr. 78:7-8; *see id*. 78:14-18 (expressing concerns about using puberty delaying treatment for any purpose because it is not "necessarily . . . safe" and "the data is not 100 percent clear that it doesn't have an effect" on cognitive function); Tr. 156:19-21 ("[M]y primary concern is about puberty blockers and giving them in adolescents and the risk associated with that."). Professor Scott claims she "doesn't know" whether her "concerns with puberty blockers for precocious puberty [are] shared by the medical community." Tr. 78:19-22. In fact, they are not shared, and indeed, run counter to the opinions of mainstream scientists and clinicians. See Corrected Edmiston Report, ¶ 38; Shumer Rebuttal Report ¶¶ 7, 54, 64 (**Exhibit D**); Dekker P.I. Hrg. Tr., at 29:16- 36:18 [ECF 62] (noting that the majority of major medical associations support gender-affirming care for adolescents and adults); *see also, e.g.*, *Brandt v. Rutledge*, 551 F.Supp.3d 882, 890 (E.D. Ark. 2021) ("The consensus recommendation of medical organizations is that the only effective treatment for individuals at risk of or suffering from gender dysphoria is to provide gender-affirming care [include puberty delaying treatment]."") (emphasis added), *aff'd*, 47 F.4th at 671. Because Professor Scott's opinions about puberty delaying treatment are "not generally accepted by the scientific community, and [are] unsupported by other studies" her testimony is unreliable. *Allison*, 184 F.3d at 1319.

D. Professor Scott's Opinions Will Not Assist the Trier of Fact.

Expert testimony is helpful to the trier of fact if it explains subjects that are beyond the understanding of the average lay person. *Frazier*, 387 F.3d at 1262. The testimony must offer more than what lawyers can argue in closing arguments. *Id*. Expert testimony is not helpful if it fails to "fit" with the facts of the case. *McDowell*, 392 F.3d at 1299. This happens when a large analytical leap must be made between the facts and the opinion. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) (offering animal studies showing one type of cancer in mice to establish causation of another type of cancer in humans is considered "too great an analytical gap").

Professor Scott's expert testimony will not assist the trier of fact for several reasons. *First*, her opinion about the ability of teenagers to fully grasp their decision to undergo treatment does not "fit" the facts of the case. She references these decisions as if they were made by the adolescent patient alone, that is, without any advice or assistance from medical professionals or other adults. Report, ¶ 16 ("All the evidence we have suggests that the complex, emotionally charged decisions required to engage with this treatment are not yet acquired as a skill at this age, both in terms of brain maturation and in terms of behaviour."). But the reality is that all decisions about whether to administer gender-affirming care are made by a group of individuals including the patient's family and healthcare providers. And, for individuals under 18, these decisions are ultimately made by the patient's parent or legal guardian. Professor Scott acknowledged this point in her deposition. Tr. 146:5-

10 (Q. But we're not talking about teenagers deciding about gender-affirming care themselves in this case, right? A. No. I understand that this would be something where the consent is not with the teenager."). Accordingly, her opinion on teenager decision-making is irrelevant to the facts of the case. *See Kadel*, 2022 WL 3226731, at *14 (excluding Dr. Lappert's opinion on informed consent in the context of gender dysphoria because the patient's father gave consent).

Second, this same opinion is well within the understanding of the average lay person, and it is certainly something counsel can argue in closing. Professor Scott concedes this point in her report when she describes the following as a "lay understanding of what neuroscience is now confirming." She says: "teenage brains on the whole are structurally and functionally different from adult brains, and this affects both their engaging with risky behaviour, and their understanding of the implications of risky behaviour." Report, ¶ 8. She confirmed the same in her deposition. Tr. 143:7-11 ("Q. Do you need to be an expert in neuroscience to understand that teenagers on the whole engage in risky behavior? A. No. Like I said in my report, it's something that all cultures recognize."). Since there already exists a "lay understanding" of her opinion about teenage behavior that "all cultures recognize," her opinion will not assist the trier of fact in this case. It is well-established that untestable "common sense" does not satisfy Rule 702's requirements. *See Fedor v. Freightliner, Inc.*, 193 F.Supp.2d 820, 832 (E.D. Pa. 2002) ("Generalized common sense does not rise to the level of expert opinion solely

because it is offered by someone with an academic pedigree.").

Third, her opinion about the unknown effects of puberty delaying medication is also within the understanding of the average person. The Court does not need an expert to explain the things we do not know. These can easily be explained in closing argument. *See Frazier*, 387 F.3d at 1262 ("Proffered expert testimony generally will not help the trier of fact when it offers nothing more than what lawyers for the parties can argue in closing arguments.").

Fourth, as noted above, her opinion about puberty delaying medication is based in part on animal studies without any connection to the treatment of gender dysphoria in humans. Report, ¶ 15; Tr. 71:11-15. Professor Scott does not even attempt to link these animal studies to humans, and as a result, such studies do not offer any support for her conclusions about the human brain. Therefore, they do not assist the trier of fact. *Joiner*, 522 U.S. at 146; *Kilpatrick*, 613 F.3d at 1338.

CONCLUSION

WHEREFORE, based on the foregoing, Plaintiffs respectfully request that the Court grant the instant Motion and exclude Professor Scott's expert report, opinions and testimony in their entirety under *Daubert* and the Federal Rules of Evidence.

* * *

Respectfully submitted this 7th day of April, 2023.

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CERTIFICATE OF WORD COUNT

According to Microsoft Word, the word-processing system used to prepare this Motion and Memorandum, there is a combined total of 5,455 words in the Motion and the Memorandum of Law.

/s/ Gary J. Shaw
Gary J. Shaw

CERTIFICATE OF SATISFACTION OF ATTORNEY-CONFERENCE REQUIREMENT

Pursuant to Local Rule 7.1(B), counsel for the Plaintiffs conferred with counsel for the Defendants on April 5, 2023. Counsel for Defendants indicated that same day that Defendants oppose the relief sought.

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing was served by email on April 7, 2023, on all counsel of record:

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TAB 127

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION TO PARTIALLY EXCLUDE EXPERT TESTIMONY OF DR. PATRICK W. LAPPERT AND INCORPORATED MEMORANDUM OF LAW

Pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403, and Rule 702, Plaintiffs move to partially exclude certain testimony of Defendants' expert Dr. Patrick W. Lappert, M.D., on the grounds that he fails to meet the qualification, reliability, and helpfulness requirements imposed by Fed. R. Evid. 702 and *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993). Specifically, Dr. Lappert's testimony should be limited to his area of expertise: the field of plastic surgery. To the extent that any of Dr. Lappert's purported opinions beyond plastic surgery hold any probative value (they do not), it is far outweighed by unfair prejudice and confusion of the issues and therefore the testimony should

be excluded pursuant to Fed. R. Evid 403. In support of this motion, Plaintiffs state as follows:

FACTUAL BACKGROUND

On February 17, 2023, Defendants served their expert witness disclosures for Dr. Lappert and thereafter provided his rebuttal opinions.[1] His rebuttal opinions were primarily directed to the reports of Dr. Loren S. Schechter, M.D., and Dr. Johanna Olson-Kennedy, M.D., M.S. Lappert Rebuttal ¶ 1.

In his reports, Dr. Lappert opines on numerous subjects that fall well outside the scope of his experience in plastic surgery, including the nature, causes, and diagnosis of gender dysphoria, non-surgical treatments for gender dysphoria, the quality of the evidence supporting medical treatments for gender dysphoria, and the development of clinical practice guidelines by professional medical associations of which he is not even a member. *See generally*, Lappert Rep.; Lappert Rebuttal.

However, as a retired plastic surgeon, Dr. Lappert is not qualified to offer expert testimony on these matters. Indeed, in a prior case in the Middle District of North Carolina involving a challenge to a categorical exclusion of gender-affirming health services from coverage through a state-sponsored health plan, the District Court precluded the vast majority of Dr. Lappert's proffered opinions based on his

[1] *See* Declaration of William Miller ("Miller Dec.") ¶¶ 4-5; Ex. A, Expert Declaration of Patrick W. Lappert, M.D. ("Lappert Rep."); Ex. B, Rebuttal Expert Report of Patrick W. Lappert, M.D. ("Lappert Rebuttal").

lack qualifications and the unreliability of his testimony, limiting his testimony solely to those opinions related to the field of plastic surgery. *Kadel v. Folwell*, Case No. 1:19CV272, 2022 WL 3226731, *13-14 (M.D.N.C. Aug. 10, 2022).[2] Notably, the Court also found that the available evidence "call[ed] Lappert's bias and reliability ***into serious question***." *Id*. at *12 (emphasis added).

Similarly, in *Brandt v. Rutledge*, the court curtailed Dr. Lappert's testimony even further, limiting Dr. Lappert to offering opinions solely "to his practice," "to what he has personally done in his practice," and "his actual interaction with patients and what the outcomes were." Miller Dec. ¶ 6; Ex. C, Excerpts of *Brandt v. Rutledge* Trial Transcript ("*Brandt* Tr."), at 1058:25, 1059:11-15. Indeed, the court sustained objections that sought to elicit Dr. Lappert's testimony about what the clinical practice guidelines pertaining to gender-affirming medical treatment entail and any specific risks for transgender individuals because Dr. Lappert "is not an expert in gender-affirming care" and such testimony "is outside the scope of the doctor's practice." *Brandt* Tr. 1058:4-10, 1067:10-14.

This Court should do the same. Dr. Lappert lacks the necessary qualifications to so testify regarding any subject matter beyond the field of plastic surgery,

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[2] Specifically, the court in *Kadel* held that Dr. Lappert was "limited to testifying to (1) the risks associated with the surgeries at issue in this case; (2) his anecdotal experience treating patients seeking to "de-transition"; and (3) the WPATH recommended role of the surgeon in treating gender dysphoria as compared to the role of the surgeon in other surgical contexts." 2022 WL 3226731, at *15.

including as to the nature, causes, or diagnosis of gender dysphoria, non-surgical treatments for gender dysphoria, the quality of evidence supporting medical treatments for gender dysphoria, and the development of clinical practice guidelines for the treatment of gender dysphoria, and any such testimony is otherwise unreliable, unhelpful, or its probative value is outweighed by potential prejudice.

LEGAL STANDARD

Federal Rule of Evidence 702 places "a special gatekeeping obligation" on the trial court to ensure that an expert's testimony is "relevant to the task at hand" and "rests on a reliable foundation." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 597 (1993). As articulated by the Eleventh Circuit, "[t]he importance of Daubert's gatekeeping requirement cannot be overstated." *United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004).

In determining admissibility under Rule 702, courts must engage in a "rigorous" inquiry to determine whether (1) the expert is qualified to testify regarding the matters they intend to address; (2) the methodology employed by the expert to reach their conclusions is sufficiently reliable, as determined by the inquiry mandated under *Daubert*; and (3) the testimony assists the trier of fact to understand the evidence or determine a fact at issue. *Id.*, at 1260; *see also City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d 548, 562 (11th Cir. 1998), *cert. denied*, 528 U.S. 812 (1999). These considerations of "qualification," "reliability," and "helpfulness"

are "distinct concepts that courts and litigants must take care not to conflate." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). Crucially, the party offering the expert testimony has the "burden of establishing qualification, reliability, and helpfulness." *Frazier*, 387 F.3d at 1260.

ARGUMENT

I. Dr. Lappert Is Not Qualified to Offer a Significant Portion of His Purported Opinions

"A witness may be qualified as an expert by virtue of his 'knowledge, skill, experience, training, or education." *Quiet Technology DC-8, Inc.*, 326 F.3d at 1342. But "expertise in one field does not qualify a witness to testify about others." *Lebron v. Sec'y of Fla. Dep't of Children & Families*, 772 F.3d 1352, 1368 (11th Cir. 2014) (holding that a psychiatrist was properly prevented from opining on rates of drug use in an economically vulnerable population because he had never conducted research on the subject and instead relied on studies to form his opinion). "A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty." *Id.* (quoting *Dura Automotive Systems of Indiana, Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002)). Indeed, even "a supremely qualified expert cannot waltz into the courtroom and render opinions unless those opinions are based upon some recognized scientific method and are reliable and relevant." *Clark v. Takata Corp.*, 192 F.3d 750, 759 n.5 (7th Cir. 1999).

If a designated expert witness does not "propose to testify about matters growing naturally and directly out of research he had conducted independent of the litigation," the expert should be disqualified. *Lebron*, 772 F.3d at 1369 (quoting Fed. R. Evid. 702 (cleaned up)). Simply put, "an expert's qualifications must be within the same technical area as the subject matter of the expert's testimony; in other words, a person with expertise may only testify as to matters within that person's expertise." *Martinez v. Sakurai Graphic Sys. Corp.*, 2007 WL 2570362, at *2 (N.D. Ill. Aug. 30, 2007).

Indeed, the qualification inquiry is subject-specific because "[g]eneralized knowledge of a particular subject will not necessarily enable an expert to testify as to a specific subset of the general field of the expert's knowledge." *Id.*, at *2. "For example, no medical doctor is automatically an expert in every medical issue merely because he or she has graduated from medical school or has achieved certification in a medical specialty." *O'Conner v. Commonwealth Edison Co.*, 807 F. Supp. 1376, 1390 (C.D. Ill. 1992), *aff'd*, 13 F.3d 1090 (7th Cir. 1994). Here, Dr. Lappert's opinions topics relating to plastic surgery fail to meet the most basic standard for admissibility and must be excluded.

A. Dr. Lappert is Not Qualified to Offer Opinions on Topics Other Than Plastic Surgery

Dr. Lappert offers a clutter of opinions far afield from his experience as a plastic surgeon, including regarding the fields of endocrinology, psychology,

psychiatry, and treatment guidelines issued within those specialties. But Dr. Lappert lacks the necessary qualifications, or any other basis, to offer an expert opinion in these areas.[3] To be clear, Dr. Lappert has previously testified he "do[es] not claim to be an expert in the treatment of gender dysphoria." *Brandt* Tr. 1042:13-15.

Recognizing Dr. Lappert's lack of expertise on precisely the same subjects on which he purports to opine in this case, the court in *Kadel* precluded Dr. Lappert from providing expert testimony on matters outside the realm of plastic surgery and his anecdotal experiences as a surgeon. *See* 2022 WL 3226731 at *12-15. Similarly, at trial, the Court in *Brandt* limited his testimony solely "to his practice," "to what he has personally done in his practice," and "his actual interaction with patients and what the outcomes were." *Brandt* Tr. 1058:25, 1059:11-15. The Court should adopt the same approach here.

For example, Dr. Lappert proselytizes on the efficacy of hormone therapy as a treatment for gender dysphoria, and on the reliability of peer-reviewed medical

[3] Although Plaintiffs do not move to exclude Dr. Lappert's opinions, however fringe, within his own field, it must be noted that he has conceded that he has "never performed any kind of gender-affirming surgery in transgender patients." Miller Dec. ¶ 7; Ex. D, Excerpts of Sept. 30, 2021 Deposition Transcript ("Lappert Tr."), at 168; *id.* at 151 ("I have never treated a patient with gender dysphoria surgically."). He has also emphatically stated that he would never perform such surgeries, because in his personal view he does not "see them as beneficial" and thinks they are "incorrect treatments." *Id.* at 150. Indeed, Dr. Lappert believes that "in all instances" gender-affirming genital surgery is "an irreversible mutilation[.]" Lappert Rep. ¶ 42.

publications, and in particular clinical practice guidelines issued by the Endocrine Society (the nationally recognized professional society for endocrinologists), cited as support for the use of such treatments. *See* Lappert Rep. ¶¶ 33, 38-42. Dr. Lappert further purports to opine on the nature of, and differences between, gender and sex. *Id.* ¶¶ 31-32. But Dr. Lappert has previously conceded that he is "not an endocrinologist" and has "no specialized training or expertise in endocrinology." Lappert Tr., at 153, 204; *see also Brandt* Tr. 1040:22-25 ("Q And you're not an endocrinologist? A I am not. Q You're not an expert in endocrinology? A I am not.").

Dr. Lappert likewise admitted that he has "never prescribed cross-sex hormones for treatment of gender dysphoria," and that he has "no firsthand experience with advising [his] patients about potential risks and benefits" of such treatment. Lappert Tr., at 214. He has acknowledged that he does not "hold [himself] out as an expert in endocrinology," and indicated in a prior case that he did not plan to offer "any expert opinions in endocrinology . . . because that's outside [his] scope of expertise." Lappert Tr., at 204. Accordingly, as previously held in *Kadel*, all of Dr. Lappert's purported opinions relating to endocrinology should be excluded. *Kadel*, 2022 WL 3226731 at *13.

Dr. Lappert likewise is not qualified to opine regarding the development or efficacy of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition ("DSM-V"), the diagnosis of gender dysphoria, or the treatment of gender dysphoria

by a mental health provider. *See, e.g.*, Lapper Rep. ¶¶ 46, 74-76, 93-94. The reasoning in *Kadel* applies equally here. Dr. Lappert "is not a psychiatrist, psychologist, or mental health professional, nor has he ever diagnosed a patient with gender dysphoria," but he nonetheless provides opinions in these areas. *Kadel*, 2022 WL 3226731 at *13. Dr. Lappert himself has acknowledged that he "do[es] not hold [himself] out as an expert in diagnosing mental health conditions[,]" and that he also does "not have special[ized] training or expertise in treating mental health conditions." Lappert Tr., at 75; *see also Brandt* Tr. 1041:6-8 ("Q You don't claim to be an expert in the diagnosis of gender dysphoria? A Expertise, no. … ."). He further admitted that he has never been involved in the development of the DSM-V, and does not know "what kind of scientific literature review was done" during that development or what went on during "different meetings or conferences" to "discuss that development[;]" thus, Dr. Lappert "do[es] ***not have expert firsthand knowledge*** of how the DSM-V was developed." Lappert Tr., at 190-93 (emphasis added).

In sum, Dr. Lappert's ability to read and regurgitate information pertaining to the treatment of gender dysphoria does not qualify him as an expert. Because Dr. Lappert's purported opinions about matters within the fields of psychology, psychiatry, and endocrinology are outside of his training and expertise, such opinions should be precluded, as they were in *Kadel* and *Brandt*. *See Kadel*, 2022 WL 3226731 at *12-15; *see also, e.g.*, *Lebron*, 772 F.3d at 1368-69.

B. Dr. Lappert is Not Qualified to Opine on the Quality of the Studies Supporting Gender-Affirming Care

Aware that his views on gender dysphoria and gender-affirming care are contradicted by the position of every major medical society and professional organization in the country, Dr. Lappert goes to great lengths to attempt to undermine the validity and basis of a select few of the multitude of medical studies that support the safety and efficacy of gender-affirming care by pointing out what he perceives as methodological flaws. *See, e.g.*, Lappert Rep ¶¶ 38-41, 58-67, 85-87; Lappert Rebuttal ¶¶ 8, 11-12, 16-22. He repeatedly contends that the existing studies do not constitute "quality evidence," and as a result, gender-affirming care is experimental or unsupported by reliable science. *See* Lappert Rep. ¶¶ 24-25, 57, 59, 106; Lappert Rebuttal ¶ 25. But once again, such opinions are far afield from Dr. Lappert's professional experience.

As the court in *Kadel* noted, Dr. Lappert is "not a statistician or epidemiologist, and there is no evidence . . . that he has any experience, specialized training, or knowledge about crafting a research study, analyzing data, or conducting a clinical trial." *Kadel*, 2022 WL 3226731 at *13. Given his lack of personal experience with the study of gender-affirming care, the court in *Brandt* similarly limited his testimony to "to what he has personally done in his practice, not what the evidence shows." *Brandt* Tr. 1059:9-13. Indeed, Dr. Lappert's prior publications (seven in total) include case reports and opinion essays, and he has not published in

a peer-reviewed journal in over ***twenty-five years***. *See* Lappert Rep., at 69 (curriculum vitae). His curriculum vitae notes a brief academic career, but that role appears limited to overseeing clinical practitioners and did not involve conducting research or clinical trials of any kind. *See id*., at 68; *see also Kadel*, 2022 WL 3226731 at *13.

In sum, as the court in *Kadel* noted, "[j]ust as an epidemiologist or statistician would not be qualified to perform surgery, a surgeon with little to no research experience is not qualified to opine of the veracity of statistical studies." *Kadel*, 2022 WL 3226731 at *13. Accordingly, Dr. Lappert's proffered opinions regarding the validity or veracity of studies pertaining to gender-affirming care or gender dysphoria should be excluded.

II. Dr. Lappert's Opinions on Topics Other than Plastic Surgery are Also Either Unreliable, Unhelpful, or Both

As a rule, an expert's testimony should only be admitted if it is sufficiently reliable. "To meet the reliability requirement, an expert's opinion must be based on scientifically valid principles, reasoning, and methodology that are properly applied to the facts at issue." *In re 3M Combat Arms Earplug Products Liab. Litig.*, 3:19MD2885, 2022 WL 1262203, at *1 (N.D. Fla. Apr. 28, 2022). The reliability requirement in Rule 702 is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). "At this stage, the court must undertake an independent analysis of each step in the logic leading to

the expert's conclusions; if the analysis is deemed unreliable at any step the expert's entire opinion must be excluded." *Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009), *aff'd sub nom. Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183 (11th Cir. 2010).

To satisfy the helpfulness requirement, the proffered testimony must have a justified scientific relationship to the facts at issue. *Daubert*, 509 U.S. at 591. Thus, helpfulness, "goes primarily to relevance." *Daubert*, 509 U.S. at 580. Relevant expert testimony "logically advances a material aspect of the proposing party's case" and "fits" the disputed facts. *McDowell v. Brown*, 392 F.3d 1283, 1298-99 (11th Cir. 2004). "The relationship must be an appropriate 'fit' with respect to the offered opinion and the facts of the case." *Id.* Where the court determines that proffered expert testimony does not "fit" the facts of the case, it is properly excluded. *See id.*, at 1301.

Here, Plaintiffs' case turns primarily on two issues, among others, (1) whether the Agency employed a process that was reasonable and (2) whether gender-affirming medical care is experimental or investigational. Many of Dr. Lappert's opinions are both unreliable and unhelpful to the issues before this Court, as detailed below.

A. Dr. Lappert's Opinions are Rejected by the Vast Majority of the Scientific and Medical Community and Lack Credible Support

General acceptance in the relevant scientific community is an important element to the reliability inquiry. *Allison v. McGhan Medical Corp*., 184 F.3d 1300, 1313 (11th Cir. 1999). Moreover, the fact that a known theory "has been able to attract only minimal support within the community may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Here, Dr. Lappert's opinions about the effectiveness and propriety of gender-affirming care, which he is not qualified to present, are far outside the mainstream of medical and scientific opinion and have been explicitly rejected by every relevant scientific and medical community. While undoubtedly Dr. Lappert "has strong beliefs," the fact that his opinions are "not generally accepted by the scientific community, and [are] unsupported by other studies" means that "his testimony is based more on personal opinion than on scientific knowledge," making it unreliable. *Allison*, 184 F.3d at 1319.

Dr. Lappert cites virtually no evidentiary support for his critiques of medical studies substantiating the need for gender-affirming care. *See generally*, Lappert Rep.; Lappert Rebuttal. And to the contrary, the evidence shows that Dr. Lappert's opinions regarding the supposedly "experimental" nature of gender-affirming care are on the scientific fringe. *See, e.g.*, Lappert Rep. ¶¶ 23, 97-98; Lappert Rebuttal ¶¶ 21-22, 25 n. 3. For example, in a recent case addressing a challenge to Arkansas' state-law ban on gender-affirming treatment for minors, Dr. Lappert offered

substantially similar opinions in support of the ban, contending that "[g]ender affirming' treatments are experimental[.]" *See Brandt v. Rutledge*, 551 F.Supp.3d 882 (E.D. Ark. 2021); Lappert Tr., at 33-35; Miller Dec. ¶ 8; Ex. E, Declaration of Dr. Lappert in *Brandt v. Rutledge*.

Nevertheless, the *Brandt* court preliminarily enjoined the ban, recognizing that "the consensus recommendation of medical organizations is that the only effective treatment for . . . gender dysphoria is to provide gender-affirming care," citing briefs from organizations like the American Medical Association, American Academy of Pediatrics, and many more. *Brandt*, 551 F.Supp.3d at 890 n.3. *Brandt* also found that "gender-affirming treatment is supported by medical evidence that has been subject to rigorous study," and that "every major expert medical association recognizes that gender-affirming care for transgender minors may be medically appropriate and necessary to improve the physical and mental health of transgender people." *Id.*, at 891; *see also Fain v. Crouch*, Case No. 3:20-0740, 2022 WL 3051015, *10 ("[m]any of the major medical organizations have opposed the blanket denial of this medically necessary [gender-affirming] care.").

Dr. Lappert himself has previously acknowledged that "every major expert medical association disagrees with [him] because they've all taken [the] position that this treatment is in fact medically necessary." Lappert Tr., at 40. Dr. Lappert's own

former association, the American Society of Plastic Surgeons[4] ("ASPS") (whose categorizations of evidence for prognostic and therapeutic studies Dr. Lappert repeatedly relies upon in critiquing the studies and evidence in support of gender-affirming care) issued a statement in February 2021 stating that it "firmly believes that plastic surgery services can help gender dysphoria patients align their bodies with whom they know themselves to be," and promising to "continue its efforts to advocate across state legislatures for full access to medically necessary transition care." Miller Dec. ¶ 9; Ex. F, Feb. 25, 2021 ASPS Statement. So as Dr. Lappert has admitted, the ASPS also "does not agree with [his] opinions that gender affirming surgery is experimental." Lappert Tr., at 112-13. In short, the overwhelming consensus confirms that, far from being generally accepted, Dr. Lappert's opinions regarding gender-affirming care are unsupported and unreliable.

B. Dr. Lappert's Critiques of the WPATH Standards of Care, the Endocrine Society Guidelines, and Other Organizations' Positions Are Unreliable

Given that his views are unsupported by any reliable scientific evidence, and indeed run contrary to the position of every major medical society and professional organization, Dr. Lappert attempts to discredit the clinical guidelines and standards of care espoused by these respected organizations, including the World Professional

[4] Dr. Lappert's report misidentifies his own former professional organization as the "American Society of Plastic Surgery." *E.g.*, Lappert Rep. ¶ 24.

Association for Transgender Health ("WPATH") and the Endocrine Society. For example, Dr. Lappert asserts that "the WPATH standard of medical necessity is not supported in reliable scientific evidence" and he purports to "examine how such guidelines are developed." Lappert Rep. ¶¶ 36, 51; *see also, e.g.,* Lappert Rebuttal ¶ 8 (contending that the "evidence cited in support of the WPATH Standard reveals a lack of evidence even to support a weak recommendation in a treatment guideline.").

But Dr. Lappert has previously conceded that he was "not involved with the development" of WPATH guidelines, he did not "know what kind of scientific literature [review] the WPATH conducted as part of drafting" the guidelines, or what other forms of "peer review," "outside experts," or "public comments" the WPATH may have relied on in developing their guidelines. Lappert Tr., at 184-87. To the point, Dr. Lappert admitted that he is "***not an expert***" in the development of either versions 7 or 8 of the WPATH standards of care. *Id.*, at 188-89. The court in *Kadel* agreed, precluding Dr. Lappert's views on the WPATH standards as "unscientific opinion and speculation." *Kadel*, 2022 WL 3226731 at *14. So did the court in *Brandt*, which sustained an objection to an attempt to elicit testimony from Dr. Lappert as to what the WPATH guidelines mean. *Brandt* Tr. 1058:4-10.

Dr. Lappert similarly opines that the "scientific evidence used to support the Endocrine Society's special treatment guidelines for gender dysphoric/gender

incongruent persons appears to be of low to very low quality[.]" Lappert Rep. ¶ 38. Yet Dr. Lappert has admitted that he does not know when these guidelines "were initially published" or "last revised;" he was "not involved with the[ir] development;" he does not know "what kind of scientific literature review" went into that development; thus, he agreed he is "not an expert in how the Endocrine Society developed the original 2009 guidelines" or "the 2017 updates." Lappert Tr., at 195-200.

At bottom, Dr. Lappert has no expertise or understanding of the development of the WPATH or Endocrine Society guidelines, and therefore his criticism of the evidence in support of these standards is unreliable. *See Kadel*, 2022 WL 3226731 at *14. Consequently, he should not be permitted to mislead a factfinder with his baseless *ipse dixit* critiques. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

C. Dr. Lappert's Opinions Regarding Informed Consent, "Desistance," and Changes in Demographics are Unreliable, Unhelpful, and Irrelevant.

Dr. Lappert dedicates a portion of his report to his opinions on whether patients diagnosed with gender dysphoria can provide "meaningful consent" to gender-affirming treatment, and he makes a number of claims regarding statistics pertaining to the supposed "resolution" of the condition of "transgenderism" absent gender-affirming care, and changes in the rates of diagnosis and makeup of the population of individuals diagnosed with gender dysphoria. *E.g.*, Lappert Rep. ¶¶

69-70, 73. But these purported opinions are unreliable, unhelpful, and irrelevant to the issues before the Court.

First, Dr. Lappert has failed to support his opinions regarding "informed consent" with any credible evidence or data. *See generally*, Lappert Rep. Accordingly, his conclusions regarding informed or meaningful consent are speculative and unreliable and should be excluded. *See Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988) ("relevant testimony from a qualified expert is admissible only if the expert knows of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation."); *see also Hendrix*, 255 F.R.D. at 578; *Kadel*, 2022 WL 3226731, at *14 (concluding that Dr. Lappert's opinions regarding informed consent to gender-affirming care were "irrelevant" and "not admissible.").

Second, Dr. Lappert's opinions that gender dysphoria may resolve on its through his mischaracterizing description of "watchful waiting" (e.g., Lappert Rep. ¶¶ 93, 94, 98) are based on a severely flawed reading of the literature, which renders his opinions unreliable, and regardless, such opinions are also irrelevant. Specifically, Dr. Lappert cites a single article by Zucker et al. in support of this proposition. But that study pertains to (1) *preadolescent/prepubertal* youth not *adolescents after the onset of puberty* and (2) who were diagnosed with *gender identity disorder* under the DSM-III or the DSM-IV not *gender dysphoria* under the

DSM-V. It is therefore inapplicable and irrelevant in this context, where the changes from the DSM-IV diagnosis of gender identity disorder to the DSM-V diagnosis of gender dysphoria in 2013 made "the diagnosis more restrictive and conservative" to reduce "false positives." *See* Miller Dec. ¶ 10; Ex. G, Memo Outlining Evidence for Change for Gender Identity Disorder, at 904-05.

Dr. Lappert's assertions are also flawed because they misrepresent Dr. Zucker's work. Indeed, Dr. Zucker authored the chapter in "Gender Dysphoria and Gender Incongruence" in the medical textbook *Lewis's Child and Adolescent Psychiatry, Fifth Edition*, published in 2018. *See* Miller Dec. ¶ 11, Ex. H, Excerpt of *Lewis's Child and Adolescent Psychiatry, Fifth Edition*. That chapter states that: (1) "it appears that the vast majority of transgender adolescents persist in their transgender identity," *id.* at 638; and (2) "Once children have reached puberty, transgender identity persists in the vast majority of cases, and medical intervention is often considered[.]" *Id.* at 640. Given that this case pertains to gender-affirming medical treatments which are not provided until after the *onset of puberty*, Dr. Lappert's opinions, premised on his flawed reading and understanding of the "desistance" literature, are irrelevant and unreliable.

Third, Dr. Lappert's opinions regarding a change of demographics are wholly unreliable and irrelevant. Lappert Rep. ¶ 73. He cites no scientific or peer-reviewed literature. To the contrary, he cites solely to a non-medical, non-scientific book by

an anti-transgender activist.[5] But Rule 703 requires that "[t]he facts or data … upon which an expert bases an opinion or inference" must be "of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject," Fed. R. Evid. 703, and the book upon which Dr. Lappert relies is *not* the type of material reasonably relied upon by experts in any field of medicine. Moreover, Dr. Lappert's opinion is irrelevant. Gender dysphoria is a real and recognized condition that requires treatment – whether the demographics have changed has no bearing on that or the questions before the Court.

D. Dr. Lappert's Commentary on Gender-Affirming Care Provided in Other Countries is Unreliable and Unhelpful

Dr. Lappert also offers opinion regarding the treatment of gender dysphoria and the provision of gender-affirming care in certain European countries, including the United Kingdom, Sweden, Finland, France, and Italy, and cites developments in those countries as evidence in support of his opinions proffered in this case. *See* Lappert Rep. ¶¶ 104-05; Lappert Rebuttal ¶ 24. But, according to the curriculum vitae he supplied, Dr. Lappert is not licensed to practice in any of those countries. *See* Lappert Rep., at 67-69. His report and rebuttal report likewise offer no

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[5] Abigail Shrier is not a doctor but an anti-transgender activist and opinion columnist. She has described transgender rights as a "war on women" and has advocated against what she considers to be a "transgender craze." GLAAD, GLAAD Accountability Project: Abigail Shrier, https://www.glaad.org/gap/abigail-shrier (accessed Apr. 6, 2023).

indication that Dr. Lappert has personal knowledge regarding the policies regarding gender-affirming care issued in those countries or how those policies were developed. *See generally*, Lappert Rep.; Lappert Rebuttal. Dr. Lappert also either wholly fails to cite any facts or data in support of his opinions regarding developments in these countries, or the data he cites is insufficient to support those opinions. *See* Lappert Rep. ¶¶ 104-05; Lappert Rebuttal ¶¶ 24-25. Consequently, the Court should exclude Dr. Lappert's testimony regarding such opinions. *See Jones*, 861 F.2d at 662.

III. Dr. Lappert's Opinions are Based on His Personal Beliefs and Not Science

Reliability is a flexible inquiry, under which "courts must ensure that an expert's opinion is based on scientific, technical, or other specialized knowledge and not on belief or speculation." *Sardis v. Overhead Door Corp.*, 10 F.4th 268, 281 (4th Cir. 2021); *see also Jones*, 861 F.2d at 662 ("relevant testimony from a qualified expert is admissible only if the expert knows of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation."). Here, there is abundant evidence that Dr. Lappert's opinions are so tainted by his strong personal views against gender-affirming care as to render those opinions unreliable. Although Plaintiffs of course do not seek to impugn any moral or religious views that Dr. Lappert may hold, those views plainly inform the opinions he proffers in this case (and indeed appear to be the primary motivation for those opinions), and

therefore the Court must consider those views in assessing the reliability of Dr. Lappert's conclusions.

Dr. Lappert has previously testified that he has "strong personal opinions on whether doctors should be providing gender-affirming treatment to minors." Lappert Tr., at 78. That is an understatement. He has previously lobbied state legislatures in, at a minimum, Utah, Arkansas, Alabama, Texas to pass laws or regulations that would ban doctors from providing gender-affirming medical care to adolescents. *See id.*, at 57, 61-62; *id.* at 54-55 (agreeing he has "actively lobbied to get these kinds of bans passed"). In Alabama he spoke in favor of a ban on gender-affirming care for adolescents, and "publish[ed] an op-ed" that urged the legislature to protect what he called "gender-confused children." *Id.*, at 76, 63-64. He argued to the Utah legislature that "you can't change a person's sex," and that "all that is happening is that the patient is undergoing an intentional mutilation in order to create a counterfeit appearance of the other sex." *Id.*, at 57-60.

Dr. Lappert also affirmed in deposition testimony that he "absolutely" considers "gender reassignment surgery to be an intentional mutilation." *Id.*, at 60. He further testified that he would like to see doctors who perform these gender-affirming surgeries to be "criminally prosecute[d] – confirming that he thinks "that's a good idea." *Id.*, at 52. Dr. Lappert went so far as to confirm in his report in this

case that "in all instances" gender-affirming genital surgery is "an irreversible mutilation[.]" Lappert Rep. ¶ 42.

Dr. Lappert has also worked hand in hand with the Alliance Defending Freedom ("ADF"), an organization he agrees has "moral objections" to gender-affirming healthcare. Lappert Tr., at 81. Among other things, he attended an ADF conference that discussed the "poverty of [experts] who are willing to testify" about these anti-gender-affirming treatments. *Id.*, at 90-91. Attendees at that conference "were asked whether they would be willing as participate as expert witnesses[;]" not coincidentally, Dr. Lappert became an expert witness for the first time after attending that conference. *Id.*, at 91; *see also Brandt* Tr. 1080:5-1081:11. In this sense, Dr. Lappert is the definition of a manufactured "expert witness" who "developed his opinions expressly for purposes of testifying" in an area that he did not otherwise specialize in. *Lebron*, 772 F.3d at 1369.

Dr. Lappert's public interviews and presentations reinforce his vehement opposition to any form of gender-affirming care. These include, for example, his views that the religious conception of "the human person" "defines the 'end' of medical and surgical care." Lappert Tr., at 459. They also include his opinions that "changing a person's sex is a lie and also a moral violation for a physician," and that gender-affirming surgery is "diabolical in every sense of the word." *Id.*, at 464-65; *see also* Miller Dec. ¶ 12; Ex. I, Article titled *Plastic surgeon: Sex-change operation*

'utterly unacceptable' and a form of 'child abuse' ("LifeSite Article"), at 1, 7; Lappert Tr., at 465 (agreeing that he "hold[s] those views"). And finally, these also include his inflammatory views that parents who "discuss[] gender identity issues with children" are "sexualizing them" (Lappert Tr., at 462), and that these conversations are "grooming a generation" for abuse. *Id.* at 461; Miller Dec. ¶ 13; Ex. J, Presentation by Dr. Lappert titled "Transgender Surgery & Christian Anthropology," at 24; *see also* LifeSite Article, at 1, 2 (reporting that "regarding children, Lappert said, sexualizing them at a young age with these ideas is grooming them for later abuse.").

As the court in *Kadel* found, these positions call "Lappert's bias and credibility into serious question." *Kadel*, 2022 WL 3226731, at *12.

IV. Dr. Lappert's Opinions Lack Probative Value and are Therefore Neither Helpful to the Fact-Finder Nor Admissible Under Fed. R. Evid. 403

Finally, the Court should exclude the opinions and testimony of Dr. Lappert outside the field of plastic surgery because introduction of those opinions will result in unfair prejudice, confusion of the issues, or in misleading testimony. Fed. R. Evid. 403. As articulated above, Dr. Lappert's non-surgical opinions are irrelevant to the issues in this case, and are otherwise speculative, unhelpful, and unreliable. His testimony outside of his discipline would also result in prejudice, as it would sow confusion about the propriety of gender-confirming care based on speculation and irrelevant, misleading, and biased opinions. Accordingly, to the extent not

excluded for the reasons detailed above, Dr. Lappert's opinions outside of plastic surgery should be precluded under Rule 403.

CONCLUSION

For the foregoing reasons, the Court should exclude any opinion proffered by Dr. Lappert outside the field of plastic surgery and limit his testimony to the provision of surgical care generally.

Dated: April 7, 2023

Respectfully Submitted,

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CERTIFICATE OF WORD COUNT

As required by Local Rule 7.1(F), I certify that this Motion and Incorporated Memorandum of Law contains 5,753 words.

/s/ William C. Miller
Attorney for Plaintiffs

CERTIFICATE OF SATISFACTION OF ATTORNEY-CONFERENCE REQUIREMENT

Pursuant to Local Rule 7.1(B), counsel for Plaintiffs and counsel for Defendants conferred regarding the instant motion during a Zoom conference on April 6, 2023. Defendants indicated they do not consent to the relief requested herein.

CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April, 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ William C. Miller
Attorney for Plaintiffs

TAB 133

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION TO EXCLUDE
EXPERT TESTIMONY OF MICHAEL LAIDLAW

Pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403, and 702, Plaintiffs respectfully move this court to exclude the expert testimony of Defendants' proposed expert, Dr. Michael Laidlaw. As explained more fully below, Dr. Laidlaw is not a qualified expert and his opinions and testimony are neither reliable nor helpful to the trier of fact pursuant to the standards set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and its progeny. His opinions and testimony are likewise inadmissible pursuant to Fed. R. Evid. 403. As grounds, Plaintiffs state:

1. Defendants propose Dr. Laidlaw, an adult endocrinologist, as their expert and submitted a report with their Rule 26 Disclosures. (Exhibit 1, Laidlaw Expert Report.)

2. According to Dr. Laidlaw's expert report, he was retained in this case to provide "expert opinion on the efficacy and safety of sex reassignment treatment." (Ex. 1, ¶ 5).

3. Yet Dr. Laidlaw's expert reports also contain opinions about the causes, diagnosis, and treatment of gender dysphoria, including the use of puberty-delaying medication, hormone treatment, and surgery, the propriety of the physician-recommended treatment received by the Plaintiffs, as well as their physical and mental health. (Ex. 1, Exhibit 2, Laidlaw Rebuttal Report, Exhibit 3, Laidlaw Declaration in support of Defendants' Opposition to Preliminary Injunction).

4. Dr. Laidlaw also submitted a declaration in support of Defendants' Response in Opposition to Plaintiffs' Motion for Preliminary Injunction. (Ex. 3).

5. Defendants have not met their burden of establishing that Dr. Laidlaw is qualified to proffer an opinion on the assessment of gender dysphoria generally, or regarding his alleged concerns related to the assessment of Plaintiffs in particular, nor have they established that Dr. Laidlaw is qualified to testify about the appropriateness of surgery to treat gender dysphoria generally, or the

appropriateness of any surgeries received by Plaintiffs in the past or any surgical procedures they might undergo in the future. Dr. Laidlaw is not a mental health professional or a surgeon, has never provided treatment for gender dysphoria, he has never conducted any original research on the issue nor published any peer-reviewed literature on these matters, has never diagnosed a patient with gender dysphoria, and has only treated one patient with gender dysphoria nearly two decades ago.

6. Defendants similarly have not met their burden of showing that Dr. Laidlaw's opinions are reliable. The opinions offered in his reports and testimony on the effectiveness of gender-affirming care, the harms it may pose, "desistence," informed consent, and WPATH fall outside of his qualifications, are based on speculation and ipse dixit, and lack any reliable scientific methodology.

7. Nor have Defendants met their burden of showing that Dr. Laidlaw's opinions are relevant. Dr. Laidlaw offers opinions and testimony regarding the number of people diagnosed with gender dysphoria, human sexual development, the difference between gender identity and biological sex (including whether biological sex can be changed), social transition, and the policies of other counties. None of this testimony has a connection to the existing data or issues in this case and are therefore not helpful to the trier of fact.

8. The probative value of Dr. Laidlaw's testimony is substantially outweighed by the danger of unfair prejudice, confusion of the issues, waste of time, undue delay, and needless presentation of cumulative evidence.

WHEREFORE, Plaintiffs Request that the Court enter an Order excluding Dr. Laidlaw's opinions in this case, except as they relate to the risks associated with puberty suppressing medication and hormone therapy, including those contained in his expert declaration (Ex. 1), and rebuttal declaration (Ex. 2), and prohibit Defendants from relying on testimony for any purpose other than describing the risks associated with puberty suppressing medication and hormone therapy for any purpose during trial.

MEMORANDUM OF LAW

The vast majority of Dr. Laidlaw's opinions and testimony lack any indicia of admissibility required under *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and the Federal Rules of Evidence. This testimony should be excluded because Dr. Laidlaw is not qualified to serve as an expert witness on matters beyond the scope of his expertise as an adult endocrinologist, and his opinions and testimony are not reliable, helpful to the trier of fact, or probative of the issues in this case.

I. LEGAL STANDARD

Federal Rule of Evidence 702 governs the admissibility of expert testimony. *Daubert* requires district courts, pursuant to Rule 702, to perform a critical "gatekeeping" function concerning the admissibility of expert scientific evidence, ensuring that the testimony or evidence is both relevant and reliable. *Daubert*, 509 U.S. at 597; *see also United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) ("The importance of Daubert's gatekeeping requirement cannot be overstated.").

In determining the admissibility of expert testimony under Rule 702, courts engage in a "rigorous" three-part inquiry and must consider whether:

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in *Daubert*; and (3) the testimony assists the trier of fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

Frazier, at 1260; *see also City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d 548, 562 (11th Cir. 1998), *cert. denied*, 528 U.S. 812 (1999). The Eleventh Circuit refers to these three considerations separately as "qualification," "reliability," and "helpfulness" and has emphasized that they are "distinct concepts that courts and litigants must take care not to conflate." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). The party offering the expert testimony has the "burden of establishing qualification, reliability, and helpfulness." *Frazier*, 387 F.3d at 1260.

To be sure, "[i]mplementing Rule 702, *Daubert* requires district courts to ensure that any and all scientific testimony or evidence admitted is both relevant and reliable." *Claire v. Fla. Dep't of Mgmt. Servs.*, 2021 WL 5982330, at *1 (N.D. Fla. Oct. 20, 2021). "[T]he trial judge must determine [this] ***at the outset***." *Daubert*, 509 U.S. at 592. (emphasis added). "Rule 702 applies whether the trier of fact is a judge or a jury." *UGI Sunbury LLC v. A Permanent Easement for 1.7575 Acres*, 949 F.3d 825, 832 (3d Cir. 2020); *see also Kadel v. Folwell*, 2022 WL 3226731, at **5-17 (M.D.N.C. Aug. 10, 2022) (granting motions to exclude in the context of summary judgment).

Finally, because of the potentially misleading effect of expert evidence, *see Daubert*, 509 U.S. at 595, on occasion expert opinions that otherwise meet admissibility requirements may still be excluded under Fed. R. Evid. 403.

Here, Defendants have failed to demonstrate that the majority of Dr. Laidlaw's proffered testimony is relevant and meets the requirements of Rule 702 as interpreted by *Daubert*, or the requirements of Rule 403. It should be excluded.

II. DR. LAIDLAW'S OPINIONS THAT GO BEYOND HIS QUALIFICATIONS AS AN ADULT ENDOCRINOLOGIST SHOULD BE EXCLUDED.

It is axiomatic that "[a] witness may be qualified as an expert by virtue of his 'knowledge, skill, experience, training, or education." *Quiet Technology DC-8, Inc.*, 326 F.3d at 1342; Fed. R. Evid. 702. However, credentials are not dispositive when determining qualification, particularly where an expert offers testimony in areas outside of their knowledge, skill, experience, training, or education. "Expertise in one field does not qualify a witness to testify about others." *Lebron v. Secretary of Florida Dept. of Children and Families*, 772 F.3d 1352, 1368 (11th Cir. 2014) (holding that a psychiatrist was properly prevented from opining on rates of drug use in an economically vulnerable population because he had never conducted research on the subject, and instead relied on studies to form his opinion). If a potential expert witness does not "propose to testify about matters

growing naturally and directly out of research he had conducted independent of the litigation," that testimony should be disqualified. *Lebron*, 772 F.3d at 1369 (quoting Fed. R. Evid. 702 (cleaned up)).

Dr. Laidlaw offers numerous opinions related to areas of medicine far afield from his experience and training as an endocrinologist. He is unqualified to offer these opinions, since "no medical doctor is automatically an expert in every medical issue merely because he or she has graduated from medical school or has achieved certification in a medical specialty." *O'Conner v. Commonwealth Edison Co.*, 807 F.Supp. 1376, 1390 (C.D. Ill. 1992), *aff'd*, 13 F.3d 1090 (7th Cir. 1994). Here, Dr. Laidlaw, an adult endocrinologist,[1] is not qualified to render most of the opinions he proffers. Dr. Laidlaw: (1) has never conducted any original, peer-reviewed research about gender identity, transgender people, or gender dysphoria, Exhibit 4, PI Hearing Transcript, at 10:15- 11:13; Exhibit 5, Deposition of Dr. Laidlaw in *C.P. v. Blue Cross*, at 29:23-30:6; (2) has not published any scientific, peer-reviewed literature on gender dysphoria or transgender people, Ex. 5 at 42:10-42:22;[2] (3) has never diagnosed a patient with gender dysphoria, Ex. 4 at 11:19-

[1] Dr. Laidlaw testified that fewer than 5% of his patients are under 18. Ex. 4 at 8:14-16.

[2] Dr. Laidlaw's only publications relating to gender dysphoria in a peer-reviewed journal are letters to the editor not based on any original research or scientific

11:21; Ex. 5 at 45:21-46:3; (4) has only treated one patient with gender dysphoria (nearly two decades ago, prior to the existence of the DSM-5's gender dysphoria diagnosis), Ex. 4 at 11:22-12:16; Ex. 5 at 43:11-43:17; (5) is not a psychiatrist, a psychologist, nor mental health care provider of any kind, Ex. 4 at 7:20-8:2; Ex 5 at 184:8-11; and (6) is not a surgeon and has never provided gender-affirming surgery, Ex. 4 at 8:9-10, 87:8-14; Ex. 5 at 184:12-13.

One. Dr. Laidlaw is not a mental health care provider, and is therefore unqualified to opine on the "[a]ssessment of the patient with gender dysphoria." (Ex. 1 ¶¶ 228-29; Ex 2 ¶¶ 15-16), or the appropriate treatment for people with suicidal ideation (Ex. 1 ¶¶ 176-78; Ex. 2 ¶¶ 78-85). For the same reasons, he is unqualified to testify as to the Plaintiffs' mental health. (Ex. 1 ¶¶ 141, 231-33, 238-42, 249-50, 253-55, 267-70, 272, 274-75, 279-84, 291-93, 294-99, 305).

The district court's decision in *Kadel v. Folwell* is most illustrative here. Like Dr. Laidlaw, Dr. Hruz, the endocrinologist at issue in *Kadel,* "offer[ed] a wide range of conclusions that fall into five main categories: mental healthcare, medical and surgical care, informed consent, criticism of medical associations, and political criticisms." *Kadel,* 2022 WL 3226731, at *8. The *Kadel* court excluded

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study, and which he cannot confirm are subjected to peer-review. Ex. 4 at 9:21-11:18; Ex. 5 at 31:14-39:23.

most of his proffered testimony and limited the testimony "to a discussion of the risks associated with prescribing hormone treatments to adolescents and adults," the only possible area of expertise for Dr. Hruz, as well as his colleague, Dr. Laidlaw. *Id.*, at *10.

Kadel found that, given his lack of experience in those areas, Dr. Hruz was "not qualified to offer expert opinions on the diagnosis of gender dysphoria, the DSM, gender dysphoria's potential causes, the likelihood that a patient will 'desist,' or the efficacy of mental health treatments." *Id.*, at *9. The *Kadel* Court emphasized that Dr. Hruz was "not a psychiatrist, psychologist, or mental healthcare professional," and "ha[d] never diagnosed a patient with gender dysphoria, treated gender dysphoria, treated a transgender patient, conducted any original research about gender dysphoria diagnosis or its causes, or published any scientific, peer-reviewed literature on gender dysphoria." *Id.*

Two. Like Dr. Hruz, Dr. Laidlaw "is not a surgeon and has no experience with surgery for gender dysphoria and, therefore, is not qualified to testify to the risks associated with surgery or the standard of care used by surgeons for obtaining informed consent for surgery." *Kadel*, 2022 *WL 3226731*, at *9; *see* Ex. 4 at 8:9-

10, 87:8-87:9; Ex. 5 at 47:16- 47:17.[3] Dr. Laidlaw bases his opinions solely on his review of literature (Ex. 4 at 15:24-16:2). Simply reading about these issues does not qualify Dr. Laidlaw as an expert, however. *See* Ex. 4 at 18:20-18:25; Fed. R. Ev. 702. "Merely reading literature in a scientific field does not qualify a witness—even an educated witness—as an expert." *Kadel*, 2022 WL 3226731, at *9; *see also Lebron*, 772 F.3d at 1369; *Dura Auto. Sys. Of Ind., Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002) ("A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty.").

* * *

In sum, Dr. Laidlaw is not qualified to serve as an expert on the diagnosis of or mental health or surgical treatment paradigms for gender dysphoria. He is "not qualified by background, training, or expertise to opine" about these issues. *Lebron*, 772 F.3d at 1369. At most, Dr. Laidlaw can testify as "to the risks associated with puberty blocking medication and hormone therapy," but much of

[3] Notwithstanding that he is not a surgeon of any kind and has no clinical or research experience with surgeries used to treat gender dysphoria, Dr. Laidlaw opines broadly about surgery (Ex. 1. ¶¶ 160-75; Ex. 2 ¶¶ 60-68, Ex. 3 at 23-25), as well as more specifically about two Plaintiffs' chest surgeries (Ex. 1 ¶¶ 257-59, 270, 295-300), and the potential for one Plaintiff to successfully undergo surgery in the future (Ex. 1 ¶ 290). Not only is Dr. Laidlaw unqualified to offer these opinions, but such testimony is wholly unreliable given Dr. Laidlaw's lack of expertise, skill, and experience with surgery.

his testimony on these subjects is not reliable, as described below. *See Kade*l, 2022 WL 3226731, at *10.

III. THE MAJORITY OF DR. LAIDLAW'S EXPERT OPINION IS WHOLLY UNRELIABLE.

An expert's testimony should only be admitted if it is sufficiently reliable. "To meet the reliability requirement, an expert's opinion must be based on scientifically valid principles, reasoning, and methodology that are properly applied to the facts at issue." *In re 3M Combat Arms Earplug Products Liab. Litig.*, 3:19MD2885, 2022 WL 1262203, at *1 (N.D. Fla. Apr. 28, 2022). The requirement of reliability found in Rule 702 is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). "At this stage, the court must undertake an independent analysis of each step in the logic leading to the expert's conclusions; if the analysis is deemed unreliable at any step the expert's entire opinion must be excluded." *Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009), *aff'd sub nom. Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183 (11th Cir. 2010).

In making this determination the court can consider a variety of factors, including whether the purported expert's theory has been subjected to peer review and publication, and whether the theory has been generally accepted in the scientific community. *See Daubert*, 509 U.S. at 593-94; *Rink v. Cheminova, Inc.*, 400 F.3d

1286, 1291-92 (11th Cir. 2005).[4] To be reliable, the expert's testimony must always be based on "good grounds," *Daubert,* 509 U.S. at 590, and must represent more than scientifically unsupported "leaps of faith." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002). As such, courts must assess "whether the evidence is genuinely scientific, as distinct from being unscientific speculation offered by a genuine scientist." *Chapman v. Procter & Gamble Distributing, LLC*, 766 F.3d 1296, 1306 (11th Cir. 2014). "In evaluating the reliability of an expert's method . . . a district court may properly consider whether the expert's methodology has been contrived to reach a particular result." *Rink*, 400 F.3d at 1293, n.7.

Here, Dr. Laidlaw offers several opinions that fail to meet any indicia of reliability. His proffered opinions are not consistent with generally accepted scientific consensus, but are based entirely on rank speculation, unfounded assumptions, and bias. These opinions should be excluded.

[4] Other factors which may be relevant include (1) the nature of the field of claimed expertise, (2) the source of the expert's knowledge, (3) the expert's level of care in using the knowledge, and (4) the expert's consideration of alternative hypotheses. *Hendrix*, 255 F.R.D. at 578-79.

A. Dr. Laidlaw's opinions about the effectiveness of gender-affirming medical care are not generally accepted and are unreliable.

General acceptance in the relevant scientific community is an important element to the reliability inquiry. *See Allison*, 184 F.3d at 1313. Not only is widespread acceptance an important factor in assessing the reliability of an expert's opinions, but the fact that a known theory "has been able to attract only minimal support within the community may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Here, Dr. Laidlaw's opinions about the effectiveness and propriety of gender-affirming medical care are far outside the mainstream of medical and scientific opinion and have been explicitly rejected by every relevant scientific and medical community. Nor do his opinions stem from any accepted scientific methodology, rather, they are frequently contradicted by existing scientific literature.

Dr. Laidlaw falsely testifies that the "'professional consensus' [supporting gender-affirming medical care] exists only within the confines of" WPATH (Ex. 1 ¶ 185; *see also* Ex. 2 ¶ 28, Ex. 3 at 27, 29-30). Dr. Laidlaw offers no evidence to support this contention, and instead attempts to legitimize his opinions by nitpicking at and mischaracterizing a few of the studies that fall within the broad consensus of clinicians, scientists, and researchers in finding that the three services at issue in this case are effective in treating gender dysphoria. Specifically:

- Dr. Laidlaw cites Dhejne (2011) for the proposition that the study showed that gender-affirming care was not effective (Ex. 1 ¶ 202 & Ex. 3 at 31). This characterization flatly contradicts the study's own conclusion that "surgery and hormonal therapy alleviates gender dysphoria" (Exhibit 6, Dhejne et al. (2011), at e16885).
- Dr. Laidlaw emphasizes the fact that Branstrom & Pachankis (2020) issued corrections after Dr. Laidlaw and others wrote letters to the editor of the journal in which it was published (Ex. 1 ¶¶ 203-09 & Ex. 3 at 31-33). Dr. Laidlaw suggests that the article was completely retracted or repudiated, which is not true. Rather, a corrected version was published which changed the conclusion from "the longitudinal association between gender-affirming surgery and lower use of mental health treatment lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them" to "the longitudinal association between gender-affirming surgery and reduced likelihood of mental health treatment lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them." (Exhibit 7, Bränström & Pachankis (2020), at 734, 727).

- Dr. Laidlaw also maligns studies based on the 2015 US Transgender Survey because it was not a randomized control study but used convenience sampling (Ex. 1 ¶¶ 210-11; Ex. 2 at ¶ 71; Ex. 3 at 33). While there are inherent limitations to convenience sampling, it is an important methodology to capture information about large cohorts. Importantly, Dr. Laidlaw does not point to any studies that contradict the findings of the 2015 USTS. And in fact, many of its findings were recently confirmed by a Kaiser Family Foundation / Washington Post survey that used a random sampling methodology, conducted in 2022 (Exhibit 8, Parks et al. (2023), at 8).
- Dr. Laidlaw similarly denigrates various studies on mastectomy for minors (Ex. 1 ¶¶ 212-19 & Ex. 3 at 33-35). He makes various complaints about the methodology used by these studies, but again, does not show that these methodological flaws render the studies completely unreliable, and he fails to point to any studies that reach contrary conclusions. No study is perfect, but the collection of imperfect studies finding similar results creates scientific consensus. Dr. Laidlaw's opinions fall outside of that consensus.

- Dr. Laidlaw also spends considerable time discussing a 2016 Center for Medicare & Medicaid Services (CMS) review of gender-affirming surgery coverage in Medicare (Ex. 1 ¶¶ 220-21, Ex. 2 at 35-36). But again, Dr. Laidlaw overstates his case. The decision memo decided not to "make a national coverage determination on surgical remedies" for gender dysphoria, and instead allow local Medicare decision-makers to "make the determination of whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances" (Exhibit 9, 2016 CMS Decision Memo, at 2). In other words, the CMS Memo ***mandated*** Medicare to cover gender-affirming surgery when clinically appropriate, but allowed local decision-makers discretion to establish medically necessity criteria for surgery, rather than establishing one uniform set of national criteria, *see id.* Dr. Laidlaw completely ignores the prior, 2014 decision, of an Administrative Appeals Board in the U.S. Department of Health & Human Services (which CMS falls within) to remove a ban on coverage of gender-affirming surgery in Medicare, finding "a consensus among researchers and mainstream medical organizations that [gender-

affirming] surgery is an effective, safe and medically necessary treatment for" gender dysphoria (Exhibit 10, 2014 Department Appeals Board Decision, at 20). That 2014 decision explicitly found that gender-affirming surgery was safe, effective, and not experimental (*id.* at 11, 15, 21).

Indeed, Dr. Laidlaw acknowledges that his "opposition to gender-affirming care for the treatment of gender dysphoria in youth and adults is contrary to the vast majority of medical associations' recommendations" (Ex. 4 at 25:22-26:1). This includes the following: American Medical Association, American Psychological Association, American Psychiatric Association, Endocrine Society, Pediatric Endocrine Society, American Academy of Pediatrics, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, American College of Physicians, (Ex. 4 at 29:16- 36:18). *See e.g., Kadel v. N. Carolina State Health Plan for Tchrs. & State Emps.*, 12 F.4th 422, 427–28 (4th Cir. 2021), *as amended* (Dec. 2, 2021) (noting the WPATH Standards of Care "have been adopted by health organizations across the country" and that gender-affirming treatments, including hormone therapy and surgical care, "are safe, effective, and often medically necessary"), *cert. denied*, 142 S. Ct. 861 (2022); *Edmo v. Corizon, Inc.*, 935 F.3d 757, 771 (9th Cir. 2019) (the provision of

gender-affirming medical care, consistent with the WPATH Standards of Care, represents "the ***broad medical consensus*** in the area of transgender health care," which "requires providers to individually diagnose, assess, and treat individuals' gender dysphoria.") (emphasis added); *see also Brandt v. Rutledge*, 551 F.Supp.3d 882, 890 (E.D. Ark. 2021) ("The ***consensus*** recommendation of medical organizations is that the only effective treatment for individuals at risk of or suffering from gender dysphoria is to provide gender-affirming care.") (emphasis added), *aff'd*, 47 F.4th at 671; *Flack v. Wisconsin Dep't of Health Servs.*, 395 F.Supp.3d 1001, 1018 (W.D. Wis. 2019); Exhibit 16, Nat'l Academies of Science, Engineering, and Medicine (2020), at 361 ("A major success of [WPATH's] guidelines has been identifying evidence and ***establishing expert consensus that gender-affirming care is medically necessary*** and, further, that withholding this care is not a neutral option. A number of professional medical organizations have joined WPATH in recognizing that gender-affirming care is medically necessary for transgender people because it reduces distress and promotes well-being, while withholding care increases distress and decreases well-being.") (emphasis added) (citations omitted).

Dr. Laidlaw's opinions regarding the effectiveness of gender-affirming medical care are wholly outside the mainstream, and he can cite to no authoritative

sources in support of his opinion. While undoubtedly Dr. Laidlaw "has strong beliefs," the fact that his opinions are "not generally accepted by the scientific community, and [are] unsupported by other studies" means that "his testimony is based more on personal opinion than on scientific knowledge," making it unreliable. *Allison*, 184 F.3d at 1319. These opinions should be excluded.

B. Several of Dr. Laidlaw's opinions about the supposed harms caused by gender-affirming treatment to Plaintiffs deliberately misrepresent the facts and evidence, and are therefore unreliable

Dr. Laidlaw offers several opinions about the potential for infertility and bone density loss resulting from the use of puberty-delaying medication in general, and as to the Plaintiffs in this litigation specifically (Ex. 1 ¶¶ 92-97, 100-09; Ex. 2 ¶¶ 35-43, 52-54). These opinions are entirely unreliable. In the first place, as discussed above, since he does not practice pediatric endocrinology, and has only ever treated one adult for gender dysphoria, Dr. Laidlaw's opinions with respect to the harms posed by puberty-delaying treatment for youth should be regarded with skepticism, (Ex. 4 at 8:14-16, 11:22-12:16 & Ex. 5 at 43:11-43:17 (fewer than 5% of Dr. Laidlaw's patients are under 18, and he has only treated one patient for gender dysphoria, more than a decade ago)).

In any event, Dr. Laidlaw's testimony that puberty-delaying medications "alter or block normal human development," deliberately misrepresents the facts and

data in order to obfuscate rather than elucidate (Ex. 1 ¶ 199). While usually the factual basis of an expert opinion goes to credibility, "it is possible for an experts' omission of articles to render his or her opinion inadmissible on reliability grounds." *Huggins v. Stryker Corp.*, 932 F.Supp.2d 972, 994 (D. Minn. 2013). Such is the case here where Dr. Laidlaw omits key information, or worse, misrepresents facts that if properly disclosed would contradict his opinions and undermine their foundation. It is appropriate to exclude expert testimony, like these opinions of Dr. Laidlaws, that is "confusing or misleading." *Hull v. Merck & Co*., 758 F.2d 1474, 1478 (11th Cir. 1985).

One. Dr. Laidlaw misconstrues the effect of puberty-delaying treatments on fertility. He speculates at length about the potential impacts of these treatments on fertility in general, and on named Plaintiffs in particular (Ex. 1 ¶¶ 92-97, 246-47, 280, 287; Ex. 2 ¶¶ 35-43). In doing so, he ignores multiple studies that have made clear that these treatments do not have long-term implications on fertility (*e.g.,* Exhibit 11, Guaraldi et al. (2016) at R83; Exhibit 12, Marinerie et al. (2021), at 529). Dr. Laidlaw correctly points out that progression through puberty – at some point – is needed for biological reproduction (Ex. 1 ¶¶ 92-97; Ex. 2 ¶¶ 35-43). But Dr. Laidlaw then reaches far beyond this well-established fact to posit that gender-

affirming hormones could possibly damage immature gonads (Ex. 1 ¶¶ 92, 94, 97), providing no data or studies to support his speculation.[5]

Two. Dr. Laidlaw speculates about the impact of puberty-delaying treatment on bone density – again, both in general, and for the Plaintiffs specifically (Ex. 1 ¶¶ 100-09, 250, 266, 289; Ex. 2 ¶¶ 52-54). His analysis of the studies regarding the impacts of these medications on bone density completely ignores that youth given puberty-delaying medications will take those medications for a relatively short period of time, and then either resume puberty associated with their birth-assigned sex, or begin hormone treatment, either of which will ameliorate any impact on bone density caused by puberty suppressing medications. Not to mention, that exact same concerns with respect to bone density are present for youth who take these medications to treat precocious puberty, a use Dr. Laidlaw approves (Ex. 1 ¶¶ 100-09).

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The Court "must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Daubert*, 509 U.S. at 589. Here, Dr.

[5] Dr. Laidlaw's testimony ignores that as long as a person retains their gonads, they have the potential for fertility. And he does not account for the fact that the same risks with respect to fertility are present when these medications are used to treat other conditions, which he approves (*See* Ex. 1 ¶¶ 74-75 (discussing the use of these medications to treat prostate cancer and precocious puberty)).

Laidlaw has misrepresented or omitted information that goes to the heart of his opinions and calls into question the reliability of his opinions. By omitting key information, or worse, misrepresenting facts that if properly disclosed would contradict his opinions and undermine their foundation, Dr. Laidlaw's testimony is not reliable but "misleading" and "quite speculative, and . . . [s]uch potentially confusing testimony is at odds with the purposes of expert testimony." *Hull*, 758 F.2d at 1478, 1477.

C. Dr. Laidlaw's other opinions about the harms posed by gender-affirming medical care are based solely on ipse dixit and conjecture and are unreliable.

Dr. Laidlaw also raises, without any research or evidentiary support, the specter of several other harms that could be posed by puberty suppressing treatment. These include his musings about treatment's potential impact on future sexual function, for which he offers no evidence or citations to support other than anecdotal reports from a reality television show (Ex. 1 ¶¶ 98-99). They also include Dr. Laidlaw's conjecture about the "unknown, but likely negative consequences … with respect to brain development," for which he can offer no evidence or reasoning to support his speculation that any consequences would be "likely negative" (Ex. 1 ¶ 110).

These opinions are the epitome of ipse dixit that courts routinely exclude as unreliable. "[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence which is connected to existing data only by the ipse dixit of the expert." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). "[T]he unremarkable observation that an expert may be qualified by experience does not mean that experience, standing alone, is a sufficient foundation rendering reliable any conceivable opinion the expert may express." *Frazier*, 387 F.3d at 1261; *see also McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1246 (11th Cir. 2005) ("[P]resumptions do not make for reliable opinions."). This is one of those circumstances in which "there is simply too great an analytical gap between the data and the opinion proffered." *Id.; see also McDowell v. Brown*, 392 F.3d 1283, 1300 (11th Cir. 2004) ("[A]n expert opinion is inadmissible when the only connection between the conclusion and the existing data is the expert's own assertions.")

D. Dr. Laidlaw's opinions about desistence are completely unreliable.

Again, Dr. Laidlaw does not diagnose or treat gender dysphoria, has not conducted any original research on gender dysphoria, gender identity, gender non-conformity in children/youth, or transgender people's experience. *See* Section II, *supra*. Yet, he opines extensively on gender dysphoria and desistence (Ex. 1 ¶¶ 28-

35; Ex. 2 ¶¶ 19-21; Ex. 3 at 5-7). To be sure, Dr. Laidlaw offers a theory that can be (and has been) subjected to peer review and publication, based on generally accepted techniques. *See Frazier*, 387 F.3d at 1262. But Dr. Laidlaw's gloss on the peer reviewed literature that has been published based on generally accepted techniques draws a conclusion exactly opposite to what that literature demonstrates: contrary to the literature, he opines that the majority of youth diagnosed with gender dysphoria will, by adulthood, "desist" (that is, their gender identity will change to align with their birth-assigned sex). This testimony is incorrect and not reliable.

A closer examination of Dr. Laidlaw's testimony reveals that he bases these opinions on a single review of antiquated studies showing that a majority of preadolescent children diagnosed with gender identity disorder—an outmoded diagnosis distinct from gender dysphoria with different diagnostic criteria—"desisted" from their gender nonconformity or cross-gender behavior (Ex. 1 ¶¶ 28-35; Ex. 2 ¶¶ 19-21; Ex. 3 at 5-7).[6] Yet Dr. Laidlaw's opinions stretch far beyond

[6] Dr. Laidlaw also cites his own, non-peer reviewed "commentary" (i.e., opinion) article on this topic, co-authored with two well-known critics of providing medical care to people with gender dysphoria, one of whom has also been retained by Defendants as an expert in this case. However, this commentary cites the same Ristoria & Steensma review as the source for its statistics (Exhibit 17, Laidlaw et al. (2019), at 76). The article is co-authored by Michelle Cretella, who has been

the "explicit[] findings, conclusions, and implications" of the Ristoria & Steensma review he cites to improperly "extrapolate from this information a finding, conclusion, or implication [that] authors themselves did not make." *In re Abilify (Aripiprazole) Prod. Liab. Litig.*, 299 F. Supp. 3d 1291, 1351 (N.D. Fla. 2018). The Ristoria & Steensma review examined outcomes from 10 studies on children with gender dysphoria or gender identity disorder conducted from 1968 to 2012 (Exhibit 13, Ristoria & Steensma (2016), at Table 1). It acknowledges that:

> The lower persistence rates in the earlier studies, compared to the more recent studies after 2000, may be the result of the inclusion of less extreme cases in the earlier studies than in later studies. For example, before . . . 1980 there was no formal diagnosis of GD for children. It could therefore be that the children included in the studies before 1980 would in retrospect not meet the full criteria for a diagnosis. Also, the recent studies consisted of clinically referred samples of children, which was not the case for the earlier studies.

Id. at 15-16. Despite the fact that the very paper on which he relies to claim that as many as 98% of children who present with gender dysphoria later "desist" makes clear that it supports no such conclusion, Dr. Laidlaw states that, "[b]ecause the

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criticized by the Society for Adolescent Health and Medicine for "pushing political and ideological agendas not based on science and facts" (Exhibit 18, Sct'y Adol. Health & Med. (2017), at 4). The other co-author is Kevin Donovan, whom Defendants have retained as an expert in this case, and who has described not only "transgender conversion surgeries" but "homosexual marriage," "homosexual behavior," contraception, cohabitation, and divorce, as "sinful" (Exhibit 19, Donovan & Sotomayor (2020), at 135).

rate of desistance is so high, gender affirmative therapy will necessarily cause serious and irreversible harm to many children and adolescents who would naturally outgrow the condition if not affirmed" (Ex. 1 ¶ 33). This opinion is based on faulty propositions. *See, e.g., Kilpatrick v. Breg, Inc*., 613 F.3d 1329, 1338 (11th Cir. 2010) (study that explicitly limited its findings to rabbits could not be the basis of expert testimony regarding humans); *McClain v. Metabolife Int'l, Inc*., 401 F.3d 1233, 1247 (11th Cir. 2005) (expert could not reasonably rely on a study to prove causation where the study concluded that the supplement at issue "*may* pose health risks to *some* persons" and the authors had specifically written "a letter to the editor explaining that the study did not prove causation") (emphasis in original).

In fact, Dr. Laidlaw has previously admitted that the "desistance" studies on which he relies speak only to preadolescent youth who were diagnosed with gender identity disorder under the DSM-III or the DSM-IV, and do not pertain to "desistance" of youth diagnosed with gender dysphoria under the DSM-5 (Ex. 5 at 103:4-104:4). He has similarly admitted that he is unaware of any studies documenting "desistance" among adolescents (people over the age of 12) or adults (*id*. at 109:2-109:14. Dr. Laidlaw's attempts to rehabilitate his asserted desistence rates in his Rebuttal Report do not hold water. He notes that the three most recent

studies included in the Ristoria & Steensma review he relies on included children aged 3 to 13, and that those studies showed desistance rates of 61-88% (Ex. 2 ¶ 21). From that information he extrapolates that "this would include children in the age range of 8-12 years old, many of whom were already adolescents going through puberty based on their age and were therefore not pre-pubertal. Therefore we can infer that a high proportion of adolescents do in fact desist" (*id.* (citation omitted)). But of course, this is pure speculation and guesswork. Dr. Laidlaw fails to acknowledge that it is just as likely that the desistence rates of older youth were much lower than those of younger children. And the studies included in the Ristoria & Steensma review, the most recent of which is over 10 years old (and some of which rely on data from the 1950s, 1960s, and 1970s), do not comport with more recent literature, which has uniformly found that youth who have a diagnosis of gender dysphoria in adolescence overwhelmingly continue to identify as transgender as they age (Exhibit 14, Olson et al. (2022), at 4; Exhibit 15, de Vries et al. (2011), at 1).[7] In any event, the fact that younger, preadolescent

[7] Notably, Thomas D Steensma, who co-authored the study on which Dr. Laidlaw improperly cites for the proposition that most youth with gender dysphoria "desist" in their gender identity, also co-authored the de Vries study, which looked 70 youth in the Netherlands referred for treatment of gender dysphoria between 2000 and 2008, found that all of them decided to continue their medical transition after 1-2 years, confirming that "young adolescents who had been carefully diagnosed

children may have a concept of their gender identity that is still changing is of no consequence to whether medical interventions are appropriate for adolescents and adults, for whom research confirms gender dysphoria usually persists (Ex. 14; Ex. 15).[8] Dr. Laidlaw's opinions with respect to desistence do not use a "reliable and sound" methodology, and the one study on which he purports to rely does not support his "ultimate conclusion." *Kilpatrick*, 613 F.3d at 1337; *Rink*, 400 F.3d at 1293 (using unsound underlying data results in "flawed methodology"). This testimony should be excluded.

E. Dr. Laidlaw's opinions about informed consent are unreliable

Dr. Laidlaw does not offer any new information or evidence to support his opinion that:

> [I]t is not possible for the parent or guardian to make a true informed consent decision for the child because of the poor quality of evidence of benefit, the known risks of harm, and the many unknown longterm risks of harm which could only truly be known after years and decades of gender affirmative therapy. A parent or guardian cannot consent to dubious treatments which result in irreversible changes to their child's body, infertility, sexual dysfunction, and in many cases eventual sterilization.

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show persisting gender dysphoria into late adolescence or young adulthood." Ex. 15 at 2281.

[8] In addition, "a discussion of risks to prepubescent children is irrelevant to this case and would likely serve only to confuse." *Kadel*, 2022 WL 3226731, at *9.

(Ex. 1 ¶ 181; *see also id.* ¶¶ 179-83, 307-08, 310; Ex. 3, at 26-27; Ex. 2 ¶¶ 86-90). Instead, his opinions regarding informed consent are simply cumulative of the same unreliable opinions he offers regarding the effectiveness and potential harm caused by gender-affirming treatments. They completely misrepresent the concept of informed consent, which can, and does allow people (including parents and guardians making decisions about their children's medical care) to authorize necessary care, even when it may result in irreversible changes to the body, including impacts on fertility and sexual function, when they have been educated about "the burdens, risks, and expected benefits of all options, including forgoing treatment" such that they are able to "make an independent, voluntary decision" about treatment (Exhibit 20, AMA Code of Medical Ethics, at § 2.1.1). Indeed, it is common for parents to make these decisions, even when not all the risks of a particular intervention are fully known. For example, many antidepressants have both known and unknown impacts on fertility, yet they are commonly prescribed, including to youth.[9] Dr. Laidlaw's opinions on informed consent lack any

[9] *See, e.g.,* Exhibit 21, Beeder & Samplaski (2020), at 45 ("At this point, it is difficult for clinicians to counsel patients on the effect that these medications might have on their fertility. We would recommend an informed discussion with patients attempting parenthood and taking these medications. Checking a baseline semen analysis and sperm DNA fragmentation might provide some level of guidance."); Exhibit 22, Casilla-Lennon et al. (2016), at 314.e1 ("Our data suggest that

"grounding in the methods and procedures of science," such that they are nothing "more than subjective belief or unsupported speculation." *Daubert*, 509 U.S. at 590. They amount to nothing more than "unscientific speculation offered by a genuine scientist," and should be excluded. *Allison,* 184 F.3d at 1317 (*quoting Rosen v. Ciba–Geigy Corp*., 78 F.3d 316, 318 (7th Cir. 1996)).

F. Dr. Laidlaw's opinions about WPATH are unreliable

Dr. Laidlaw's opinions about the WPATH Standards of Care for gender-affirming medical care should similarly be disregarded as unreliable. In particular he offers the completely unfounded, and therefore unreliable "professional opinion WPATH SOC 8 represents a grave and immediate danger to minors, young adults, and adults and should not be followed by any physician, mental health care provider, or other medical professional" (Ex. 1 ¶ 198; *see also id.* ¶¶ 184-85, 192-98, 309; Ex. 3 at 27, 29-30; Ex. 2 ¶¶ 28-30).[10] Dr. Laidlaw is not privy to the actual

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antidepressants may reduce the probability of a woman with a history of depression to conceive naturally. Future studies are needed to differentiate the extent to which this association is due to the antidepressant itself versus the underlying depression.").

[10] When pressed on the basis for his opinions regarding WPATH in another case, Dr. Laidlaw did not cite any literature, study, or publication but rather stated that it was based on his opinion that "one would expect them [WPATH] not to exclusively follow one, say, politically based point of view," and that (again, in his opinion) WPATH is not "open to a variety of points of view" Ex. 5 at 89:7-89:18. When pressed further for his basis for this opinion, Dr. Laidlaw simply stated that

internal conversations of WPATH, has not participated in WPATH conferences, is not a member of WPATH, and has not participated in any of its internal discussions (Ex. 5 at 90:1-90:16). He therefore lacks knowledge "of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation." *Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988). In short, Dr. Laidlaw does not have "any experience with . . . WPATH. . . upon which to base his criticisms," nor does he cite to any meaningful data or evidence to support them, making his speculation as WPATH's credibility completely unreliable. *Kadel,* 2022 WL 3226731, at *10.

G. Dr. Laidlaw's testimony is motivated by bias, rendering it unreliable

"In evaluating the reliability of an expert's method . . . a district court may properly consider whether the expert's methodology has been contrived to reach a particular result." *Rink*, 400 F.3d at 1293, n.7. Here, Dr. Laidlaw has already confirmed the basis for all his opinions offered: He opposes affirmation of a transgender person's identity in any circumstances (Ex. 4 at 87:15-87:21; *id.* at 39:22-40:19). In other words, the entire basis for all his opinions offered rests on his non-scientific opposition to treatment for gender dysphoria, especially for

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his opinion is based on a conversation with one psychologist and the fact that WPATH published the Standards of Care. *Id.*, at 92:2-92:12.

children. *But see Brandt,* 551 F. Supp. at 891 ("[G]ender-affirming care for transgender minors may be medically appropriate and necessary to improve the physical and mental health of transgender people."). While Plaintiffs are cognizant of the fact that bias in an expert witness's testimony is usually an issue of credibility as opposed to one of admissibility, when an expert's opinions are based on bias as opposed to scientific or medical knowledge, then the question of bias becomes one of reliability and admissibility. Indeed, reliability is a flexible inquiry wherein "courts must ensure that an expert's opinion is based on scientific, technical, or other specialized knowledge and not on belief or speculation." *Sardis v. Overhead Door Corp.,* 10 F.4th 268, 281 (4th Cir. 2021). Here, there is ample evidence that Dr. Laidlaw's testimony is so permeated and tainted by his unscientific views and personal bias as to render it unreliable. *Cf. Sanchez v. Esso Standard Oil de Puerto Rico, Inc.,* No. CIV 08-2151, 2010 WL 3809990, at *4 (D.P.R. Sept. 29, 2010).

IV. DR. LAIDLAW OFFERS SEVERAL UNHELPFUL AND IRRELEVANT OPINIONS.

"The gatekeeping inquiry must be tied to the facts of a particular case." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 150 (1999) (quotations omitted). The proponent of the expert testimony bears the burden of proving that the

testimony is relevant and "logically advances a material aspect" of the case. *Boca Raton Cmty. Hosp., Inc. v. Tenet Health Care Corp.*, 582 F.3d 1227, 1232 (11th Cir. 2009) (citations omitted). Here, Dr. Laidlaw offers several opinions that simply are not relevant to this inquiry as they will not "help the trier of fact to understand the evidence or to determine a fact in issue." Fed. R. Ev. 702(a); *Id.* 401, 402 & 403; *Daubert*, 509 U.S. at 591 ("Expert testimony which does not relate to any issue in the case is not relevant and, ergo, non-helpful.") (cleaned up).

The primary issues before this Court, among others, are: (1) whether medical treatment for gender dysphoria is experimental, such that it could be appropriately excluded from Medicaid coverage, *Rush v. Parham*, 625 F.2d 1150, 1156 (5th Cir. 1980); *K.G. ex rel. Garrido v. Dudek*, 864 F. Supp. 2d 1314, 1321 (S.D. Fla. 2012), *aff'd in part, rev'd in part sub nom. Garrido v. Dudek*, 731 F.3d 1152 (11th Cir. 2013); and (2) whether the process Florida underwent to exclude coverage of such care in its Medicaid program made "classifications that are 'arbitrary or irrational' and that reflect a 'bare desire to harm a politically unpopular group,'" *Glenn v. Brumby*, 663 F.3d 1312, 1315 (11th Cir. 2011) (*quoting City of Cleburne v. Cleburne Living Ctr., Inc.*, 473 U.S. 432, 446-47 (1985)). Because this case is about gender-affirming medical care, much of the testimony offered by Dr. Laidlaw has no bearing on the issues:

- He offers unsupported musings on the increased number of people diagnosed with gender dysphoria (Ex. 1 ¶¶ 29-31; *see* Ex. 3 at 5-6). His ideas in this regard are based only on his conjecture, and ignore several plausible alternative explanations for the increased number of people diagnosed with gender dysphoria. In any event, the number of people diagnosed with gender dysphoria (increasing or not) is simply not pertinent to the question of what treatment for the condition is medically appropriate, or whether refusing to cover treatment is discriminatory. Dr. Laidlaw does not and cannot dispute that gender dysphoria is a legitimate medical condition (Ex. 4 at 16:14-23).
- Similarly, Dr. Laidlaw takes pains to establish that gender dysphoria is a psychological condition and not an endocrine one (Ex. 1 ¶¶ 23-26; Ex. 2 ¶¶ 13-14; *see* Ex. 3 at 4-5). But again, it is not relevant to the issues in this case whether gender dysphoria is a psychological condition, an endocrine condition, or a health condition. Dr. Laidlaw does not and cannot dispute that gender dysphoria is a legitimate condition for which treatment is indicated (Ex. 4 at 16:14-23).

- He provides speculation about human sexual development (Ex. 1 ¶¶ 41-55; *see* Ex. 3 at 8-11). Again, human sexual development is entirely irrelevant to the legal questions presented in this case.
- He opines, without citing studies or data, as to the difference between gender identity and "biological sex," including as to whether "biological sex" can be changed (Ex. 1 ¶¶ 36-40, 53-55, 306; Ex. 2 ¶¶ 3-12; *see* Ex. 3 at 5-7). But this case is not about changing one's sex. It is about treatment for gender dysphoria. His unsupported speculation is irrelevant.
- His ideas about "social transition" are also irrelevant, since this case does not address social transition, but medical treatment for gender dysphoria (Ex. 1 ¶¶ 61-65; *see* Ex. 3 at 12-13).
- Dr. Laidlaw's opinions about the policies of other countries are similarly irrelevant, since what other countries cover in their state health care programs has no relation to Florida Medicaid's obligation to cover services under U.S. Law (Ex. 1 ¶¶ 29-31, 222-27; Ex. 2 ¶¶ 72-77; *see* Ex. 3 at 36-37).[11]

[11] Dr. Laidlaw does not have first-hand knowledge of these countries' policies, and misrepresents them, since none of the identified countries wholly exclude coverage for gender-affirming medical care. *See Brandt by & through Brandt v. Rutledge*, 47 F.4th 661, 671 (8th Cir. 2022) (discussing Finland's policy); Ex. 4 at 106:2-108:5.

Because each of these opinions offered lacks any "valid scientific connection to the disputed facts in the case," they should be excluded. *Allison v. McGhan Medical Corp.*, 184 F.3d 1300, 1312 (11th Cir. 1999).

V. THE OPINION OF DR. LAIDLAW LACKS PROBATIVE VALUE AND IS THEREFORE NEITHER HELPFUL TO THE FACT-FINDER NOR ADMISSIBLE UNDER FEDERAL RULE OF EVIDENCE 403.

Finally, the Court should exclude the majority of the opinion and testimony of Dr. Laidlaw because its introduction will result in unfair prejudice, confusion of the issues, or in duplicative or misleading testimony. Fed. R. Evid. 403. As articulated above, the majority of opinions offered by Dr. Laidlaw are irrelevant, speculative, and unreliable. In addition, Defendants have proffered two other endocrinologists to provide testimony in this case, and making Dr. Laidlaw's proposed testimony largely "cumulative or needlessly time consuming." *Hendrix*, 255 F.R.D. at 579. His testimony would also result in prejudice, as the testimony seeks to sow confusion about the propriety of gender-confirming care based on speculation, irrelevant, misleading, and biased opinions.

CONCLUSION

For the foregoing reasons, the Court should exclude the reports, opinions, and testimony of Dr. Laidlaw, except as they relate to "to the risks associated with puberty blocking medication and hormone therapy." *Kadel*, 2022 WL 3226731, at *10.

Dated: April 7, 2023

Respectfully Submitted,

/s/ Abigail Coursolle

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CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April, 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

CERTIFICATE OF SATISFACTION OF ATTORNEY-CONFERENCE REQUIREMENT

Pursuant to Local Rule 7.1(B), counsel for Plaintiffs and counsel for Defendants conferred regarding the instant motion during a Zoom conference on April 6, 2023. Defendants indicated they do not consent to the relief requested herein

CERTIFICATE OF WORD COUNT

According to Microsoft Word, the word-processing system used to prepare this Motion and Memorandum, there is a combined total of 7,381 words in the Motion and the Memorandum of Law.

/s/ Abigail K. Coursolle
Attorney for Plaintiffs

TAB 136

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, *et al.*,

Plaintiffs,

v.

JASON WEIDA, *et al.*,

Defendants.

Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION TO EXCLUDE EXPERT TESTIMONY OF DR. PAUL W. HRUZ AND SUPPORTING MEMORANDUM OF LAW

TABLE OF CONTENTS

Pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403, and Rule 702, Plaintiffs move to partially exclude certain testimony of Defendants' expert Dr. Paul Hruz, on the grounds that he fails to meet the qualification, reliability, and helpfulness requirements imposed by Fed. R. Evid. 702 and *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993).

Dr. Hruz is a pediatric endocrinologist. Many of the opinions he purports to offer in this case have previously been excluded. *See Kadel v. Folwell,* No. 1:19CV272, 2022 WL 3226731, at *9-10 (M.D.N.C. Aug. 10, 2022). He has no experience treating or diagnosing gender dysphoria; he has never provided gender-affirming care, has never done any original research on the issue, has never published any peer-reviewed literature on the matter, and holds opinions that are purely speculative and far afield from the mainstream of the medical and scientific communities. Indeed, as he does here, in *Kadel,* Dr. Hruz "offer[ed] a wide range of conclusions that fall into five main categories: mental healthcare, medical and surgical care, informed consent, criticism of medical associations, and political criticisms." *Kadel,* 2022 WL 3226731, at *8. Despite the broad ranging categories on which he was offered to testify, after reviewing his qualifications, the *Kadel* Court limited Dr. Hruz's testimony to "the risks associated with puberty blocking medication and hormone therapy." *Id.* at *9.

The Court here should similarly impose the same limitation on Dr. Hruz's

testimony. Accordingly, Dr. Hruz is not a qualified expert on gender dysphoria or its treatment, and his opinions and testimony are neither relevant nor reliable. Additionally, his opinions and testimony are likewise inadmissible because any probative value they may have (and they have none) is substantially outweighed by the danger of unfair prejudice, confusion of the issues, waste of time, undue delay, and needless presentation of cumulative evidence. *See* Fed. R. Evid. 403. In support of this motion, Plaintiffs state as follows:

MEMORANDUM OF LAW

LEGAL STANDARD

Federal Rule of Evidence 702 places gatekeeping obligation on a trial court, to ensure that an expert's testimony "both rests on a reliable foundation and is relevant to the task at hand." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 597 (1993); *see also United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) ("The importance of Daubert's gatekeeping requirement cannot be overstated."). In determining the admissibility of expert testimony under Rule 702, courts engage in a "rigorous" three-part inquiry and must consider whether:

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in *Daubert*; and (3) the testimony assists the trier of fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

Frazier, at 1260; *see also City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d

548, 562 (11th Cir. 1998), *cert. denied*, 528 U.S. 812 (1999).

The Eleventh Circuit refers to these three considerations separately as "qualification," "reliability," and "helpfulness" and has emphasized that they are "distinct concepts that courts and litigants must take care not to conflate." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). The party offering the expert testimony has the "burden of establishing qualification, reliability, and helpfulness." *Frazier*, 387 F.3d at 1260. As detailed below, Dr. Hruz's proposed opinions fail to meet these requirements and should be excluded.

ARGUMENT

I. Dr. Hruz is not qualified to offer an expert opinion on the diagnosis and the mental health treatment of gender dysphoria.

A witness must be "qualified to testify competently regarding the matter he intends to address." *Frazier*, at 1260. "A witness may be qualified as an expert by virtue of his 'knowledge, skill, experience, training, or education." *Quiet Technology DC-8, Inc.*, 326 F.3d at 1342. However, credentials are not dispositive when determining qualification. Each of the three analytical prongs (including qualifications) is assessed in reference to the matter to which the expert seeks to testify—i.e., "to the task at hand." *Daubert*, 509 U.S. at 597. It is for that reason that "expertise in one field does not qualify a witness to testify about others." *Lebron v. Sec'y of Fla. Dep't of Children & Families*, 772 F.3d 1352, 1368 (11th Cir. 2014)

(holding that a psychiatrist was properly prevented from opining on rates of drug use in an economically vulnerable population because he had never conducted research on the subject, and instead relied on studies to form his opinion). Rather, an expert's qualifications must be within the same technical area as the subject matter of the expert's testimony; in other words, a person with expertise may only testify as to matters within that person's expertise." *Id.* at 1369. "A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty." *Dura Automotive Systems of Indiana, Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002). If a proposed expert witness does not "propose to testify about matters growing naturally and directly out of research he had conducted independent of the litigation," such expert should be disqualified. *Lebron*, 772 F.3d at 1369 (quoting Fed. R. Evid. 702 (cleaned up)).

Therefore "[d]etermining whether a witness is qualified to testify as an expert requires the trial court to examine the credentials of the proposed expert in light of the subject matter of the proposed testimony." *Banuchi v. City of Homestead*, 606 F.Supp.3d 1262, 1272 (S.D. Fla. 2022) (cleaned up). Here, Dr. Hruz does not have the medical specialty required to discuss the diagnosis and treatment for gender dysphoria, particularly the diagnosis and assessment of gender dysphoria and non-endocrine treatments that are wholly outside his expertise as an endocrinologist.

The Court in *Kadel* succinctly determined based on Dr. Hruz's deposition

testimony that:

> Hruz is not qualified to offer expert opinions on the diagnosis of gender dysphoria, the DSM, gender dysphoria's potential; causes, the likelihood that a patient will "desist," or the efficacy of mental health treatments. He has never diagnosed a patient with gender dysphoria, treated gender dysphoria, treated a transgender patient, conducted any original research about gender dysphoria diagnosis or its causes, or published any scientific, peer reviewed literature on gender dysphoria.

Kadel, 2022 WL 3226731, at *9; Ex. A at ¶142 Hruz Expert Report[1] ("I have never personally engaged in the delivery of gender affirming medical interventions to children with gender dysphoria"); Ex. C at 88:18-89:8, 89:17-25 (Dr. Hruz discussing his lack of qualifications and treatment for gender dysphoria); Ex. E at 24:11-24:14, 25:20-25:23. Indeed, Dr. Hruz has also not sat in on a meeting with a patient discussing the treatment options for gender dysphoria. Ex. C at 40:6-40:11. Nor has he conducted any original research about transgender people or gender dysphoria. Ex. C at 35:5-36:1; Ex. E at 62:25-63:9; Ex. F at 25:24-28:13. He has not published any scientific, peer-reviewed literature on gender dysphoria or transgender people either. Ex. C at 42:14-49:19; Ex. E at 61:17-64:7, 295:19-

[1] Unless otherwise specified, all exhibits cited herein are attached to the contemporaneously filed Declaration of Shani Rivaux.

295:23.[2] Dr. Hruz is neither a psychiatrist[3], a psychologist, nor a mental health care provider of any kind qualified to diagnose gender dysphoria or to opine on the reliability of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition ("DSM-5"). Ex. C at 112:9-11, 55:23-56:15; Ex. E at 41:21-42:2, 42:11-42:18.

Like the Court in *Kadel,* this Court should exclude Dr. Hruz on these topics due to his lack of expertise. *See Dura Auto. Sys. of Indiana, Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002) ("The *Daubert* test must be applied with due regard for the specialization of modern science. A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty. That would not be responsible science."). Instead, Dr. Hruz bases his opinions solely on his review of literature and conversations he has had with others. The fact that Dr. Hruz has read about gender dysphoria and

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[2] Dr. Hruz's only publication relating to gender dysphoria in a peer-reviewed journal is a letter to the editor not based on any original research or scientific study, and for which it is unclear if letters to the editor are subjected to peer-review. Ex. C at 43:9-45:15. *See also* Ex. P (noting that letters to the editor are typically not peer reviewed). His other publications pertaining to gender dysphoria are all in non-scientific, non-medical, non-peer-reviewed journals affiliated with religious organizations.

[3] In his rebuttal report, Dr. Hruz claims that his opinions are supported by his "professional experience as a psychiatrist." Ex. B at ¶3. However, none of his qualifications or his prior testimony have demonstrated any credentials of a psychiatrist.

transgender people does not qualify him as an expert on these issues, however. That is precisely the sort of "generalized knowledge of a particular subject" that courts have rejected as a qualification under Rule 702. As with the disqualified expert in *Lebron* who "reached his opinion instead by relying on studies," this is insufficient to serve as an expert witness. *Lebron*, 772 F.3d at 1369.

Aside from his lack of expertise, Dr. Hruz is the definition of a manufactured "expert witness" as his involvement originates from and dates back to a conference by the Alliance Defending Freedom ("ADF")[4] organized specifically to cultivate professional "experts" who would testify against the gender-affirmation of transgender people. Ex. C at 241:10-246:20; Ex. E at 92:21-93:24; Ex. F at 147:11-21; *cf.* Ex. O at 84:3-85:12, 90:13-91:13 (Dr. Lappert testifying that he attended the same ADF conference as Dr. Hruz in 2017 where the "poverty of [experts] who are willing to testify" against gender-confirming policies was discussed and that attendees "were asked whether they would be

[4] ADF is well-known for pushing anti-LGBT policies across the country and internationally. *See*, *e.g.*, Nico Lang, *A Hate Group Is Reportedly Behind 2021's Dangerous Wave of Anti-Trans Bills*, them. (Feb. 19, 2021), https://bit.ly/3HEqCR9; Julie Compton, *Activists take aim at anti-LGBTQ 'hate group,' Alliance Defending Freedom*, NBC News (Nov. 14, 2018), https://nbcnews.to/3oEe9Es. The Southern Poverty Law Center has designated ADF a hate group. *See* S. Poverty Law Ctr., *Why is Alliance Defending Freedom a Hate Group?* (Apr. 10, 2020), https://bit.ly/3HE6LS1 (accessed Nov. 19, 2021).

willing to participate as expert witnesses"); Ex. Q at 169:18-171:4. Like the disqualified expert in *Lebron*, Dr. Hruz "developed his opinions expressly for purposes of testifying" in an area outside his specialty. *Lebron*, 772 F.3d at 1369.

In sum, Dr. Hruz is not qualified to serve as an expert on the diagnosis or the mental health treatment paradigms for gender dysphoria and his testimony should be limited to "the risks associated with puberty blocking medication and hormone therapy." *Kadel,* 2022 WL 3226731, at *9.

II. Dr. Hruz's opinions and testimony are not relevant to this case.

To satisfy the helpfulness requirement, the testimony must have a justified scientific relationship to the facts at issue. *Daubert*, 509 U.S. at 591. Thus, helpfulness, "goes primarily to relevance." *Id.* at 580. Relevant expert testimony "logically advances a material aspect of the proposing party's case" and "fits" the disputed facts. *McDowell v. Brown*, 392 F.3d 1283, 1298-99 (11th Cir. 2004). "The relationship must be an appropriate 'fit' with respect to the offered opinion and the facts of the case." *Id.* The "court must satisfy itself that the proffered testimony is relevant to the issue at hand, for that is a precondition to admissibility." *Sardis v. Overhead Door Corp.*, 10 F.4th 268, 282 (4th Cir. 2021) (cleaned up). "The touchstone of this inquiry is the concept of relevance." *Prosper v. Martin*, 989 F.3d 1242, 1249 (11th Cir. 2021). Thus, "expert testimony which does not relate to any issue in the case is not relevant and non-helpful." *Knight v. Boehringer Ingelheim*

Pharms., Inc., 323 F.Supp.3d 837, 846 (S.D. W.Va. 2018). In order to be relevant, an opinion needs to "fit" with the facts at issue. *Simmons v. Augusta Aviation, Inc.*, 596 F. Supp. 3d 1363, 1374 (S.D. Ga. 2022) "To satisfy this requirement, the testimony must concern matters beyond the understanding of the average lay person and logically advance a material aspect of the proponent's case." *Id.* Testimony that "offers nothing more than what lawyers for the parties can argue in closing arguments" or that consists of "subjective portrayals of factual information" "generally will not help the trier of fact." *Giusto v. Int'l Paper Co.*, 2021 WL 3603374, at *4 (N.D. Ga. Aug. 13, 2021).

This case is about whether Defendants' exclusion of coverage for medically necessary gender-affirming health care treatments violates Plaintiffs' rights. Many of Dr. Hruz's opinions are not relevant to this inquiry as they do not have a "valid scientific connection to the pertinent inquiry" *Boca Raton Cmty. Hosp., Inc. v. Tenet Health Care Corp.*, 582 F.3d 1227, 1232 (11th Cir.2009). His opinions do not "fit" because they are not sufficiently tied to the facts of the case so that they will aid a factfinder.

A. Dr. Hruz's opinions about "desistance" are irrelevant.

Take for example Dr. Hruz's opinions about purported "desistance" rates as a reason to question the provision of gender-confirming care. Another subject matter area in which the *Kadel* Court excluded Dr. Hruz's testimony. *Kadel*, 2022

WL 3226731, at *9. Dr. Hruz spends considerable time on (and builds most of his testimony questioning the propriety of gender-affirming health care upon) antiquated studies showing that a majority of *prepubertal* children diagnosed with *gender identity disorder*—an outmoded diagnosis *distinct from gender dysphoria* with different diagnostic criteria—"desisted" from their gender nonconformity or cross-gender behavior. *See*, *e.g.*, Ex. A at ¶¶63-64; 141. But not only are such opinions based on faulty propositions, they simply do not fit the facts of this case.

Dr. Hruz's testimony that focuses on the risks associated with providing hormone therapy to prepubescent children—children who have not begun puberty—is not relevant. Ex. C at 125:23-126:5. By his own admission, "no medical and surgical interventions are initiated until after the onset of puberty" under any model of treatment. *Id.* But again, no hormonal or surgical care is recommended for or provided to *prepubertal* children, nor are any of the plaintiffs prepubertal children. Accordingly, Dr. Hruz's opinions regarding "desistance" are thus irrelevant to this case.

B. Dr. Hruz's opinions about an "international response" in other countries is irrelevant.

Dr. Hruz's opinions about a purported "international response" regarding the provision of gender-confirming care in Finland, Sweden, and the United Kingdom are both misleading and wholly irrelevant. Ex. A at ¶¶123-126; Ex. D at 91-96. In the first place, Dr. Hruz has offered no firsthand knowledge of other

countries' policies, so he is not qualified to testify about them. And his testimony is false, or at best, misleading, since, each of these countries *provides and covers* some gender-confirming hormonal and surgical treatment for gender dysphoria for adolescents and adults, whereas AHCA excludes treatment completely from Medicaid coverage. *See*, *e.g.*, Ex. C at 183:23-184:4, 185:3-10, 189:14-190:7; *see also Brandt by & through Brandt v. Rutledge*, 47 F.4th 661, 671 (8th Cir. 2022) ("Similarly, the WPATH Standards of Care and the Finnish council both recommend that cross-sex hormones be considered only where the adolescent is experiencing persistent gender dysphoria, other mental health conditions are well-managed, and the minor is able to meet the standards to consent to the treatment."). Moreover, how care is provided and covered in countries with nationalized health care systems is not relevant to whether gender-confirming care should be covered by Medicaid in Florida.[5]

C. Dr. Hruz's musings about the causes of gender dysphoria are irrelevant.

Dr. Hruz opines, without any evidence, that gender dysphoria *may be* caused by social contagion and social pressure. Ex. A at ¶¶ 31, 91, 116-118; Ex. D at 40-43, 99. But whether gender dysphoria is caused by social contagion is both wholly

[5] For example, in Sweden standards of care are developed through legislation and thus part of a political process, which contrasts with the process in the Florida. *See* Socialstyrelsen, *About the National Board of Health and Welfare*, https://www.socialstyrelsen.se/en/about-us/ (accessed Nov. 19, 2021) (noting that standards are based on legislation).

unsupported, as described below, and irrelevant to the case at hand. It is undisputed that gender dysphoria is a recognized medical condition that necessitates medical treatment. *See*, *e.g.*, Ex. C at 57:24-58:9 ("Q. Would you agree there are transgender people in this world? A. … That's undeniable that … there are individuals that have this experience of discordance between their gender identity and their sex."); *see also Grimm v. Gloucester Cnty. Sch. Bd.*, 972 F.3d 586, 594-95 (4th Cir. 2020). Likewise his musings about as to the difference between gender identity and "biological sex," including as to whether "biological sex" can be changed, are immaterial since this case is about access to gender-affirming care, not changing sex. Ex. A at ¶¶ 14, 58, 66. Because each of these opinions offered lacks any "valid scientific connection to the disputed facts in the case," they should be excluded. *Allison v. McGhan Medical Corp.*, 184 F.3d 1300, 1312 (11th Cir. 1999).

D. Dr. Hruz's Opinions about WPATH Standards of Care are irrelevant.

Dr. Hruz opines that WPATH should be disregarded as an "advocacy group" and that its recommendations "represent ideological positions devoid of rigorous scientific evidence"[6] and that the Endocrine Society Guidelines should be rejected because some of the committee members are also WPATH members. Ex. A at ¶¶

[6] Without any support, Dr. Hruz also claims that the American Academy of Pediatrics is a "politically influenced, non-science association." Ex. A at ¶140.

88-97. However, Dr. Hruz has not demonstrated any personal knowledge regarding the internal conversations at WPATH, has not participated in WPATH conferences, is not a member of WPATH and therefore lacks knowledge "of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation." *Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988). In short, Dr. Hruz does not have "any experience with . . . WPATH. . . upon which to base his criticisms[and] is therefore not qualified to testify about the credibility of th[at] organization[]." *Kadel,* 2022 WL 3226731, at *10.

E. Dr. Hruz's Hypothetical and Speculative opinions are irrelevant.

Finally, and perhaps most crucially, essentially all of Dr. Hruz's opinions are irrelevant because they are not based on fact, let alone "fit" within the facts of case. Dr. Hruz's report in this case is substantially similar to the report he submitted in *Kadel*. *Compare* Ex. A and Ex. D. Two years ago, when asked about his opinions in the report submitted in *Kadel*, he testified that they were hypotheses. More specifically, he testified that the entirety of his opinions is based on *hypotheses*, meaning they are based on speculation. Ex. C at 154:4-8 ("A. You know, all along here, … I've been stating, and I hope very clearly, that much of my opinion is based upon hypotheses and alternative hypotheses, because there is no definitive answer to this question."); *id.* at 57:1-3 ("A. Because I present many things in my report as hypotheses. And without making definitive statements.").

Indeed, Dr. Hruz purportedly has no view as to what modality of treatment should be provided to transgender people suffering gender dysphoria. *Id.* at 61:21-62:2. Such "speculation is unreliable evidence and is inadmissible." *Dunn*, 275 F.Supp.2d at 684; *see Allison v. McGhan Medical Corp.*, 184 F.3d 1300, 1312 (11th Cir. 1999). In other words, Dr. Hruz lacks knowledge "of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation." *Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988). And opinions based on "subjective belief or unsupported speculation" should be rejected. *Daubert*, 509 U.S. at 589-590.

* * *

The opinions expressed by Dr. Hruz are insufficiently tied to the facts of this case so that they will aid a factfinder and should be excluded as irrelevant.

III. Dr. Hruz's opinions and testimony are unreliable.

An expert's testimony should only be admitted if it is sufficiently reliable. "To meet the reliability requirement, an expert's opinion must be based on scientifically valid principles, reasoning, and methodology that are properly applied to the facts at issue." *In re 3M Combat Arms Earplug Products Liab. Litig.*, 3:19MD2885, 2022 WL 1262203, at *1 (N.D. Fla. Apr. 28, 2022). The requirement of reliability found in Rule 702 is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). "At this stage,

the court must undertake an independent analysis of each step in the logic leading to the expert's conclusions; if the analysis is deemed unreliable at any step the expert's entire opinion must be excluded." *Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009), *aff'd sub nom. Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183 (11th Cir. 2010). In making this determination the court can consider a variety of factors, including whether the purported expert's theory has been tested, whether it has been subjected to peer review and publication, and whether the theory has been generally accepted in the scientific community. *See Daubert*, 509 U.S. at 593-94; *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1291-92 (11th Cir. 2005).[7] To be reliable the expert's testimony must always be based on "good grounds." *Daubert,* 509 U.S. at 590. Moreover, *Daubert* requires that reliable expert testimony be more than scientifically unsupported "leaps of faith." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d at 1202. Here, Dr. Hruz's opinions fail all indicia of reliability. Dr. Hruz's proffered opinions are based on nothing more than rank speculation, "untested" theories, uncorroborated anecdotes, and assumptions that are obsolete, flawed, unethical, and expressed opinions based upon "unsettled science." What is more, some of his opinions are patently false.

[7] Other factors which may be relevant include (1) the nature of the field of claimed expertise, (2) the source of the expert's knowledge, (3) the expert's level of care in using the knowledge, and (4) the expert's consideration of alternative hypotheses. Hendrix, 255 F.R.D. at 578-79.

A. Dr. Hruz's opinions are unreliable because they are based on untested hypotheses and speculation.

As noted above, ***Dr. Hruz's opinions are hypotheses***; hypotheses that he himself has not tested or studied. *See, e.g.,* Ex. A at ¶¶31; 76; 90-91; 116-118; 130-131. And "[w]hile hypothesis is essential in the scientific community because it leads to advances in science, speculation in the courtroom cannot aid the fact finder in making a determination." *Dunn v. Sandoz Pharms. Corp.*, 275 F.Supp.2d 672, 684 (M.D.N.C. 2003). "[T]he courtroom is not the place for scientific guesswork, even of the inspired sort." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). Indeed, "[w]here an expert's opinion testimony is founded on an unsupported premise, it gives rise to an inference that is based on speculation and has no evidentiary value." *Walker v. Blitz USA, Inc.*, 663 F. Supp. 2d 1344, 1364 (N.D. Ga. 2009). At bottom, such speculation is unreliable evidence and is inadmissible.

B. Dr. Hruz's opinions are unreliable because they are misleading and therefore do not serve to enlighten the trier of fact.

In addition, some of Dr. Hruz's opinions are misleading at best, or flat out false. For example:

One. Dr. Hruz opines that the literature around gender-affirming care is "in a state insufficient to enable sound conclusions about the efficacy of "affirming treatments." Ex. A at ¶¶93; 122; 142; Ex. D at 100 ("treatments – hormones and

surgery – for gender dysphoria and 'transitioning' have not been accepted by the relevant scientific communities (biology, genetics, neonatolgy [sic], medicine, psychology, etc.)."). Not true. It is the official, consensus, evidence-based position of the National Academies of Science, Engineering, and Medicine that, "[a] major success of these guidelines has been identifying evidence and establishing expert consensus that gender-affirming care is medically necessary and, further, that withholding this care is not a neutral option." Ex. H at 361;[8] Ex. C at 205:20-206:22. Indeed, "[a] number of professional medical organizations have joined WPATH in recognizing that gender affirming care is medically necessary for transgender people." Ex. H at 361. This includes, among others, the American Medical Association, American Psychiatric Association, American Psychological Association, American Academy of Family Physicians, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, and the Endocrine Society. *Id.*; Ex. E at 58:21-61:9. It also includes Dr. Hruz's own employer, Washington University in St. Louis. Ex. C at 85:14-86:11.

Two. In his report, Dr. Hruz presented a number of modalities of treatment for the care of patients with gender dysphoria, including: (1) "conversion" or "reparative therapy"; (2) "watchful waiting"; and (3) the "affirming" approach, as

[8] Ex. H, a report of the National Academies, is self-authenticating as a publication issued by a public authority, Fed. R. Evid. 902(5), and is appropriate for judicial notice, *United States v. Doe*, 962 F.3d 139, 147 n.6 (4th Cir. 2020).

if these did not endorse the provision of gender-affirming medical care for adolescents and adults. Ex. A at ¶¶54-65; Ex. D at 49-50. In doing so, Dr. Hruz opined that the approach advocated by Dr. Kenneth Zucker and the "watchful waiting" model use "modern psychotherapeutic approaches to address suicidal ideation in children with gender dysphoria." Ex. A at ¶¶63-64; *see also* Ex. D at 50-51 (Dr. Hruz explaining that treatment "involve[] no medical treatment and is currently the best scientifically supported intervention."). But Dr. Hruz misrepresents these approaches by failing to explain that Dr. Zucker's approach and the "watchful waiting" model, which recommends the provision of gender-affirming medical care if a patient's gender dysphoria persists into adolescence. Ex. G; Ex. C at 121:6-12, 125:11-17. For example, with regards to Dr. Zucker, his approach has been described as follows by the APA:

> For adolescent patients (including those who first came to the clinic as young children), Dr. Zucker follows the Standards of Care Guidelines of the World Professional Association for Transgender Health. The treatment options include helping patients make a satisfactory transition to the opposite sex, including the institution of hormonal treatment to facilitate transition. In some cases, treatment may include helping an interested adolescent obtain sex-reassignment surgery.

Ex. R; Ex. G at 61. Indeed, "All of the three models of care … share in common the administration of hormonal treatment in adolescence." *Id.* at 64.

Three. In that same vein Dr. Hruz falsely presented "reparative therapy" as if it was an accepted modality of treatment. Ex. A at ¶60. Nothing could be further

from the truth, however. The provision of conversion/reparative therapy represents a fringe view completely contrary to the mainstream medical and scientific community in the United States. As Dr. Hruz has previously acknowledged in deposition, the American Psychiatric Association and the American Psychological Association oppose "reparative therapy" or gender identity change efforts as unethical and harmful. Ex. C at 164:1-170:8. The same position adopted by the National Academies. *Id.* at 176:9-177:24; Ex. H at 361-363. Indeed, per the American Psychological Association's Resolution on Gender Identity Change Efforts, "individuals who have experienced pressure or coercion to conform to their sex assigned at birth or therapy that was biased toward conformity to one's assigned sex at birth have reported harm resulting from these experiences such as emotional distress, loss of relationships, and low self-worth." Ex. S. What is more, Dr. Hruz cites to no authority—let alone any original, peer-reviewed study, in support of this so-called approach to treatment.[9]

Four. Dr. Hruz's misrepresents "desistance" rates as a reason to question the provision of gender-confirming care. This is a subject matter area in which the *Kadel* Court excluded Dr. Hruz's testimony. *Kadel v. Folwell,* 2022 WL 3226731at *9.

[9] Hruz cites to Dr. Ken Zucker's work as supportive of this therapeutic approach. However, as outlined above, Dr. Hruz grossly misrepresents Dr. Zucker's approach. What is more, the citation to Dr. Zucker is to an opinion article not any peer-reviewed original research.

Dr. Hruz spends considerable time on (and builds most of his testimony questioning the propriety of gender-affirming health care upon) antiquated studies showing that a majority of *prepubertal* children diagnosed with *gender identity disorder*—an outmoded diagnosis *distinct from gender dysphoria* with different diagnostic criteria—"desisted" from their gender nonconformity or cross-gender behavior. Ex. A at ¶¶ 63-64. But, his presentation of this literature is extremely misleading since, not only due to his reliance on outdated studies, but also because he ignores the more recent literature which has uniformly found that youth who have a diagnosis of gender dysphoria in adolescence overwhelmingly continue to identify as transgender as they age.[10] Moreover, as Dr. Hruz has previously admitted that absolutely no gender-affirming medical or surgical care is provided to *prepubertal* children. Ex. C at 125:23-126:5. That is true for each of the treatment paradigms Dr. Hruz discusses (apart from "conversion" or "reparative therapy"), a fact Dr. Hruz did not disclose.

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[10] *See, e.g.,* Kristina R. Olson, *Gender Identity 5 Years After Social Transition*, 150 Ped. e2021056082 (2022) (of 300 youth with gender dysphoria, at the end of the five years, 94% of participants still identified as transgender); Annelou L C de Vries et al., *Puberty Suppression in Adolescents with Gender Identity Disorder: A Prospective Follow-Up Study*, 8 J. Sex. Med. 2276 (2011). Notably, Thomas D Steensma, who co-authored the study on which Dr. Laidlaw improperly cites for the proposition that most youth with gender dysphoria "desist" in their gender identity, also co-authored the de Vries study, which looked 70 youth in the Netherlands referred for treatment of gender dysphoria between 2000 and 2008, found that all of them decided to continue their medical transition after 1-2 years, confirming that "young adolescents who had been carefully diagnosed show persisting gender dysphoria into late adolescence or young adulthood." *Id.* at 2281.

Id. at 119:22-140:12. His opinions are therefore not only misleading, but also irrelevant, since this case is about the coverage for medically necessary gender-affirming medical care, and none of the plaintiffs are prepubertal children.

Five. Dr. Hruz provides no scientific bases for his conclusions that "A currently unknown percentage and number of patients reporting gender dysphoria suffer from mental illness(es) that complicate and may distort their judgments and perceptions of gender identity" or that "A currently unknown percentage and number of patients reporting gender dysphoria may be manipulated by a social contagion and social pressure processes, including peer group, social media, YouTube role modeling, and parental pressures." Ex. A at ¶¶ 130-131. But "Hruz is not a statistician and does not discuss in his report how he came to those conclusions, what data he relied upon, or what methodology he applied to that data." *Kadel*, 2022 WL 3226731, at *9. "This testimony will therefore be excluded as unreliable." *Id.*

* * *

The Court "must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Daubert*, 509 U.S. at 589. Here, Dr. Hruz has misrepresented or omitted information that goes to the heart of his opinions and calls into question the reliability of his opinions. While usually the factual basis of an expert opinion goes to credibility, "it is possible for an experts'

omission of articles to render his or her opinion inadmissible on reliability grounds." *Huggins v. Stryker Corp.*, 932 F.Supp.2d 972, 994 (D. Minn. 2013). Such is the case here where Dr. Hruz omits key information, or worse, misrepresents facts that if properly disclosed would contradict his opinions and undermine their foundation. In such circumstances, the "potential to mislead" rather "than to enlighten" is too great. *In re Lipitor*, 892 F.3d at 632.

C. Dr. Hruz's opinions are unreliable because they are not generally accepted in the scientific and medical community.

General acceptance in the relevant scientific community is also relevant to the reliability inquiry. *Nease*, 848 F.3d at 229. Not only is widespread acceptance an important factor in assessing the reliability of an expert's opinions, but the fact that a known technique or theory "has been able to attract only minimal support within the community may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Here, Dr. Hruz's opinions are outside the mainstream of medical and scientific opinion and have been explicitly rejected by these relevant communities.

The provision of gender-confirming care has been accepted and endorsed, *inter alia*, by the: American Medical Association; American Psychiatric Association; American Psychological Association; Endocrine Society; Pediatric Endocrine Society; American Academy of Pediatrics; National Academies of Science, Engineering, and Medicine; and Dr. Hruz's own employer. Ex. C at 164:5-11; Ex. E at 70:25-71:22; *id.* 57:11-59:14; Ex. H at 361-363. The Fourth

Circuit has described it as "the consensus approach of the medical and mental health community." *Grimm*, 972 F.3d at 595; *Edmo v. Corizon, Inc.*, 935 F.3d 757, 771 (9th Cir. 2019) (the provision of gender-affirming care, consistent with the WPATH Standards of Care, represents "the ***broad medical consensus*** in the area of transgender health care," which "requires providers to individually diagnose, assess, and treat individuals' gender dysphoria.") (emphasis added); *see also Brandt v. Rutledge*, 551 F.Supp.3d 882, 890 (E.D. Ark. 2021) ("The consensus recommendation of medical organizations is that the only effective treatment for individuals at risk of or suffering from gender dysphoria is to provide gender-affirming care."), *aff'd*, 47 F.4th 661 (8th Cir. 2022); *Flack v. Wisconsin Dep't of Health Servs.*, 395 F.Supp.3d 1001, 1018 (W.D. Wis. 2019).

In fact, another federal district court found as much when it enjoined Arkansas' state law seeking to ban gender-confirming treatment for minors. *See Brandt*, 551 F.Supp.3d 882. In doing so, the *Brandt* court explicitly found that: (a) "Gender-affirming treatment is *supported by medical evidence* that has been *subject to rigorous study*;" and (b) "*Every major expert medical association* recognizes that gender-affirming care for transgender minors may be *medically appropriate and necessary* to improve the physical and mental health of transgender people." *Id.* at 891 (emphasis added). Notably, Dr. Hruz filed an expert declaration in the *Brandt* case that is virtually identical to the report he filed in this

case. As such, the *Brandt* court's findings stand as a stark repudiation of Dr. Hruz's opinion that gender-affirming care is "experimental" and "not medically necessary." Ex. A at ¶¶137-138; Ex. D at 17. It is for these reasons that the Court in *Kadel* excluded much of Dr. Hruz's opinions in that case on these issues. *Kadel v. Folwell,* 2022 WL 3226731at *9.

Conversely, Dr. Hruz's opinions in support of reparative therapy or gender identity change efforts has also been rejected by the general scientific community, among others. Ex. C at 164:1-170:8; Ex. E at 118:7-19, 237:1-23. *See also King v. Governor of the State of New Jersey*, 767 F.3d 216, 221–22 (3d Cir. 2014); *Pickup v. Brown*, 740 F.3d 1208, 1223–24 (9th Cir. 2014). This again shows that Dr. Hruz's opinions are wildly outside the mainstream and his failure to notify the Court of the rejection of these purported alternative treatment renders his testimony unreliable.

D. Dr. Hruz's opinions are unreliable because they have no support and are based on ipse dixit.

As noted herein, Dr. Hruz's opinions are based on untested hypotheses and do not have any factual support. For example, Dr. Hruz opines that gender dysphoria *may be* caused by social contagion and social pressure. Ex. A at ¶131. But he offers no evidence for this hypothesis, which he admits has not been tested. *Id.* Of course, "nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence which is connected to existing data only

by the *ipse dixit* of the expert." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). And this is one of those circumstances in which "there is simply too great an analytical gap between the data and the opinion proffered." *Id*. In fact, the only study to have looked at this hypothesis found no support for the hypothesis. Ex. N.

* * *

Given that Dr. Hruz's opinions fail to meet the most basic indicia of reliability, the Court should exclude Dr. Hruz's opinions and testimony as unreliable.

IV. Dr. Hruz's opinions are so tainted by his personal bias as to render his opinions unreliable.

While Plaintiffs are cognizant of the fact that bias in an expert witness's testimony is usually an issue of credibility as opposed to one of admissibility, when an expert's opinions are based on bias as opposed to scientific or medical knowledge, then the question of bias becomes one of reliability and admissibility. Indeed, reliability is a flexible inquiry wherein "courts must ensure that an expert's opinion is based on scientific, technical, or other specialized knowledge and not on belief or speculation." *Sardis*, 10 F.4th at 281. Here, there is ample evidence that Dr. Hruz's testimony is so permeated and tainted by his unscientific views and personal bias as to render it unreliable. *See Kadel*, 2022 WL 3226731, at *9 ("Plaintiffs have offered evidence that calls Hruz's motivations—and thereby, his reliability—into serious question."); *cf. Sanchez v. Esso Standard Oil de Puerto*

Rico, Inc., No. CIV 08-2151, 2010 WL 3809990, at *4 (D.P.R. Sept. 29, 2010).

More specifically, Dr. Hruz's testimony appears to be motivated by his personal and religious views regarding transgender people. To be clear, Plaintiffs do not seek to impugn or malign whatever moral or religious views Dr. Hruz may hold. However, to the extent Dr. Hruz's moral and religious views have influenced his purported expert opinions— indeed, they seem to be the motivating factor— that is something the Court must be aware of and should consider as it assesses the reliability of his testimony.

In his report, Dr. Hruz discusses meeting with Dr. Norman Spack, a noted pediatric endocrinologist and the co-founder of Boston Children's Hospital Gender Management Service Program, as someone he consulted when he first began to study issues relating to gender dysphoria from a scientific standpoint. Ex. Ex. A at ¶9; D at 6. But Dr. Spack's account of this encounter is quite different. Dr. Spack asserts that "Dr. Hruz did not discuss or mention that his issues or concerns were based on science." Ex. K at ¶ 13. To the contrary, Dr. Hruz expressed to Dr. Spack that he had "a significant problem with the entire issue" and "whole idea of transgender," and that for him, it was "a matter of [his] faith." *Id.* at ¶¶ 11-12. When confronted with Dr. Spack's account, Dr. Hruz notably did not deny he made such statements. Ex. C at 247:10-251:4.

Similarly, Dr. Hruz misrepresents the nature of his conversations with

"dozens of parents of children with gender dysphoria" as that of seeking "to understand the unique difficulties experienced by this patient population." Ex. A at ¶9; Ex. D at 6. One of these parents gives quite a different account of meeting with Dr. Hruz, however. Dr. Hruz met with Kim Hutton, the mother of a transgender child, in 2013. Ex. E 102:24-103:9, 126:12-129:25. Dr. Hruz says he met with the parent of a transgender child who was affiliated with an organization called TransParent, during a "very early investigative phase" of his study of gender dysphoria. Ex. E 103:25-104-7, 102:24-103:9. By Ms. Hutton's account, the nature of Dr. Hruz's conversation with her revealed that that he was firmly opposed to gender-affirming care, as well as opposed to a having a Transgender Center at St. Louis Children's Hospital, and that this opposition was rooted in his personal moral and religious views. Indeed, Dr. Hruz reportedly told Ms. Hutton, "there will never be a pediatric gender center at St. Louis Children's Hospital. I won't allow it." Ex. L at 30:8-30:11. Dr. Hruz also told Ms. Hutton that her "child was not normal and would never be normal," Ex. L at 28:20-28:23; that "the idea of doing surgeries on transgender people is -- is wrong," *id.* at 21:21-27:24; and repeatedly encouraged Ms. Hutton to "read Pope John Paul II's writings on gender," because it would explain everything. *id.* at 29:17-29:20. And in response to Ms. Hutton's statement that transgender children "are at a 41 percent risk of suicide if they don't have acceptance and -- and care from their parents and -- and

if they don't get their medical needs met," Dr. Hruz responded that, "Some children are born in this world to suffer and die." *Id.* at 29:21-30:4. As a result, Ms. Hutton left her conversation with Dr. Hruz—a conversation Dr. Hruz says he "was approaching [] in a purely investigative manner," Ex. E at 126:16-127:3—"perplexed" due to "the religious tone of the conversation," which she "figured [] would at least be based on science." Ex. L at 37:11-37:19.

The bias illuminated by Dr. Spack's and Ms. Hutton's testimony is further confirmed by the nature of Dr. Hruz's publications and presentations on this issue. With one exception, all of Dr. Hruz's publications pertaining to gender dysphoria have been in religiously affiliated, non-scientific publications. Ex. C at 42:10-49:19. Similarly, aside from a handful of grand rounds, Dr. Hruz has not made any presentations about this topic at scientific conferences, *id.* at 90:17-93:3; instead, presenting on this topic to religious organizations. For instance, in November 2017, Dr. Hruz gave a presentation at the Saint John Paul II Bioethics Center at the Holy Apostles College & Seminary, where he referred to being transgender as something that "probably goes back to some of the early heresies in the church," and to pictures of transgender people as "disturbing." Ex. E at 83:5-85:20. When confronted with these statements, Dr. Hruz did not disavow or deny making them. *Id.* And in February 2018, Dr. Hruz presented at an "International Conference on Gender, Sex and Education" that was billed as "the world's first great public

objection to totalitarian LGBTI laws," "a conference to oppose gender ideology," and "against the LGBTI doctrine… taking hold of Western Countries." Ex. M; Ex. C at 93:4-97:10.

The foregoing, coupled with Dr. Hruz's departure with generally accepted medical and scientific standards, demonstrates that Dr. Hruz's purported expert testimony lacks any indicia of reliability. And while the Federal Rules of Evidence state that "[e]vidence of a witness's religious beliefs or opinions is not admissible to attack or support the witness's credibility," Fed. R. Evid. 610, the Advisory Committee Notes to Rule 610 make clear that "an inquiry for the purpose of showing interest or bias because of them is not within the prohibition." Advisory Committee Notes to Rule 610. Indeed, "[w]ithout this critical information," the Court would be "deprived of the necessary facts from which it could appropriately draw inferences about [Dr. Hruz's] reliability." *State v. Heinz*, 485 A.2d 1321, 1328 (Conn. App. 1984). Here, it is evident that Dr. Hruz has not been candid regarding his experiences or the bases for his "opinions." The record evidence demonstrates a clear bias by Dr. Hruz against transgender people generally, which infects his reliability as a purported expert witness in this case.

V. Dr. Hruz's opinions lack probative value and are therefore inadmissible under Federal Rule of Evidence 403.

Finally, because of the potentially misleading effect of expert evidence, *see Daubert*, 509 U.S. at 595, on occasion expert opinions that otherwise meet

admissibility requirements may still be excluded under Fed. R. Evid. 403. Exclusion under Rule 403 is appropriate if the probative value of otherwise admissible expert testimony is substantially outweighed by its potential to confuse or mislead the jury, or if the testimony is cumulative or needlessly time consuming. *See, e.g., Hull v. Merck & Co., Inc.*, 758 F.2d 1474, 1477 (11th Cir.1985) (admission of speculative and "potentially confusing testimony is at odds with the purposes of expert testimony as envisioned in Fed. R. Evid. 702"); *Tran v. Toyota Motor Corp.*, 420 F.3d 1310, 1316 (11th Cir. 2005) (affirming exclusion of expert testimony as cumulative). Consequently, "the judge in weighing possible prejudice against probative force under Rule 403 . . . exercises *more* control over experts than over lay witnesses." *Daubert*, 509 U.S. at 595 (cleaned up).

Accordingly, the Court should exclude Dr. Hruz's opinions because its introduction will result in unfair prejudice, confusion of the issues, or in misleading testimony. Fed. R. Evid. 403. Dr. Hruz offers opinions that are irrelevant to the issues in this case, and, in any event, the opinions he offers are speculative and unreliable. The testimony would also result in prejudice, as the testimony seeks to sow confusion about the propriety of gender- confirming care based on speculation, irrelevant, misleading, or biased opinions.

CONCLUSION

For the foregoing reasons, the Court should exclude Dr. Hruz's report,

opinions, and testimony and limit his opinions to those permitted in *Kadel*.

Respectfully submitted this 7th day of April, 2023.

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CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

CERTIFICATE OF WORD COUNT

As required by Local Rule 7.1(F), I certify that this Memorandum of Law contains 7,463 words.

/s/ Shani Rivaux
Counsel for Plaintiffs

TAB 138

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
Tallahassee Division

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION TO EXCLUDE
EXPERT TESTIMONY OF DR. KRISTOPHER KALIEBE

Now come, Plaintiffs, by and through their counsel, and respectfully move this Court to exclude the expert report, opinions, and testimony of Defendants' proposed expert, Dr. Kristopher Kaliebe, pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403, and 702.

Dr. Kaliebe is not a qualified expert on gender dysphoria or its treatment, and his opinions and testimony are neither relevant nor reliable, under Federal Rule of Evidence 702 and the standards set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and its progeny. His opinions and testimony are likewise inadmissible because any probative value they may have (and they have none) is substantially outweighed by the danger of unfair prejudice, confusion of the issues,

waste of time, undue delay, and needless presentation of cumulative evidence. *See* Fed. R. Evid. 403.

Based on Dr. Kaliebe's lack of qualifications and the unreliability and unhelpfulness of his testimony and opinions, at minimum, the Court should exclude any portions of the expert report, opinions, and testimony of Dr. Kaliebe that go beyond his experience regarding the diagnosis of gender dysphoria in children and adolescents.

A memorandum of law is filed contemporaneously herewith.

Dated this 7th day of April 2023.

Respectfully Submitted,

/s/ Omar Gonzalez-Pagan

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LOCAL RULE 7.1(B) CERTIFICATION

The undersigned certifies that he attempted in good faith to resolve the issues raised in this motion through a meaningful conference with Defendants' counsel, including through a meet and confer Zoom conference on April 6, 2023.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan
Counsel for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan
Counsel for Plaintiffs

TAB 139

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
Tallahassee Division

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE EXPERT TESTIMONY OF DR. KRISTOPHER KALIEBE

TABLE OF CONTENTS

Plaintiffs respectfully submit this memorandum of law in support of their motion to exclude the expert testimony of Dr. Kristopher Kaliebe.[1]

INTRODUCTION AND STATEMENT OF THE CASE

Plaintiffs are transgender Medicaid beneficiaries who have been diagnosed with gender dysphoria. In August 2022, Defendants adopted a rule, Florida Administrative Code 59G-1.050(7) (the "Challenged Exclusion"), prohibiting Medicaid coverage of services for the treatment of gender dysphoria. Defendants adopted the Challenged Exclusion after undergoing a process with a predetermined outcome that concluded that the provision of medical treatment for the treatment of gender dysphoria, including puberty blockers, hormone therapy, and surgery, "do not conform to GAPMS [("generally accepted professional medical standards")] and are experimental and investigational." Defendants thus deny equal treatment to Plaintiffs based on sex because they are transgender.

In response, Defendants have put forward an expert, Dr. Kristopher Kaliebe, a child and adolescent psychiatrist, who has no experience regarding the treatment of gender dysphoria, nor has ever studied or written any literature—alone scientific, peer-reviewed literature—on gender identity or gender dysphoria. However, Dr. Kaliebe is not a qualified expert on gender dysphoria or its treatment, and his

[1] Unless otherwise specified, all exhibits cited herein are attached to the contemporaneously filed Declaration of Omar Gonzalez-Pagan.

opinions and testimony are neither relevant nor reliable, under Federal Rule of Evidence 702 and the standards set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and its progeny.

Accordingly, and for the reasons set forth below, the Court should exclude the expert report, opinions, and testimony of Dr. Kaliebe. At minimum, based on Dr. Kaliebe's lack of qualifications and the unreliability and unhelpfulness of his testimony and opinions, the Court should exclude any portions of the expert report, opinions, and testimony of Dr. Kaliebe that go beyond his experience regarding the diagnosis—not treatment—of gender dysphoria in children and adolescents.

LEGAL STANDARD

"The admission of expert evidence is governed by Federal Rule of Evidence 702, as explained by *Daubert* and its progeny." *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1291 (11th Cir. 2005). "District courts are [thus] charged with [a] gatekeeping function." *Id.*; *see also United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) ("The importance of *Daubert*'s gatekeeping requirement cannot be overstated.").

In conducting their gatekeeping function, courts must "engage in a rigorous three-part inquiry" and determine whether

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in *Daubert*; and (3) the testimony assists the trier of

> fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

Frazier, 387 F.3d at 1260 (quoting *City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d 548, 562 (11th Cir. 1998)). The Eleventh Circuit refers to these three considerations separately as "qualification," "reliability," and "helpfulness" and has emphasized they are "distinct concepts that courts and litigants must take care not to conflate." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). "The party offering the expert has the burden of satisfying each of these three elements by a preponderance of the evidence." *Rink*, 400 F.3d at 1292.

To be sure, "[i]mplementing Rule 702, *Daubert* requires district courts to ensure that any and all scientific testimony or evidence admitted is both relevant and reliable." *Claire v. Fla. Dep't of Mgmt. Servs.*, 2021 WL 5982330, at *1 (N.D. Fla. Oct. 20, 2021). "[T]he trial judge must determine [this] ***at the outset***." *Daubert*, 509 U.S. at 592 (emphasis added). "Rule 702 applies whether the trier of fact is a judge or a jury." *UGI Sunbury LLC v. A Permanent Easement for 1.7575 Acres*, 949 F.3d 825, 832 (3d Cir. 2020). Even rigorous cross-examination is not a substitute for the court's gatekeeping role. *See Nease v. Ford Motor Co.*, 848 F.3d 219, 231 (4th Cir. 2017). As such, the court's gatekeeping role and the test for admissibility of expert testimony are applicable even at a bench trial or at the summary judgment stage. *See, e.g.*, *Rink*, 400 F.3d at 1294 (finding no abuse of discretion by the district court in motions to exclude in the context of summary judgment); *Kadel v. Folwell*, 2022

WL 3226731, at **5-17 (M.D.N.C. Aug. 10, 2022) (granting motions to exclude in the context of summary judgment); *Lo v. United States*, 2022 WL 1014902, at *12 (W.D. Wash. Apr. 5, 2022) (excluding unqualified expert evidence in the context of a bench trial); *cf. UGI Sunbury*, 949 F.3d at 833 (holding the district court abused its discretion in a bench trial when it "ignored rule [702]'s clear mandate" by "sidestepping Rule 702 altogether and declining to perform any assessment of [expert]'s testimony before trial").

Finally, because of the potentially misleading effect of expert evidence, *see Daubert*, 509 U.S. at 595, on occasion expert opinions that otherwise meet admissibility requirements may still be excluded under Fed. R. Evid. 403.

ARGUMENT

I. Qualification – Dr. Kaliebe is not qualified to offer expert opinions on the treatment or causes of gender dysphoria, nor on the development of clinical practice guidelines.

An expert witness may be qualified "by knowledge, skill, experience, training, or education." Fed. R. Evid. 702. "Determining whether a witness is qualified to testify as an expert requires the trial court to examine the credentials of the proposed expert in light of the subject matter of the proposed testimony." *Banuchi v. City of Homestead*, 606 F.Supp.3d 1262, 1272 (S.D. Fla. 2022) (cleaned up). "Whether [an expert] is qualified is a threshold question, and vigorous cross-examination is no substitute." *Griffin v. Coffee Cnty.*, 608 F.Supp.3d 1363, 1373 (S.D. Ga. 2022),

objections overruled, 2022 WL 2805037 (S.D. Ga. July 18, 2022). If not qualified, the expert's testimony is unreliable. *See Reliastar Life Ins. Co. v. Laschkewitsch*, 2014 WL 1430729, at *1 (E.D.N.C. Apr. 14, 2014).

However, "qualifications alone do not suffice." *Clark v. Takata Corp.*, 192 F.3d 750, 759 n.5 (7th Cir. 1999); *see also Patel ex rel. Patel v. Menard, Inc.*, 2011 WL 4738339, at *1 (S.D. Ind. Oct. 6, 2011). Even "[a] supremely qualified expert cannot waltz into the courtroom and render opinions unless those opinions are based upon some recognized scientific method and are reliable and relevant under … *Daubert*." *Clark*, 192 F.3d at 759 n.5.

Moreover, "an expert's qualifications must be within the same technical area as the subject matter of the expert's testimony; in other words, a person with expertise may only testify as to matters within that person's expertise." *Martinez v. Sakurai Graphic Sys. Corp.*, 2007 WL 2570362, at *2 (N.D. Ill. Aug. 30, 2007); *see also Lebron v. Sec. of Fla. Dept. of Children and Families*, 772 F.3d 1352, 1369 (11th Cir. 2014) ("Expertise in one field does not qualify a witness to testify about others."). "Generalized knowledge of a particular subject will not necessarily enable an expert to testify as to a specific subset of the general field of the expert's knowledge." *Martinez*, 2007 WL 2570362, at *2.

This is particularly true in medicine where "no medical doctor is automatically an expert in every medical issue merely because he or she has graduated from

medical school or has achieved certification in a medical specialty." *O'Conner v. Commonwealth Edison Co.*, 807 F.Supp. 1376, 1390 (C.D. Ill. 1992), *aff'd*, 13 F.3d 1090 (7th Cir. 1994); *see also*, *e.g.*, *Hartke v. McKelway*, 526 F.Supp. 97, 100-101 (D.D.C. 1981). For example, a clinical psychologist may not be necessarily qualified to testify about stress worsening a preexisting heart condition, and a pediatrician experienced as a children's accident preventionist may not be qualified to testify to the conduct of an adult driver. *See Diviero v. Uniroyal Goodrich Tire Co.*, 919 F.Supp. 1353, 1355–56 (D. Ariz. 1996) (citing *Kloepfer v. Honda Motor Co.*, 898 F.2d 1452, 1458–59 (10th Cir. 1990), and *Edmonds v. Illinois Central Gulf Railroad*, 910 F.2d 1284, 1287 (5th Cir. 1990), as examples).

Here, Dr. Kaliebe opines that: gender dysphoria has been rare until the last two decades; there is no consensus in the field regarding the treatment of gender dysphoria, nor is there an evidence-base sufficient to lead to any confident recommendations; the evidence for affirmative treatment is low-quality; spread of ideology combined with technologically induced contagion effects leading the recent increase in gender dysphoria; and on criticisms of medical associations as well as political criticisms. Ex. A, at ¶ 4. But Dr. Kaliebe, a child and adolescent psychiatrist, is not qualified to render most, if any, of the opinions he proffers.

Dr. Kaliebe (1) has never conducted any original, peer-reviewed research about gender identity, transgender people, or gender dysphoria, Ex. B, at 43:17-44:1;

(2) has not published any literature, let alone scientific, peer-reviewed literature, on gender dysphoria or transgender people, Ex. B, at 25:5-14; (3) has never treated a patient for gender dysphoria, Ex. B, at 33:18-21 ("So you wouldn't be providing treatment for the dysphoria at Silver Clinic? A. I think we would not be directly addressing gender dysphoria in psychotherapy."); *id.* at 33:15-16 ("A. … I don't know that we would say we were giving therapy for gender dysphoria"); *id.* at 138:24-139:1 ("Q. You do not provide medical treatment for gender dysphoria; is that right? A. Medicines, correct.");[2] and (4) is not an endocrinologist, pediatrician, adolescent medicine doctor, surgeon, or other kind of physician qualified to medically treat gender dysphoria. Ex. B, at 44:2-8; Curriculum vitae attached to Ex. A.

Given the above, the district court's decision in *Kadel*, 2022 WL 3226731, at **5-17, is most instructive here. Like other experts in *Kadel*, Dr. Kaliebe "has never … treated gender dysphoria, … conducted any original research about gender dysphoria diagnosis or its causes, or published any *scientific*, *peer-reviewed*

[2] At most, Dr. Kaliebe can claim that he has supervised psychiatric residents (Ex. B, at 29:9-10) in overseeing the care of twelve (12) patients with gender dysphoria (Ex. B, at 28:15-20) for "comorbidities," like "depression or anxiety or trauma or personality disorders or whatever," by "trying to provide them skills and sort of basic coping mechanisms, self-regulation, all the standard things you provide to someone who has emotional dysregulation or behavioral problems or, you know, emotional problems, standard care." Ex. B, at 33:21-34:5. But as Dr. Kaliebe has acknowledged, "[p]roviding treatment for comorbidities doesn't necessarily address a patient's gender dysphoria." Ex. B, 35:10-16.

literature on gender dysphoria." *Kadel*, 2022 WL 3226731, at *9 (emphasis added). Dr. Kaliebe "is not an endocrinologist, nor has he ever treated a patient with hormone therapies." *Id.* at at *13; Ex. B, at 32:15-17 ("A. … nor are we involved with providing hormones or those type of things."); *id.* at 138:24-139:4. In fact, Dr. Kaliebe had to consult his wife, an adult endocrinologist, ahead of his deposition in order to familiarize with the effects of puberty-delaying medications and hormone therapy. Ex. B, at 12:24-13:11, 139:5-8. Thus, Dr. Kaliebe "is not qualified to render opinions about … the efficacy of puberty blocking medication or hormone treatments, the appropriate standard of informed consent for … endocrinologists." *Kadel*, 2022 WL 3226731, at *13. Additionally, Dr. Kaliebe "is not a surgeon and has no experience with surgery for gender dysphoria and, therefore, is not qualified to testify to the risks associated with surgery or the standard of care used by surgeons for obtaining informed consent for surgery." *Id.* at *9.

Moreover, Dr. Kaliebe is not qualified to opine on the diagnosis and treatment of gender dysphoria in adults. During his deposition, Dr. Kaliebe acknowledged that he "definitely ha[s] more expertise and more experience in child psychiatry" and that "would be more where I'm comfortable." Ex. B, at 44:16-17, 45:1. While Dr. Kaliebe "was asked to review and opine generally," he "did [his] best to try to catch up on adult literature and know more about adult issues." Ex. B, at 44:21-22. But

that is not enough. *See* Ex. B, at 86:1-2 ("And I will admit that I know less about and am less up to date everything about adult transgender care.").

Dr. Kaliebe "is also not qualified to opine on the efficacy of randomized clinical trials, cohort studies, or other longitudinal, epidemiological, or statistical studies of gender dysphoria." *Kadel*, 2022 WL 3226731, at *13; *see*, *e.g.*, Ex. A, at ¶¶ 47, 163, 164. "He is not a statistician or epidemiologist, and there is no evidence in his report or deposition that he has any experience, specialized training, or knowledge about crafting a research study, analyzing data, or conducting a clinical trial." *Id.* A psychiatrist "with little to no research experience is not qualified to opine on the veracity of statistical studies." *Id.*

In large part, Dr. Kaliebe bases his opinions on his review of other people's scholarship—in fact, on non-primary sources, those being non-peer reviewed reports about the scientific literature. But "[m]erely reading literature in a scientific field does not qualify a witness—even an educated witness—as an expert." *Kadel*, 2022 WL 3226731, at *9; *see also Dura Auto. Sys. of Ind., Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002) ("The *Daubert* test must be applied with due regard for the specialization of modern science. A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty. That would not be responsible science."). Indeed, this is precisely the sort of "generalized knowledge of a particular subject" that courts have rejected as a qualification under

Rule 702. As with the disqualified expert in *Lebron* who "reached his opinion instead by relying on studies," this is not a sufficient qualification to serve as an expert witness. 772 F.3d at 1369.

Nor can Dr. Kaliebe claim to be qualified based on his conversations with the twelve (12) transgender minor patients, to whom he has provided no treatment for gender dysphoria and only supervised others' psychotherapeutic care of the patients. Such "reliance on anecdotal evidence" is a "red flag[] that caution[s] against certifying an expert." *Newell Rubbermaid, Inc. v. Raymond Corp.*, 676 F.3d 521, 527 (6th Cir. 2012).

Moreover, Dr. Kaliebe, who opines at length about the development of clinical practice guidelines by WPATH and the Endocrine Society (*see*, *e.g.*, Ex. A, at ¶¶ 62-63; Ex. C, at ¶¶ 19-26, 31-33), admits he is not an expert on the development of clinical practice guidelines. Ex. B, at 101:3-10; s*ee Solaia Tech. LLC v. ArvinMeritor, Inc.*, 361 F.Supp.2d 797, 813–14 (N.D. Ill. 2005) (finding expert was not qualified "to testify about areas in which he has admitted he has no expertise"); *accord Lifewise Master Funding v. Telebank*, 374 F.3d 917, 928 (10th Cir. 2004) (affirming trial court's ruling that purported expert could not testify where the court noted, inter alia, that witness admitted that he was not expert in areas pertinent to damages modeling). And Dr. Kaliebe does not profess any training or experience on the development of clinical practice guidelines.

The Court should find that Dr. Kaliebe is not qualified to testify about gender dysphoria and its treatment, the conduct and efficacy of scientific studies and the weighing of these, and the promulgation of clinical practice guidelines. At most, based on his purported experience diagnosing twelve (12) patients with gender dysphoria over his career, Dr. Kaliebe could testify to the diagnosis of gender dysphoria in children and adolescents.

II. Reliability – Dr. Kaliebe's opinions and testimony are unreliable.

An expert's testimony should only be admitted if it is sufficiently reliable. The requirement of reliability found in Rule 702 is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). "To meet the reliability requirement, an expert's opinion must be based on scientifically valid principles, reasoning, and methodology that are properly applied to the facts at issue." *In re 3M Combat Arms Earplug Products Liab. Litig.*, 3:19MD2885, 2022 WL 1262203, at *1 (N.D. Fla. Apr. 28, 2022). It must be based on "good grounds," *Daubert,* 509 U.S. at 590, and cannot be based on "leaps of faith." *Rider*, 295 F.3d at 1202.

Thus, when determining the reliability of proposed expert testimony, courts "consider, to the extent possible: (1) whether the expert's theory can be and has been tested; (2) whether the theory has been subjected to peer review and publication; (3) the known or potential rate of error of the particular scientific technique; and (4)

whether the technique is generally accepted in the scientific community." *Quiet Tech.*, 326 F.3d at 1341. Other factors which may be relevant include (1) the nature of the field of claimed expertise, (2) the source of the expert's knowledge, (3) the expert's level of care in using the knowledge, and (4) the expert's consideration of alternative hypotheses. *See Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 578-79 (N.D. Fla. 2009), *aff'd sub nom. Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183 (11th Cir. 2010).

"At this stage, the court must undertake an independent analysis of each step in the logic leading to the expert's conclusions; if the analysis is deemed unreliable at any step the expert's entire opinion must be excluded." *Id.* at 578. And "proffered evidence that has a greater potential to mislead than to enlighten should be excluded." *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prod. Liab. Litig. (No II) MDL 2502*, 892 F.3d 624, 632 (4th Cir. 2018).

Here, Dr. Kaliebe's report, testimony, and opinions fail all indicia of reliability. Dr. Kaliebe's proffered opinions are based on nothing more than speculation, "untested" theories, uncorroborated anecdotes, and assumptions that are obsolete, flawed, unethical, or expressed opinions based upon "unsettled science." What is more, some of his opinions are patently false.

A. Dr. Kaliebe's opinions are unreliable because they are based on unsupported premises, untested hypotheses, and speculation.

"While hypothesis is essential in the scientific community because it leads to advances in science, speculation in the courtroom cannot aid the fact finder in making a determination." *Dunn v. Sandoz Pharms. Corp.*, 275 F.Supp.2d 672, 684 (M.D.N.C. 2003). "[T]he courtroom is not the place for scientific guesswork, even of the inspired sort." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). Indeed, such "speculation is unreliable evidence and is inadmissible." *Dunn*, 275 F.Supp.2d at 684. "Where an expert's opinion testimony is founded on an unsupported premise, it gives rise to an inference that is based on speculation and has no evidentiary value." *Walker v. Blitz USA, Inc.*, 663 F.Supp.2d 1344, 1364 (N.D. Ga. 2009).

Here, several of Dr. Kaliebe's opinions are based on speculation, unsupported premises, or mere guesswork. Take the following examples:

One. Dr. Kaliebe opines that "Significant evidence points to a spread of ideology combined with technologically induced contagion effects leading the recent increase in gender dysphoria." Ex. A, at ¶ 4(e); *id.* at ¶¶ 30, 39-41. But Dr.

Kaliebe admits there is no evidence to support this opinion,[3] rather, in his words, "We are all *hypothesizing*, obviously." Ex. B, at 58:23-59:3 (emphasis added).[4]

Two. Dr. Kaliebe repeatedly opines about a purported failure of the scientific and medical community to study what he calls "body affirmation" as a psychotherapeutic approach to treatment. Ex. A, at ¶ 66(a) ("SOC 8 makes no analysis of privileging gender affirmation over body affirmation."); Ex. C, at ¶ 12 ("Body positivity and body acceptance are laudable goals and should be compared against the use of hormones and surgeries in order to determine which is a more effective and humane treatment."), *id.* at ¶ 13 ("Further research may well find psychotherapies or mind-body approaches with better results than gender affirmation through hormones and surgery."). However, Dr. Kaliebe cites no literature—none—in support this hypothetical treatment modality he repeatedly proposes. In fact, he concedes there is no literature at all to support this hypothetical approach to therapy. Ex. B, at 111:20-21; Ex. C, at ¶ 13. In other words, it is a hypothesis built upon unsupported premises.

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[3] For example, the literature to which Dr. Kaliebe cites to support his opinion does not relate to gender dysphoria, Ex. B, at 58:8-11, and the Littman article to which he cites "actually doesn't reach any conclusions as to social contagions," but rather "at best … raises hypotheses," Ex. B, at 71:15-18.

[4] To the extent Dr. Kaliebe points to two unscientific polls of the attendees to two conference panel sessions and a single personal anecdote, such evidence has no indicia of reliability. *See* Section II.C, *infra*.

Upon questioning, Dr. Kaliebe clarified that what he refers to as "body affirmation" has nothing to do with treating gender dysphoria or resolving a person's incongruence. At his deposition, Dr. Kaliebe explained that what he terms "body affirmation" "is purely about [a person] being comfortable with their body," such that "somebody that identifies as female" would be "completely comfortable with their stereotypically male body, notwithstanding that they identify as female." Ex. B, at 111:11-17. However, upon questioning Dr. Kaliebe admits that "part of somebody's gender dysphoria [is] the distress associated with that incongruence due in part to how they are perceived by others in the world." Ex. B, at 113:1-5. It is thus unclear how his hypothetical approach would treat gender dysphoria.

Indeed, Dr. Kaliebe posits that "if we could help people become more comfortable in the body that they are in, you know, perhaps, that would mean that they could be somewhat more comfortable and *maybe the gender dysphoria never goes away*, but we might be able to help them with their depression or anxiety or self-harm or other things." Ex. B, at 113:6-11 (emphasis added). But again, Dr. Kaliebe cites to nothing in support of this hypothetical, and until now unheard of, approach to treating gender dysphoria.

Three. Dr. Kaliebe repeatedly makes broad assertions that "in private, but not in public, most psychiatrists will acknowledge their doubts regarding affirmative care," Ex. A, at ¶ 123; "[m]ost psychiatrists are willing to admit we don't have

enough research to really know how to proceed," *id.*; and "[m]ost physicians have doubts about a gender medicine," Ex. C, at ¶ 36. However, Dr. Kaliebe fails to cite to any study, literature, or evidence in support of such broad assertions in every instance in which he makes them. Instead, Dr. Kaliebe bases these opinions on a few conversations he has had and then extrapolates them to the population of physicians and psychiatrists at large. *See*, *e.g.*, Ex. B, at 60:17-61:6, 63:19-64:4, 127:8-10, 146:10-25. But when Dr. Kaliebe's opinions are based on a select few anecdotes, it is a circumstance where "there is simply too great an analytical gap between the data and the opinion proffered," such that the expert testimony must be excluded. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 144 (1997).

Four. Dr. Kaliebe suggests that cognitive behavioral therapy (CBT) or yoga could be effective modes of psychotherapy for gender dysphoria. Ex. A, at ¶¶ 136, 142. But he admits he does not know if CBT could be effective to treat gender dysphoria (it cannot), because according to him it has not been studied. Ex. B, 152:7-22. Likewise, Dr. Kaliebe admits there are no studies on yoga as treatment of any mental health conditions, let alone gender dysphoria. Ex. B, at 164:21-165:9, 166:5-11. Such speculative opinions are wholly unreliable.

Similarly, Dr. Kaliebe suggests that "more specific and nuanced approaches for gender dysphoria exist," such as gender exploratory therapy. Ex. A, at ¶ 137 (citing to https://genderexploratory.com/). However, not only does he not cite to any

literature in support for this modality of treatment, but he admits that there is no evidence that gender exploratory therapy is safe or effective. Ex. B, at 159:2-4. Again, his opinion about gender exploratory therapy is speculative, at best.[5]

Five. Dr. Kaliebe opines in his rebuttal report that "[i]n childhood, most gender dysphoria spontaneously resolves without treatment." Ex. C, at ¶ 16. He provides no citation or evidence for this opinion, making it an unsupported premise that should be excluded as unreliable.

Six. Dr. Kaliebe opines that "it is clear the SOC 8 guidelines are at odds with the stated policies of most countries." Ex. C, at ¶ 6. He provides no citation or support for this extremely broad statement. What is more, he concedes he has no awareness "of which countries have adopted SOC 8." *Id.* The Court should reject this wholly unsupported opinion as unreliable.

Seven. Dr. Kaliebe's opinions about the innerworkings of WPATH or the motivations and opinions of its membership is wholly speculative and unreliable. *See*, *e.g.*, Ex. C, at ¶¶ 3-4. The same holds true for his criticisms of the Endocrine

[5] "Whereas gender-affirmative approaches follow the client's lead when it comes to gender, gender-exploratory therapy discourages gender affirmation in favor of exploring through talk therapy the potential pathological roots of youths' trans identities or gender dysphoria." Ex. D, at 472. "The surge of gender-exploratory therapy coincides with ongoing attempts to criminalize gender-affirming care for trans youths, sometimes masquerading as a compromise between gender-affirmative care and conversion practices and at other times functioning as the intellectual arm of political movements calling for the criminalization of gender-affirming care." *Id.* at 473.

Society. *E.g.*, Ex. A, at ¶ 105 ("While I have little direct experience with the Endocrine Society, my assessment is that many endocrinologists, and perhaps most, also believe their professional organization is also too strongly influenced by activist physicians."). Dr. Kaliebe has no experience with these organizations upon which to base his criticisms. "He is therefore not qualified to testify about the credibility of those organizations." *Kadel*, 2022 WL 3226731, at *10. Indeed, Dr. Kaliebe can "not offer[] any reliable testimony on this subject that will help the trier of fact." *Id.*

* * *

Dr. Kaliebe lacks knowledge "of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation." *Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988). Indeed, much of Dr. Kaliebe's testimony and opinions "appears to be based more on supposition than science." *O'Neill v. Windshire-Copeland Assocs.*, 372 F.3d 281, 285 (4th Cir. 2004). And opinions based on "subjective belief or unsupported speculation" should be rejected. *Daubert*, 509 U.S. at 589-590.

B. Dr. Kaliebe's opinions are unreliable because they are misleading, employ flawed methodologies, and do not serve to enlighten the trier of fact.

In addition, many of Dr. Kaliebe's opinions are misleading at best, or flat out false. Take the following examples:

One. Dr. Kaliebe spends much ink criticizing the development of the WPATH Standards of Care, Version 7 and Version 8. Dr. Kaliebe does so by quoting

and repeating criticisms made by others. *See*, *e.g.*, Ex. A, at ¶¶ 62-63; Ex. C, at ¶¶ 19-26, 31-33. But these criticisms are unreliable for, at least, two independent reasons.

First, Dr. Kaliebe admits that he is not an expert in the development of clinical practice guidelines. Ex. B, at 101:3-10. And an expert, "however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty." *Dura Auto. Sys.*, 285 F.3d at 614. Indeed, because Dr. Kaliebe is not qualified "to testify about areas in which he has admitted he has no expertise," such testimony is unreliable. *Solaia Tech.*, 361 F.Supp.2d at 813–14.

Second, while an expert may properly rely on the opinion of another expert, an expert cannot simply repeat or adopt the findings of other experts without investigating them. *See In re Polypropylene Carpet Antitrust Litig.*, 93 F.Supp.2d 1348, 1357 (N.D. Ga. 2000) (citing *In re TMI Litig.*, 193 F.3d 613, 715–16 (3d Cir. 1999) (finding blind reliance by expert on other expert opinions demonstrates flawed methodology under *Daubert*); *TK–7 Corp. v. Estate of Barbouti*, 993 F.2d 722, 732–33 (10th Cir. 1993) (excluding expert opinion relying on another expert's report because witness failed to demonstrate a basis for concluding report was reliable and showed no familiarity with methods and reasons underlying the hearsay report)).

Two. Dr. Kaliebe opines throughout his reports on the efficacy of gender-affirming medical treatment. However, Dr. Kaliebe does not discuss any single

original, peer-reviewed study in detail and in fact, only cites four original studies in the references for his original report. *See* Ex. B, at 88:2-22; Ex. A, at 69-75. Specifically, he cites to four studies Branstrom, et al. (2020), Chen, et al. (2023), Dhejne, et al. (2011), and Kaltiala, et al. (2020). However, the universe of original peer-review research looking into the safety and effectiveness of gender-affirming medical treatments is orders of magnitude larger.

For example, a systematic literature review of peer-reviewed studies published in English between 1991 and 2017 looked at 56 original peer-reviewed studies into whether gender transition, including medical treatments such as hormone therapy and surgeries, improves the overall well-being of transgender adults. *See* Exs. E and F.[6] Similarly, a review from 1998 looked at data from 80 studies spanning 30 years. Ex. G (Expert Report of Johanna Olson-Kennedy, M.D., M.S.), at ¶ 44. In other words, *a meta-analysis review from 25 years looked at 20 times the number of studies that Dr. Kaliebe reviewed for his report*. There is likewise a multitude of original peer-reviewed studies looking into the effect of gender-affirming medical treatment on the mental health and well-being of transgender adolescents with gender dysphoria. *See*, *e.g.*, Ex. G, at ¶¶ 25-30, 33-39,

[6] Though not relevant for purposes of this Motion to Exclude, it is worth noting that this systematic literature review "found a robust international consensus in the peer-reviewed literature that gender transition, including medical treatments such as hormone therapy and surgeries, improves the overall well-being of transgender individuals." Ex. E.

46 (discussing over 13 original peer-reviewed studies looking specifically at transgender adolescents); Ex. H (Expert Report of Daniel Shumer), at ¶¶ 82, 86 (discussing over 15 original peer-reviewed studies looking specifically at transgender adolescents); Ex. I (discussing 16 original peer-reviewed studies examining the impacts of gender-affirming medical care for transgender adolescents).

Plaintiffs do not point to the aforementioned vast expanse of scientific literature to argue the merits of Dr. Kaliebe's opinions (as wrong as they are), but to illustrate the lack of reliability of Dr. Kaliebe's opinions based on his methodology (or lack thereof). Dr. Kaliebe is unfamiliar with and does not reference—let alone, discuss—the original peer-reviewed studies that he criticizes. Rather, Dr. Kaliebe parrots the criticisms of others. His references are primarily opinion pieces and literature reviews by others, not original peer-reviewed studies. *See generally* Ex. A, at 69-75. But Dr. Kaliebe cannot serve as a mouthpiece for others. His criticisms of the scientific evidence supporting gender-affirming medical care must be based on his own review of that evidence. The fact that Dr. Kaliebe is unfamiliar with the expansive universe of literature at issue here demonstrates the lack of reliability for his opinions about the effectiveness of gender-affirming medical care.

Three. Dr. Kaliebe disputes that gender identity has a biological basis. He cites to an article by Marianowicz-Szczygiel (2022) outlining an apparent rise of

people presenting to gender clinics and an article by Littman (2018) discussing the perceptions of the non-affirming parents of transgender adolescents. Ex. C, at ¶ 10. But neither article disputes there is a biological basis for gender identity. For example, Dr. Kaliebe conceded that "the fact that more people have been showing up at clinics could be explained by the fact that, A, the care is more available; and, B, more people feel comfortable seeking the care." Ex. B, at 54:5-10. And Dr. Kaliebe conceded that the Littman article, given its multiple limitations, could not reach any conclusions regarding social contagion and, at most, raised hypotheses. Ex. B, at 71:16-18. What is more, scientific, peer-reviewed literature that Dr. Kaliebe has encountered shows the opposite, namely, that "there is empirical evidence that there is a biological basis for a person's gender identity." Ex. J; *see also* Ex. B, at 150:17 ("A. I've seen it cited.").

Dr. Kaliebe's opinions about whether there is a biological basis for gender identity are unreliable because (a) he employed a flawed methodology that omitted discussion of existing, on point peer-reviewed scientific literature, and (b) his opinions are based on unproven hypotheses and not any data. While usually the factual basis of an expert opinion goes to credibility, "it is possible for an experts' omission of articles to render his or her opinion inadmissible on reliability grounds." *Huggins v. Stryker Corp.*, 932 F.Supp.2d 972, 994 (D. Minn. 2013). Such is the case

here where Dr. Kaliebe omits key information, or worse, misrepresents facts that if properly disclosed would contradict his opinions and undermine their foundation.

* * *

The Court "must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Daubert*, 509 U.S. at 589. Here, Dr. Kaliebe has employed flawed methodologies and misrepresented or omitted information that goes to the heart of his opinions, all of which calls into question the reliability of his opinions. In such circumstances, the "potential to mislead" rather "than to enlighten" is too great. *In re Lipitor*, 892 F.3d at 632.

C. Dr. Kaliebe's opinions are unreliable because they are based on facts or data not typically relied on by physician or scientists.

Rule 703 requires that "[t]he facts or data … upon which an expert bases an opinion or inference" must be "of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject." Fed. R. Evid. 703.

One. Based on his alleged "review of the research," Dr. Kaliebe opines "that the evidence base for gender dysphoria treatment is mixed and generally low quality." Ex. A, at ¶ 45. However, Dr. Kaliebe bases his opinions on his review of reports of government entities in Finland, Sweden, and the United Kingdom, as well as the GAPMS Report. Ex. B, at 86:25-87:8. But, as Dr. Kaliebe acknowledges, none of those are published, peer-reviewed literature. *Id.*; *see also* Ex. B, at 99:17-25. And

such unpublished, non-peer-reviewed reports *are not* the types of materials reasonably relied upon by experts in any field of medicine. When asked what actual peer-reviewed, original studies he reviewed, he could not identify any and his original report cites to only four (4) original studies (none of which relate to the provision of puberty-delaying medications as treatment for an adolescent's gender dysphoria). Ex. B, at 86:21-88:22.

Two. As noted above, Dr. Kaliebe *hypothesizes* that "direct social influences and online and social media contagion" are "major contributors" to a rise in gender dysphoria. *E.g.*, Ex. A, at ¶ 30; *see also id.* at ¶¶ 40, 41. However, he points to no *reliable* evidence to support his *hypothesis* (which itself is an unreliable basis for an expert opinion, *see* Section II.A, *supra*). For example, Dr. Kaliebe points to a single case anecdote in support for his hypothesis. Ex. B, 59:13-16. But such "anecdotal information … is scientifically unreliable and not supported by any … scientifically reliable studies." *Soldo v. Sandoz Pharms. Corp.*, 244 F.Supp.2d 434, 571 (W.D. Pa. 2003);[7] *see also McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1252, 1253-54 (11th Cir. 2005).

In addition, Dr. Kaliebe relies on two non-published, non-peer-reviewed, unscientific polls of the attendees of two conference panel sessions to support his

[7] In *Soldo*, the excluded expert's testimony was based on anecdotal evidence contained *in published case reports*. Here, Dr. Kaliebe has not even attempted to publish his anecdotal evidence as a case report.

opinion that "Psychiatrists also believe social media has significantly contributed to the rise in gender dysphoria." Ex. A, at ¶ 41; *see also id.* at ¶¶ 42-43. Dr. Kaliebe admits that he did not do any regression or statistical significance analysis regarding these polls, Ex. B, at 66:15-19, and that all the polls tell us "is the views of the attendees of that particular seminar." Ex. B, at 67:1-4. Indeed, there are about 45,000 psychiatrists in the United States, Ex. B, at 63:15-18, and as Dr. Kaliebe admits his "conversations are not a representative sample of all childhood adolescent psychiatrists." Ex. B, at 64:8-11.

Dr. Kaliebe also cites as a support a *press release* from the French Academies, Ex. A, at ¶ 40, but admits that "a press release is not peer-reviewed or scientific literature." Ex. B, at 68:7-13.

Of course, it should be noted that, as Dr. Kaliebe admits, "it is not shocking that teens find like-minded teens online and they speak to each other about their similar experiences," and "that, in particular, small populations that tend to be isolated and/or discrete tend to turn to social media actually as a way to connect and find one another." Ex. B, at 67:21-68:6.

In sum, none of the sources upon which Dr. Kaliebe relies for his opinions are of reliable or of the type upon which any serious physician or scientist would rely on.

Three. Dr. Kaliebe also spends much ink discussing the apparent politicized nature of conversations surrounding the treatment of gender dysphoria and *hypothesizes* that such politicization and moralization has led to the silencing of contrary views. *See*, *e.g.*, Ex. A, at ¶¶ 71-89 (discussing apparent "lack of consensus"); *id.* at ¶¶ 90-124 (discussing "breakdown in scholarly dialogue"). Dr. Kaliebe bases these opinions on conjecture and anecdotes he has purportedly collected based on a few conversations. However, neither of these are the type of "facts or data" other experts in psychiatry or medicine "would reasonably rely on … in forming an opinion in the subject." Fed. R. Evid. 703. Indeed, "broad opinions [that] are based solely on … generalized views, anecdotal accounts, and speculation … are not reliable." *In re 3M*, 2021 WL 684183, at *3 (N.D. Fla. Feb. 11, 2021). Similarly, opinions "based on mere conjecture, assumption, credibility calls, and amounting to no more than ipse dixit" are "neither reliable nor helpful." *Day v. Edenfield*, 2022 WL 972430, at *10 (N.D. Fla. Mar. 31, 2022).

What is more, in some instances, some of these opinions are demonstrably false. For example, Dr. Kaliebe states that "skeptical voices have been difficult to find within any of the journals of the Endocrine Society, American Academy of Pediatrics, American Psychiatric Association or American Academy of Child and Adolescent Psychiatry" and that he "ha[s] not found a single skeptical or even ideologically balanced article in any of these journals." Ex. A, at ¶ 82. But

notwithstanding that Dr Kaliebe was aware of two letters to the editor published in the *Journal of the Endocrine Society* that were critical of gender-affirming medical care, he still made the false statement.[8] *See* Ex. B, at 131:15-132:13.

In sum, none of Dr. Kaliebe's "opinions" about the politicized nature of the debate surrounding transgender issues and the treatment of gender dysphoria are medical or scientific opinions. They do not require "the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue." *Frazier*, 387 F.3d at 1260. To the contrary, they are at best personal opinions and gripes with those with whom he disagrees. They are both unreliable and irrelevant, and at times, outright false. Allowing Dr. Kaliebe to testify "based on limited personal accounts and information relayed to [him] by an unspecified number of third parties would be to sanction [his] use as a vehicle for introducing hearsay testimony." *In re 3M*, 2021 WL 684183, at *2.

* * *

Dr. Kaliebe's opinions are thus "unsupported by reliable principles and methods and lack[s] hallmarks of scientific rigor: peer-reviewed research, studies, or experiments in support of his opinions." *United States v. Geanakos*, 2017 WL 4883294, at *3 (E.D. Cal. Oct. 30, 2017).

[8] To be sure, neither of these two letters were based on original research or were peer-reviewed.

D. Dr. Kaliebe's opinions are unreliable because they are not generally accepted in the scientific and medical community.

General acceptance in the relevant scientific community is also relevant to the reliability inquiry. *Nease*, 848 F.3d at 229. Not only is widespread acceptance an important factor in assessing the reliability of an expert's opinions, but the fact that a known technique or theory "has been able to attract only minimal support within the community may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Here, Dr. Kaliebe's opinions are outside the mainstream of medical and scientific opinion and have been explicitly rejected by these relevant communities.

The provision of gender-affirming medical care has been accepted and endorsed, *inter alia*, by the: American Medical Association; American Psychiatric Association; American Psychological Association; Endocrine Society; Pediatric Endocrine Society; American Academy of Pediatrics; and the National Academies of Science, Engineering, and Medicine. *See* Ex. K at 361.

In fact, another federal district court found as much when it enjoined Arkansas' state law seeking to ban gender-confirming treatment for minors. *See Brandt v. Rutledge*, 551 F.Supp.3d 882 (E.D. Ark. 2021), *aff'd*, 47 F.4th 661 (8th Cir. 2022). In doing so, the *Brandt* court explicitly found that: (a) "Gender-affirming treatment is *supported by medical evidence* that has been *subject to rigorous study*;" and (b) "*Every major expert medical association* recognizes that gender-affirming care for transgender minors may be *medically appropriate and necessary* to improve

the physical and mental health of transgender people." *Id.* at 891 (emphasis added). The *Brandt* court's findings stand as a stark repudiation of Dr. Kaliebe's opinion that the provision of gender-affirming medical care to adolescents with gender dysphoria is an "experiment," for which "there is clearly no consensus of opinion." Ex. A, at ¶¶ 11, 21-22.

* * *

Given that Dr. Kaliebe's opinions fail to meet the most basic indicia of reliability, the Court should exclude Dr. Kaliebe's opinions and testimony as unreliable.

III. Helpfulness – Dr. Kaliebe's opinions and testimony are not relevant to this case.

Helpfulness "goes primarily to relevance." *Daubert*, 509 U.S. at 580; *see also Prosper v. Martin*, 989 F.3d 1242, 1249 (11th Cir. 2021) ("The touchstone of this inquiry is the concept of relevance."). Under the helpfulness prong, the "court must satisfy itself that the proffered testimony is relevant to the issue at hand, for that is a precondition to admissibility." *Sardis v. Overhead Door Corp.*, 10 F.4th 268, 282 (4th Cir. 2021) (cleaned up). Relevant expert testimony "logically advances a material aspect of the proposing party's case" and "fits" the disputed facts. *McDowell v. Brown*, 392 F.3d 1283, 1298-99 (11th Cir. 2004). Thus, "expert testimony which does not relate to any issue in the case is not relevant and non-

helpful." *Knight v. Boehringer Ingelheim Pharms., Inc.*, 323 F.Supp.3d 837, 846 (S.D. W.Va. 2018).

In order to be relevant, an opinion needs to "fit" with the facts at issue. *Simmons v. Augusta Aviation, Inc.*, 596 F.Supp.3d 1363, 1374 (S.D. Ga. 2022) "To satisfy this requirement, the testimony must concern matters beyond the understanding of the average lay person and logically advance a material aspect of the proponent's case." *Id.* Testimony that "offers nothing more than what lawyers for the parties can argue in closing arguments" or that consists of "subjective portrayals of factual information" "generally will not help the trier of fact." *Giusto v. Int'l Paper Co.*, 2021 WL 3603374, at *4 (N.D. Ga. Aug. 13, 2021).

This case is about whether Defendants' exclusion of coverage for medical treatments for gender dysphoria violates Plaintiffs' rights under the equal protection clause, Section 1557 of the Affordable Care Act, and the Medicaid Act. Dr. Kaliebe's opinions are not relevant to this inquiry as they will not help the trier of fact to understand the evidence or to determine a fact in issue. His opinions do not "fit" because they are not sufficiently tied to the facts of the case so that they will aid a factfinder.

A. Dr. Kaliebe's opinions about "desistance" are irrelevant.

Dr. Kaliebe's opinion that "[i]n childhood, most gender dysphoria spontaneously resolves without treatment" is wholly irrelevant. Ex. C, ¶ 16. But no

medical or surgical treatment is recommended or provided to *prepubertal* children. And this case is about the coverage for medical treatment for gender dysphoria. Dr. Kaliebe's (unsupported) opinions about "spontaneous desistance" are thus irrelevant to this case.[9]

B. Dr. Kaliebe's opinions about supposed controversies in other countries are irrelevant.

Likewise, Dr. Kaliebe's opinions about "controversies" regarding the provision of medical treatment for gender dysphoria in other countries, such as Finland, Sweden, and the United Kingdom, are both misleading and wholly irrelevant. *See*, *e.g.*, Ex. A, at ¶¶ 49-60, 160, 161. Dr. Kaliebe failed to disclose that each of these countries *provides and covers* gender-affirming hormonal and surgical treatment for gender dysphoria for adolescents in certain circumstances and adults, without any restriction, whereas Defendants exclude coverage for treatments for both these populations categorically. *See*, *e.g.*, Ex. B, at 100:17-101:2; Ex. L; *see also Brandt*, 47 F.4th at 671; *Eknes-Tucker v. Marshall*, 603 F.Supp.3d 1131, 1146 (M.D. Ala. 2022) ("According to Dr. Cantor, Defendants' own expert witness, no state or country in the entire world has enacted a blanket ban of these medications other than Alabama.").

[9] These opinions are methodologically flawed and unreliable because Dr. Kaliebe cites to no authority and provides no basis for his opinion.

Moreover, each of the reports and reviews of the provision of gender-affirming care in these three countries pertained to medical care for minors and not adults, unlike the Challenged Exclusion. Ex. B, at 100:1-16.

In the end, how care is provided and covered in countries with nationalized health care systems is not relevant to whether coverage of gender-affirming medical care should be provided by Medicaid in Florida.[10]

C. Dr. Kaliebe's musings about the causes of gender dysphoria are irrelevant.

As noted above, Dr. Kaliebe *hypothesizes*, without any evidence, that gender dysphoria *may be* caused by social contagion and social pressure. But whether gender dysphoria is caused by social contagion is both wholly unsupported, as described above, and irrelevant to the case at hand. It is undisputed that gender dysphoria is a recognized medical condition that necessitates treatment. *See*, *e.g.*, Ex. B, at 34:9-11 ("Q. … Would you agree with me that gender dysphoria is a very real condition? A. Yes."); *see also Grimm v. Gloucester Cnty. Sch. Bd.*, 972 F.3d 586, 594-95 (4th Cir. 2020); *Eknes-Tucker*, 603 F.Supp.3d at 1138 ("Gender dysphoria is a clinically diagnosed incongruence between one's gender identity and assigned gender. If untreated, gender dysphoria may cause or lead to anxiety,

[10] For example, in Sweden standards of care are developed through legislation and thus part of a political process. *See* Socialstyrelsen, *About the National Board of Health and Welfare*, https://www.socialstyrelsen.se/en/about-us/ (accessed Apr. 7, 2023) (noting that standards are based on legislation).

depression, eating disorders, substance abuse, self-harm, and suicide." (citations omitted)).

* * *

The opinions expressed by Dr. Kaliebe are insufficiently tied to the facts of this case so that they will aid a factfinder and should be excluded as irrelevant.

IV. Dr. Kaliebe's opinions lack probative value and are therefore inadmissible under Rule 403.

Finally, the Court should exclude Dr. Kaliebe's opinions because their introduction will result in unfair prejudice, confusion of the issues, or in misleading testimony. Fed. R. Evid. 403. Dr. Kaliebe offers no opinions relevant to the issues in this case, and, in any event, the opinions he offers are unfounded, speculative, and unreliable. The testimony would also result in prejudice, as the testimony seeks to sow confusion about the propriety of gender-confirming care based on speculation, irrelevant, misleading, or biased opinions.

CONCLUSION

For the foregoing reasons, the Court should exclude Dr. Kaliebe's report, opinions, and testimony. More specifically, at minimum, the Court should limit Dr. Kaliebe's opinions and testimony solely to those regarding the diagnosis of gender dysphoria in children and adolescents, and otherwise exclude Dr. Kaliebe's report, opinions, and testimony in full.

Dated this 7th day of April 2023.

Respectfully Submitted,

/s/ Omar Gonzalez-Pagan

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LOCAL RULE 7.1(B) CERTIFICATION

The undersigned certifies that he attempted in good faith to resolve the issues raised in this motion through a meaningful conference with Defendants' counsel, including through a meet and confer Zoom conference on April 6, 2023.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan
Counsel for Plaintiffs

LOCAL RULE 7.1(F) WORD COUNT CERTIFICATION

As required by Local Rule 7.1(F), I certify that this Opposition contains 7,948 words.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan
Counsel for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan
Counsel for Plaintiffs

TAB 141

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF
FLORIDA
Tallahassee Division

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION TO EXCLUDE EXPERT TESTIMONY OF STEPHEN B. LEVINE, M.D.

Now come, Plaintiffs, by and through their counsel, and respectfully move this Court to exclude the expert report, opinions, and testimony of Defendants' proposed expert, Stephen B. Levine, M.D., pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403, and 702.

Dr. Levine's opinions should be excluded because (1) many are unhelpful as they are not opposed to the relief Plaintiffs seek and (2) the remaining opinions are unreliable because they are not based on scientifically valid principles, reasoning, and methodology as required under Federal Rule of Evidence 702 and the standards set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and its progeny. His opinions and testimony are likewise inadmissible because any

probative value they may have is substantially outweighed by the danger of unfair prejudice, confusion of the issues, waste of time, undue delay, and needless presentation of cumulative evidence. *See* Fed. R. Evid. 403.

Based on the unhelpfulness and unreliability of Dr. Levine's testimony and opinions, at minimum, the Court should exclude any portions of his expert report, opinions, and testimony that go beyond (1) identifying risks associated with prescribing medication and surgery to adolescents, (2) and criticizing the quality of the research on treatments for gender dysphoria.

A memorandum of law is filed contemporaneously herewith.

Dated this 7th day of April 2023.

Respectfully Submitted,

/s/ Carl S. Charles

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LOCAL RULE 7.1(B) CERTIFICATION

The undersigned certifies that Plaintiffs' counsel attempted in good faith to resolve the issues raised in this motion through a meaningful conference with Defendants' counsel, including through a meet and confer Zoom conference on April 6, 2023.

/s/ Carl S. Charles
Carl S. Charles
Counsel for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ Carl S. Charles
Carl S. Charles
Counsel for Plaintiffs

TAB 145

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
Tallahassee Division

AUGUST DEKKER *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH MAF

PLAINTIFFS' MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE EXPERT TESTIMONY OF STEPHEN B. LEVINE, M.D.

TABLE OF CONTENTS

I. INTRODUCTION

Plaintiffs are transgender Medicaid beneficiaries who have been diagnosed with gender dysphoria. In August 2022, Defendants adopted a rule, Florida Administrative Code 59G-1.050(7) (the "Challenged Exclusion"), prohibiting Medicaid coverage of services for the treatment of gender dysphoria. Defendants adopted the Challenged Exclusion after undergoing a process with a predetermined outcome that concluded that the provision of medical treatment for the treatment of gender dysphoria, including puberty blockers, hormone therapy, and surgery, "do not conform to GAPMS [("generally accepted professional medical standards")] and are experimental and investigational." Defendants thus deny equal treatment to Plaintiffs based on sex because they are transgender.

In response, Defendants have put forward an expert, Dr. Stephen Levine, a psychiatrist, whose opinions other federal courts have significantly narrowed, excluded in part, and in one case, dismissed altogether. The same is true here. Dr. Levine's opinions should be excluded because (1) many are unhelpful because they are not opposed to the relief Plaintiffs seek and (2) the remaining opinions are unreliable because they are not based on scientifically valid principles, reasoning, and methodology. The Court should therefore, with narrow exception, exclude Dr.

Levine's opinions.[1]

II. LEGAL STANDARD

The admission of expert testimony is governed by Federal Rule of Evidence 702, as explained by *Daubert* [v. *Merrell Dow Pharm*., *Inc*., 509 U.S. 579, 597 (1993)] and its progeny." *Rink* v. *Cheminova*, Inc., 400 F.3d 1286, 1291 (11th Cir. 2005). "District courts are [thus] charged with [a] gatekeeping function." *Id*.; see also *United States* v. *Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) ("The importance of *Daubert*'s gatekeeping requirement cannot be overstated."). In conducting their gatekeeping function, courts must "engage in a rigorous three-part inquiry and determine whether:

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in *Daubert*; and (3) the testimony assists the trier of fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

Frazier, at 1260; *see also City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d 548, 562 (11th Cir. 1998), *cert. denied*, 528 U.S. 812 (1999). The Eleventh Circuit refers to these three considerations separately as "qualification," "reliability," and "helpfulness" and has emphasized that they are "distinct concepts that courts and

[1] Excerpts of the Expert Disclosure of Stephen B. Levine, M.D., signed February 16, 2023, is attached as Exhibit A to the concurrently filed Declaration of Carl S. Charles ("Charles Decl.")

litigants must take care not to conflate." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). "The party offering the expert has the burden of satisfying each of these three elements by a preponderance of the evidence." *Rink*, 400 F.3d at 1292.

To be sure, "[i]mplementing Rule 702, *Daubert* requires district courts to ensure that any and all scientific testimony or evidence admitted is both relevant and reliable." *Claire v. Fla. Dep't of Mgmt. Servs.*, 2021 WL 5982330, at *1 (N.D. Fla. Oct. 20, 2021). "[T]he trial judge must determine [this] ***at the outset***." *Daubert*, 509 U.S. at 592 (emphasis added). The court's gatekeeping role and the test for admissibility of expert testimony are applicable even at a bench trial or at the summary judgment stage. *See*, *e.g.*, *Rink v. Cheminova*, 400 F.3d 1286 (11th Cir.) (granting motions to exclude in the context of summary judgment); *Kadel v. Folwell*, 2022 WL 3226731, at **5-17 (M.D.N.C. Aug. 10, 2022) (same); *Lo v. United States*, 2022 WL 1014902, at *12 (W.D. Wash. Apr. 5, 2022) (excluding unqualified expert evidence in the context of a bench trial); *cf. UGI Sunbury*, 949 F.3d at 833 (holding the district court abused its discretion in a bench trial when it "ignored rule [702]'s clear mandate" by "sidestepping Rule 702 altogether and declining to perform any assessment of [expert]'s testimony before trial").

It is axiomatic that "[a] witness may be qualified as an expert by virtue of his 'knowledge, skill, experience, training, or education." *Quiet Technology DC-8, Inc.*,

326 F.3d at 1342. However, credentials are not dispositive when determining qualification. In conducting the *Daubert* inquiry, each of the three analytical prongs is assessed in reference to the matter to which the expert seeks to testify—i.e., "to the task at hand." *Daubert*, 509 U.S. at 597. It is for that reason that "expertise in one field does not qualify a witness to testify about others." *Lebron v. Sec'y of Fla. Dep't of Children & Families*, 772 F.3d 1352, 1368 (11th Cir. 2014) (holding that a psychiatrist was properly prevented from opining on rates of drug use in an economically vulnerable population because he had never conducted research on the subject, and instead relied on studies to form his opinion). If a proposed expert witness does not "propose to testify about matters growing naturally and directly out of research he had conducted independent of the litigation," such an expert should be disqualified. *Lebron*, 772 F.3d at 1369 (quoting Fed. R. Evid. 702 (cleaned up)).

An expert's testimony should only be admitted if it is sufficiently reliable. "To meet the reliability requirement, an expert's opinion must be based on scientifically valid principles, reasoning, and methodology that are properly applied to the facts at issue." *In re 3M Combat Arms Earplug Products Liab. Litig.*, 3:19MD2885, 2022 WL 1262203, at *1 (N.D. Fla. Apr. 28, 2022). The requirement of reliability found in Rule 702 is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). In making this determination the court can consider a variety of factors, including whether the

purported expert's theory has been tested, whether it has been subjected to peer review and publication, and whether the theory has been generally accepted in the scientific community. *See Daubert*, 509 U.S. at 593-94; *Rink*, 400 F.3d at 1291-92.[2] To be reliable the expert's testimony must always be based on "good grounds." *Daubert,* 509 U.S. at 590. Moreover, *Daubert* requires that reliable expert testimony be more than scientifically unsupported "leaps of faith." *Rider* v. *Sandoz Pharm. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002).

To satisfy the helpfulness requirement, the testimony must have a justified scientific relationship to the facts at issue. *Daubert*, 509 U.S. at 591. Thus, helpfulness, "goes primarily to relevance." *Id.* at 580. Relevant expert testimony "logically advances a material aspect of the proposing party's case" and "fits" the disputed facts. *McDowell v. Brown*, 392 F.3d 1283, 1298-99 (11th Cir. 2004). "The relationship must be an appropriate 'fit' with respect to the offered opinion and the facts of the case." *Id.* Expert testimony does not "fit" when there is "too great an analytical gap" between the facts and the opinion offered. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 147 (1997) (offering animal studies showing one type of cancer in mice to establish causation of another type of cancer in humans is "simply too great

[2] Other factors that may be relevant include (1) the nature of the field of claimed expertise, (2) the source of the expert's knowledge, (3) the expert's level of care in using the knowledge, and (4) the expert's consideration of alternative hypotheses. *Hendrix*, 255 F.R.D. at 578-79.

an analytical gap between the data and the opinion offered"); *Boca Raton Cmty. Hosp., Inc. v. Tenet Health Care Corp.*, 582 F.3d 1227, 1232 (11th Cir.2009) ("if an expert opinion does not have a 'valid scientific connection to the pertinent inquiry' it should be excluded because there is no 'fit.'").

Finally, because of the potentially misleading effect of expert evidence, *see Daubert*, 509 U.S. at 595, expert opinions that otherwise meet admissibility requirements may still be excluded under Fed. R. Evid. 403. Exclusion under Rule 403 is appropriate if the testimony is cumulative or needlessly time consuming. *See, e.g., Hull v. Merck & Co., Inc.*, 758 F.2d 1474, 1477 (11th Cir.1985) (admission of speculative and "potentially confusing testimony is at odds with the purposes of expert testimony as envisioned in Fed. R. Evid. 702"); *Tran v. Toyota Motor Corp.*, 420 F.3d 1310, 1316 (11th Cir. 2005) (affirming exclusion of expert testimony as cumulative). Consequently, because "[e]xpert evidence can be both powerful and quite misleading because of the difficulty in evaluating it…[T]he judge in weighing possible prejudice against probative force under Rule 403…exercises *more* control over experts than over lay witnesses." *Daubert,* 509 U.S. at 595 (cleaned up) (emphasis added).

III. ARGUMENT

As noted above, other federal courts have narrowed, excluded, and in one case, entirely dismissed Dr. Levine's opinions about transgender people and the

treatment of gender dysphoria.[3] This began several years ago with district court's holding in *Norsworthy v. Beard*, that "the Court gives very little weight to the opinions of Levine, whose report misrepresents the Standards of Care; overwhelmingly relies on generalizations about gender dysphoric prisoners, rather than an individualized assessment of Norsworthy; contains illogical inferences; and admittedly includes references to a fabricated anecdote." 87 F. Supp. 3d 1164, 1188 (N.D. Cal. 2015). This holding was echoed in *Edmo v. Idaho Dep't of Corr.*, 358 F. Supp. 3d 1103, 1125-1126 (D. Idaho 2018) (holding that Dr. Levine "is considered an outlier in the field of gender dysphoria" and gave "virtually no weight" to his opinions), *vacated in part on other grounds sub nom. in Edmo v. Corizon, Inc.*, 935 F.3d 757 (9th Cir. 2019). Dr. Levine's opinions were likewise excluded in *Hecox v. Little,* where the Court dismissed his opinion that "gender-affirming policies … are … harmful to transgender individuals," and instead "accept[ed] Plaintiffs' evidence regarding the harm forcing transgender individuals to deny their gender identity can cause." 479 F. Supp. 3d 930, 977 n.33 (D. Idaho 2020).

Of most relevance to this case, several of Dr. Levine's proposed opinions were

[3] Because of the numerical limitation on the parties depositions, Plaintiffs opted not to depose Dr. Levine and instead rely on his prior deposition and trial testimony in cases similar to this one, where his expert reports and proffered opinions have been nearly identical to his report submitted here. *See Brandt et al.*, v. *Rutledge et al*. No. 4:21-cv-00450-JM (E.D. Ark., 2022); *Fain et al.*, v. *Crouch et al.*, No. CV 3:20-0740, 2022 WL 3051015 (S.D.W. Va. Aug. 2, 2022); *Kadel et al.,* v. *Folwell et al.*, No. 1:19CV272, 2022 WL 3226731 (M.D.N.C. Aug. 10, 2022).

excluded based on irrelevance and unreliable methodology by the U.S. District Court for the Middle District of North Carolina in *Kadel* v. *Folwell*, No. 1:19CV272, 2022 WL 3226731 (M.D.N.C. Aug. 10, 2022). Judge Loretta C. Biggs granted in part a motion to exclude Dr. Levine's testimony, noting that he would be limited to offering opinions primarily to the following matters: (1) identifying risks associated with prescribing medication and surgery to adolescents, (2) and criticizing the quality of the research on treatments for gender dysphoria.[4] At a minimum, Dr. Levine's proposed opinions in this matter should be so limited as well, with his remaining testimony, opinions and content of reports otherwise excluded.

A. Many Of Dr. Levine's Opinions Will Not Help the Trier of Fact Because They Support Plaintiffs' Position.

Many of Dr. Levine's opinions do not "logically advance a material aspect *of the proposing party's case*" and do not "fit" the disputed facts because his proposed opinions do not oppose the relief Plaintiffs seek. *McDowell v. Brown*, 392 F.3d 1283, 1298-99 (11th Cir. 2004) (emphasis added). For that reason, Dr. Levine's opinions "fit" with the facts relevant to resolving this matter in favor of Plaintiffs' claims, not those of Defendants. *Id*. And even though several of Dr. Levine's opinions, and the clinical experience upon which they are based, do not stand in opposition to the relief

[4] The court in *Kadel* also found that Dr. Levine was permitted to testify as to his opinions of WPATH but for the reasons stated herein, infra, this Court should not so permit.

Plaintiffs seek, many do, and admitting this unreliable and unhelpful testimony wholesale would not meet the standard set forth by *Daubert* and its progeny.

Significantly, several of Dr. Levine's proposed opinions regarding gender-affirming medical care, and his clinical experience upon which those opinions are based, are not contrary to the relief Plaintiffs seek in this case: that Florida Medicaid beneficiaries diagnosed with gender dysphoria receive appropriate medical care. Charles Decl., Ex. A at ¶6. On November 28, 2022, Dr. Levine testified at length about his proposed opinions regarding gender-affirming care at the bench trial in *Brandt* v. *Rutledge,* No. 4:21-cv-00450-JM (E.D. Ark., 2022).[5] There, as here, Dr. Levine was Defendants' only expert witness to have ever treated patients for gender dysphoria, and he testified that removing gender affirming medical care from patients currently receiving it would have "shocking and devastating" psychological consequences. Charles Decl. Ex. B at 912:3-19. Dr. Levine testified there, as he does in his report in this matter, that "there is no evidence beyond anecdotal reports that psychotherapy can enable a return to male identification for genetically male boys, adolescents, and men, or return to female identification for genetically female girls, adolescents, and women." Charles Decl., Ex. A at ¶49; Charles Decl., Ex. B at 920:18-24. And to be sure, "broad opinions [that] are based solely on … anecdotal accounts, and speculation … are not reliable." *In re 3M Combat Arms Earplug Prod.*

[5] The Plaintiffs in *Brandt* did move to exclude or limit Dr. Levine's testimony.

Liab. Litig., 2021 WL 684183, at *3. Dr. Levine also testified that reliance on self-report from the patients and information from parents is not unique to the diagnosis of gender dysphoria and is "ideally" how psychiatry works. Charles Decl. Ex. B at 894:24-895:6. He also testified that the use of medications to treat gender dysphoria is off-label—meaning not FDA approved for this specific indication—does not mean the drugs are experimental. Charles Decl. Ex B. at 930:14-17. And while Dr. Levine agreed that the "overwhelming majority" of his patients have been adults, he testified that he has written letters of authorization for hormone therapy for some patients under 18 and, going forward, would consider doing so on a case-by-case basis. Charles Decl. Ex. B at 886:13-18, 897:1-898:18, 900:21-902:15, 902:25-903:6.

Similarly, in *Fain* v. *Crouch*, No. CV 3:20-0740, 2022 WL 3051015 (S.D.W. Va. Aug. 2, 2022), where plaintiffs challenged a Medicaid coverage restriction of gender-affirming care in West Virginia, similar to the one at issue in this case, Dr. Levine testified at deposition that in the previous seven months he had provided several letters of approval for gender-affirming surgeries for transgender people incarcerated at Framingham, a correctional institution in Massachusetts. Charles Decl. Ex. C at 84:4-85:4. Dr. Levine has also previously testified that he has written similar letters for gender-affirming hormones and surgery in accordance with the medical community's widely accepted and authoritative guidance for transgender care, World Professional Association of Transgender Health ("WPATH") Standards

of Care ("SOC"). Charles Decl., Ex. C. at 139:14-19; Ex. D at 55:13-17; 56:2-5; 112:16-21; 176:8-16; Ex. E at 1-90:15-22. He also testified that he does not provide such letters unless he has sufficiently informed his patients of possible risks and received a reasonable assurance that they understand. Charles Decl., Ex. D at 176: 8-16; 225:24-226:17. For almost 50 years, Dr. Levine's clinical practice has generally adhered to the WPATH SOC. Charles Decl. Ex. C at 136:8-11. And, as WPATH's former Chairman of the SOC Committee, Dr. Levine helped to write Version 5 of the SOC, recognized his own writing in Version 7, and asked if he could help draft the recently published Version 8. Charles Decl., Ex. A at ¶5; Ex. C at 147:12-149:18. He testified at deposition in *Fain*, and under oath previously, that he "is not advocating denying endocrine treatment or surgical treatment" to transgender people, a position he described as "draconian."[6]

Finally, Dr. Levine testified at deposition in *Fain* and that he was not offering

[6] Charles Decl., Ex. C at 88:10-13; Ex. D at 73:4-7 ("Q: Is the worrisomeness about a patient's future health, is that a reason to ban all medical care for gender dysphoria? A: Absolutely not."); 84:21-85:1 ("Q: Given all those concerns you have, is that a reason to deny all medical interventions to people with gender dysphoria? A: No …."); 85:4-11 ("Q: Are those concerns you raised justifications in your mind for denying medical interventions to people who have gender dysphoria? A: You know, I'm not advocating denying endocrine treatment or surgical treatment."); 152:1-6 ("Q: Do you think because that study showed that some people committed suicide after gender affirming surgery that no patient should be able to access gender affirming surgery? A: That would be illogical"); 154:3-5 ("Q: But you're not recommending total bans on gender affirming surgery? A: I'm not recommending total bans."); 160:23-25 ("I did not say that gender affirming treatment in general should be stopped. I've never said that.").

any opinions about whether Defendants should have an exclusion in their Medicaid program for coverage of gender-affirming medical care. Charles Decl. Ex. C at 86:25-87:19. He also testified that he does not feel his "expertise extends to how the insurance industry works and how governments and legislatives work," nor "does he consider himself an expert" on whether the West Virginia Medicaid exclusion should exist. Charles Decl., Ex. C at 87:14-22. Nevertheless, Dr. Levine has testified that he is "an agent of the patient, I want what's best for the patient, and especially if the patient couldn't otherwise afford it, I would wish for my patient to have it, yes." Charles Decl., Ex. F at 157:7.

At bottom, Dr. Levine has repeatedly and consistently testified in federal court that he does not support banning the provision or coverage of gender-affirming medical care, that for 50 years he has and continues to provide letters of authorization for gender affirming medical treatments for adult and minor patients, and that he is not an expert about insurance coverage of gender-affirming medical care. *See* e.g. Charles Decl., Ex. D at 86:1-8. Many of his opinions do not "logically advance a material aspect *of the proposing party's case*," do not "fit" the disputed facts, and will ultimately not assist the trier of fact because his proposed opinions do not oppose the relief Plaintiffs seek. *McDowell*, 392 F.3d at 1298-99 (emphasis added).

B. Dr. Levine's Opinions That Do Not Support Plaintiffs' Position Are Methodologically Unreliable and Scientifically Unsupported.

An expert's opinion should only be admitted if it is based on scientifically

valid methodology that is properly applied to the facts. *In re 3M*, 2022 WL 1262203, *at *1*. Dr. Levine's opinions fall far short of the reliability standard, a reality he has admitted to as recently as November 2022. Dr. Levine admits in his report submitted here, at trial in *Brandt*, and at deposition in *Fain* and other recent cases, that theories upon which he relies lack *any* scientific support and have not been tested or subjected to peer review or publication. Charles Decl., Ex. A at ¶49; Ex. B 797:8-19, 887:19-888:25, 921:21-922:7, 924:12-25, 949:24-954:22; Ex. C at 140:12-143:2, 145:19-25; Ex. D at 109:20-25; 116:4-7, 122:8-124:22, 200:11-201:25.

Even putting that aside, although Dr. Levine claims many times that his "experience" is sufficient foundation for his opinions, he fails to address how this purported experience leads to his conclusions and how such experience is reliably applied to the facts here. Afterall, "At this stage, the court must undertake an independent analysis of each step in the logic leading to the expert's conclusions; if the analysis is deemed unreliable at any step the expert's entire opinion must be excluded." *Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009), *aff'd sub nom. Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183 (11th Cir. 2010).

1. Dr. Levine's Assertion that the WPATH SOC Version 8 Is Not the Widely Accepted and Authoritative Protocol for the Treatment of Gender Dysphoria Is Misleading and Unreliable Because It Is Demonstrably False.

Chief among Dr. Levine's many unreliable opinions is his assertion that the

widely-accepted and utilized WPATH SOC are not widely-accepted and considered to be authoritative treatment protocols for gender dysphoria. Contradicting himself, Dr. Levine has repeatedly testified that he generally adheres to the WPATH SOC in his own clinical practice. Charles Decl., Ex. C at 136:8-11; Ex. D at 55:13-17; 56:2-5; 112:16-21; 176:8-16; 225:24-226:17; Ex. F at 29:10-18; 37:2-13; 47:22-49:3; 103:11-19. Nevertheless, Dr. Levine's attempt to undermine the WPATH SOC fail because he lacks evidence to support his assertions, contradicts his assertions with other binding testimony, misrepresents sources in his report, and fails to include relevant information that is contrary to his assertion—ultimately undermining the reliability and overall admissibility of his opinions.

First, Dr. Levine alleges that "reviews" of the 7th Version of the SOC ("SOC 7") "published in 2021 by Dahlen et al [sic] and Sapir in 2022 have clarified the low reliability and bias inherent in its recommendations. (Dahlen et al 2022)." The Dahlen et al. 2021 article does not characterize the SOC 7 as having "low reliability" or "inherent bias." Charles Decl., Ex. A at ¶69; Ex. G. The article does state that the SOC 7 are due for an update and acknowledges that evaluations of clinical practice guidelines in other medical areas including cancer, diabetes, pregnancy, and depression "tend to show room for improvement," and that "finding poor quality CPGs is not confined to this area of healthcare." Charles Decl., Ex. G at 8. Again, without evidence, Dr. Levine claims the 8th Version of the SOC ("SOC 8") has "not

gained additional confidence in its scientific merit." Charles Decl., Ex. A ¶69. He also claims that the presence of transgender participants at WPATH meetings "makes it difficult for professionals to raise their concerns." Charles Decl., Ex. A ¶69. But Dr. Levine admits he has not been a member of WPATH for more than 20 years and does not provide evidence to support these claims. *Id*. at ¶66.[7] The reality is that no one, not transgender people or other health professionals (whether transgender or cisgender), are preventing Dr. Levine from "raising his concerns." As Dr. Levine testified, he presented alongside other panelists with dissenting views, without interruption, at an American Psychiatric Association conference in 2022. Charles Decl., Ex. B at 925:16-926:23, 927:10-17.

Second, Dr. Levine makes inaccurate statements about other countries' treatment protocols for gender dysphoria in youth to support his claim that "opinions

[7] Dr. Levine claims in his report that "Two groups of individuals that I regularly work with have attended recent and separate WPATH continuing education sessions. There, questions about alternative approaches were quickly dismissed with 'There are none. This is how it is done.'" Charles Decl. Ex. A at ¶68. But Dr. Levine fails to name these groups he works with, the people who attended the WPATH sessions, the dates, times and other identifying information about the alleged sessions, or the people who supposedly "quickly dismissed" questions. This assertion is mere conjecture, and methodologically unreliable. Not only is such "reliance on anecdotal evidence" a "red flag[] that caution[s] against certifying an expert," *Newell Rubbermaid, Inc. v. Raymond Corp.*, 676 F.3d 521, 527 (6th Cir. 2012), but the Court should not countenance Dr. Levine testifying "based on limited personal accounts and information relayed to [him] by an unspecified number of third parties," as doing so "would be to sanction [his] use as a vehicle for introducing hearsay testimony." *In re 3M Combat Arms Earplug Prod. Liab. Litig.*, 2021 WL 684183, at *2.

and practices vary widely with respect to puberty blockers and hormones" and as evidence that the WPATH SOC 8 are not authoritative. Charles Decl., Ex. A at ¶82. However, Dr. Levine admitted in his *Brandt* trial testimony that in Finland, gender affirming medical care is provided to adolescents with gender dysphoria when indicated under their guidelines. Charles Decl., Ex. B at 938:16-939:3. He also testified that France does not have a prohibition on minors receiving gender affirming medical care, nor does Canada. Charles Decl., Ex. B at 939:23-940:9, 944:2-5. And Dr. Levine conceded he does not know how the provision of gender affirming care for minors works in Sweden but agreed that the Swedish National Board of Health stated puberty blockers and cross sex hormones may be given in exceptional cases in accordance with their guidelines criteria. Charles Decl., Ex. B at 960:1-17, 961:11-962:1. Dr. Levine has admitted these facts when asked at deposition in *Fain*. Ex. C at 106:4-108:8. Dr. Levine also acknowledged that the United Kingdom's Cass Review, which is still underway and not final, begins from the premise that some youth experience gender dysphoria and will need clinical support and medical interventions and that such care is not prohibited in their health system. Charles Decl., Ex H; Ex. C at 191:20-192:16.

Dr. Levine's own testimony at trial and at deposition contradict the opinions offered by his expert report here, which underscores serious flaws in his methodology and demonstrates that his opinions about the WPATH SOC do not

meet the reliability burden under *Daubert* or related standards for admissibility of expert testimony.

2. Dr. Levine's Opinions That Gender-Affirming Medical Care Is Experimental, Is Provided Without Mental Health Assessments or Sufficiently Informed Consent and Is Without Lasting Benefit are Inaccurate and Unsupported.

Dr. Levine opines that gender-affirming medical care is experimental, is provided without mental health assessments or sufficiently informed consent and is without lasting benefit. Charles Decl., Ex. A at VIII, X, ¶73, ¶176. But Dr. Levine has, and continues to, write letters authorizing gender affirming medical care for his patients, including for hormone therapy for some patients under 18 and, going forward, would consider doing so on a case-by-case basis. Charles Decl., Ex. B at 897:1-898:18, 900:21-902:15, 902:25-903:6. The *Kadel* court cites to an opinion that Dr. Levine has identically asserted here: that it is impossible "to make a single, categorical statement about the proper treatment of children presenting with gender dysphoria or other gender-related issues." Charles Decl., Ex. A at ¶61. As a result, the *Kadel* court observed, "Notably, Levine does not testify that medical or surgical care for gender dysphoria is categorically inappropriate." *Kadel*, 2022 WL 322673, at *15. And when asked if based on his publication from March 2022 "Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults," he claimed that "gender affirming medical care, specifically hormone therapy or

blockers or surgeries, should be categorically prohibited for minors," he replied "No, I don't." Charles Decl., Ex. B at 905:11-16. Dr. Levine is "not motivated to prohibit care." *Id*. at 906:11-14.

Dr. Levine asserts repeatedly that gender-affirming medical care is provided by doctors who encourage patients to identify as transgender and provide hormones without assessing patients and addressing other mental health conditions or without informing patients and their parents of the risks and limitations of the evidence regarding treatments. Charles Decl. Ex. A at ¶¶50, 64, 74, 83. As an initial matter, Dr. Levine admits in his report that he cannot confirm if any practitioners engage in this "affirmation care/therapy model" he describes. Charles Decl. Ex. A at ¶53. And he confirmed his lack of support for this assertion during his testimony in *Brandt*, when on cross-examination, he admitted that he does not know how common it is for doctors to provide care the way he described, which is contrary to WPATH SOC 8 and Endocrine Society clinical guideline, both of which require comprehensive psychological assessments prior to initiation of any medical treatment for adolescents. Charles Decl., Ex. B at 887:19-888:21, 890:24, 933:2-7; Charles Decl. Ex. I at 3870, 3876-3878; Charles Decl., Ex. J at S48-51.

Finally, the *Kadel* court also recognized that Dr. Levine's assertions that healthcare providers are prescribing treatment without due caution or informed consent were not admissible:

> Fourth, as discussed, it does not appear that he offers any categorical opinion as to the medical necessity of medical and surgical treatments of gender dysphoria, nor does he testify that healthcare providers are prescribing such treatment without due caution and informed consent beyond his anecdotal "experience." To the extent that Defendants seek to introduce testimony from Levine to that effect, he has not provided the Court with any data or methodology from which such claims could be made. Levine has conducted no research to identify which physicians are proceeding as he does, and which do not, rendering any broader opinion about the practice of such healthcare providers pure speculation.

Kadel, 2022 WL 322673, at *17. This is no less true here.

Dr. Levine's opinions that gender-affirming medical care is without lasting benefit also fail the reliability test because he ignores studies contrary to his personal belief or distorts studies' findings beyond the authors' explicit intentions, conclusion, or study design. Significantly, he omits recent studies demonstrating that medical treatments for transgender adolescents and adults have favorable outcomes across many measures. Charles Decl., Ex. K at ¶55. A plethora of studies show that transgender people experience pervasive stigma and discrimination, resulting in health disparities. But Dr. Levine omits any reference to that evidence and instead suggests that "long-term life in a transgender identity, however, correlates with very high rates of completed suicide," and goes on to discuss four studies that reviewed the rate of suicide among transgender adults who received gender-affirming medical care. Charles Decl., Ex. A at ¶¶166-171. While Dr. Levine admits, as he must, that "None of the studies demonstrated the hormonal or surgical intervention *caused* [sic]

suicide," he goes on in the same paragraph to assert a different unsupported conclusion, that "what these studies demonstrate" is that transgender people "are in need of extensive psychological care they don't receive," and that "neither hormonal nor surgical transition and 'affirmation' resolve their underlying problems and put them on the path to a stable and healthy life." *Id*. at ¶172. This is unreliable methodology at its finest. First, none of the four studies purport to analyze the efficacy of "hormonal or surgical transition," or whether gender-affirming medical care "resolves underlying problems" or "puts [people] on a path to a stable and healthy life." As least one of the studies' authors, Cecilia Dhejne, has explicitly said as much, both in the study itself (it is not designed to "address whether sex reassignment is an effective treatment or not.") and in direct response to Dr. Levine's misuse of her work. Charles Decl., Ex. L at 2; Charles Decl., Ex. M at 65. Another major flaw in Dr. Levine's methodology is that three of the studies' control groups were comprised of the general Dutch population, not of other transgender people with gender dysphoria who did not receiving any gender-affirming medical care. In other words, it is comparing apples to oranges. But Dr. Levine has acknowledged that the Dhejne study does not lend the study to be used to draw any conclusions about the efficacy of gender-affirming care. Charles Decl., Ex. D at 156:7-11. Finally, Dr. Levine's description of the Hall et al. 2021 study obscures the study's actual rate of suicide for the cohort by, without explanation but presumably to

support his description of a "rather shocking result," focusing on the number of transgender women in the group who died by suicide, rather than the total number of deaths by suicide for the entire cohort—which was 3 out of 175 participants, or 1.7%. Charles Decl., Ex. A at ¶171.

Furthermore, as the *Kadel* court observed, Dr. Levine himself has conceded that:

> he does not know how often medical or surgical care helps alleviate symptoms of gender dysphoria and does not offer an opinion as to the portion of these procedures that are necessary and unnecessary. (*Id.* at 67:24–68:3 ("It is not our [clinic's] knowledge base to know who's going to do better and who's going to do worse and who is not going to have any difference at all with hormones or with surgery.").)

Kadel, 2022 WL 322673, at *15.

Ultimately, Dr. Levine fails to cite any literature or clinical experience of his own to support this opinion, and regardless, he has testified that studies like these should not prevent youth and adults with gender dysphoria from receiving gender affirming care. When asked recently if he believes that because a study showed that some people committed suicide *no patient* should be able to access gender-affirming surgery, Dr. Levine responded, "that would be illogical." Charles Decl., Ex. D at 151:25-152:6. And when asked if his concerns justify denying medical interventions to all people with gender dysphoria, he responded "I'm not advocating denying endocrine treatment or surgical treatment." *Id.* at 85:4-11.

At bottom, Dr. Levine's report and the opinions contained therein are wildly

inconsistent with his oral testimony, making both unreliable.

3. Dr. Levine's Opinions About Gender Dysphoria "Naturally Resolving" in Children and Adolescents Are Not Based In Fact.

Another unreliable opinion presented by Dr. Levine is that "the large majority" of *prepubertal* children diagnosed with gender dysphoria will, absent intervention, cease to be transgender (or "desist") through puberty. Charles Decl., Ex. A at ¶¶109-111, 113-114. Putting aside that Dr. Levine has almost no clinical experience with children during his 50-year career treating patients with gender dysphoria to support this opinion, it is unreliable and methodologically unsound for other reasons.

First, Dr. Levine has conceded that some children are and will continue to be transgender and that as they progress into adolescence and adulthood, they would need medical care that he has, and would, authorize. Charles Decl., Ex. D. at 173:7-15, 137:14-23, 173:22-174:5, 53:2-10. Second, as the scholarly basis for this opinion, Dr. Levine cites three articles that share the same core characteristic that reveals the methodological flaw in Dr. Levine's analysis: they rely on previous studies whose underlying data included gender non-conforming children who never identified as a sex different from their birth-assigned sex in the first place. In other words, they included children who were never transgender. That is because the diagnosis at the time these studies were conducted— "Gender Identity Disorder in

Children" —did not include a cross-gender identification or clinically significant distress requirement for the diagnosis. *See*, *e.g.*, Diagnostic Statistical Manuals ("DSM") III, III-R, IV, and IV-R. Under these outdated diagnostic criteria, most of the children diagnosed with "Gender Identity Disorder in Children" were not actually transgender but were gender non-conforming boys who grew up to be gay or bisexual. Because the years of initial visits in the study samples were from 1952-2008, none of these children were diagnosed under the current, and relevant to the case at hand, diagnostic criteria for "Gender Dysphoria in Children," in the DSM 5, published in 2013, which requires for diagnosis "a strong desire to be of the other gender or an insistence that one is the other sex" and "clinically significant distress or impairment in social, school, or other important areas of functioning."[8] Charles Decl., Ex. N at 452. Dr. Levine confirmed this fact as to these and others of the "11 studies," at his deposition in *Fain*. Charles Decl., Ex. C at 221:2-229:14. Therefore, the "desistance rates" from the studies upon which Dr. Levine bases his opinion reflect children who, while they exhibited gender non-conforming behaviors, were

[8] Based on Dr. Levine's failure to identify at deposition in *Kadel* any of the underlying "11 studies" upon which this opinion is based, the court found his methodology to be unreliable and therefore inadmissible: "Levine's testimony regarding desistance rates does not appear to be based on reliable methodology. During deposition, Levine was unable to recall many of the studies that purportedly support his conclusion. (ECF No. 213-3 at 191:20-192:14.)" *Kadel*, 2022 WL 322673, at *16.

not transgender, or suffering from gender dysphoria.

4. Dr. Levine's Assertion that "Rapid Onset Gender Dysphoria," as a Cause of Gender Dysphoria or the Concept of "Detransition" Justifies Denying Treatment to Florida Medicaid Beneficiaries Is Unsupported By Scientific Evidence.

A stark example of one of Dr. Levine's opinions failing to meet methodological reliability is the assertion that "rapid onset gender dysphoria" is a credible phenomenon caused by "social influences through friend groups or through the internet." Charles Decl., Ex. A at II(1)(f), ¶38, ¶96, ¶114. Dr. Levine admitted at the *Brandt* trial, just six months ago, that such a conclusion is based on speculation, not science. Ex. B at 797:8-19. Furthermore, "rapid onset gender dysphoria" ("ROGD") is a scientifically unsupported hypothesis and the only article Dr. Levine routinely cites or discusses regarding ROGD was withdrawn and republished with a significant correction. Dr. Levine testified at deposition in *Kadel* he had not read the correction. Charles Decl., Ex. D at 116:22-117:9. Had he done so, Dr. Levine would be forced to acknowledge the correction's explicit disclaimers that "rapid onset gender dysphoria is not a formal mental health diagnosis," "the report did not collect data from adolescents and young adults or clinicians and therefore does not validate the phenomenon," and "the use of the term, 'rapid onset gender dysphoria' should be used cautiously by clinicians and parents to describe youth." Charles Decl., Ex. O at 1. Despite this, at deposition in *Fain*, Dr. Levine attempted to conflate an

increased number of transgender young people presenting to clinics for care with the theory of "rapid onset gender dysphoria" and asserted, without evidence, it is not a hypothesis but "a fact," that he "assumes everyone understands [this] is true." Charles Decl. Ex. C at 151:18-152:6, 152:22-153:5. When pressed to provide peer-reviewed articles, sources, or studies as scientific support he referenced presentations without title or date, admitted he could not remember the names of "authors from Europe" but asserted it had been documented by "DiAngelo and Clayton in Australia." To date, the only peer-reviewed study that interrogates this hypothesis using adolescent clinical data "did not support the ROGD hypothesis." Charles Decl., Ex. P at 1.

Similarly, Dr. Levine's opinions that there is "a growing number of detransitioners [sic]," or that the number of detransitioners is "accelerating," are also methodologically unreliable, largely because he lacks any evidence to support this belief. Charles Decl., Ex. A at ¶120. The three papers he cites for support of this assertion, "Entwistle 2020, Littman 2021, and Vandenbussche 2021," are purely descriptive, not statistical, or quantitative studies. These, respectively, include a description of anecdotal experiences of "detransitioners," describe the results of "a survey of 100 detransitioners," and report on responses from an online survey about the needs and support for people who detransition. None of the three articles purports to establish that the rate of detransition is growing or accelerating, a fact

Dr. Levine admitted as to two of the studies at deposition in *Fain*. Charles Decl., Ex. C at 155:8-163:24. Indeed, Dr. Levine's own clinical experience is contrary to this assertion—in 50 years of seeing patients with gender dysphoria, he is aware of only two patients who detransitioned. Charles Decl., Ex. B at 920:25-921:5. Nevertheless, Dr. Levine doubles down in his expert rebuttal report, relying on a reference to a "detransition subreddit" with 16,000 members as evidence that "the assumption that [detransition] was a rare occurrence began to lose traction." Ex. Q at ¶30. When confronted about this so-called evidence at deposition in *Kadel*, Dr. Levine admitted he had no evidence that *even one* of the 16,000 members of the subreddit had actually "detransitioned." Charles Decl., Ex. D at 200:6-201:25. Unsurprisingly, the *Kadel* court found such testimony lacking:

> His anecdotal testimony concerning adults and adolescents who regret their transitions appears to be based on a misreading of an article that reviewed entries on the website Reddit. (See ECF No. 215-1 ¶¶ 35, 56, 98.) He admitted during deposition that the article referred to 16,000 entries—not 60,000, as he repeatedly stated in his report—and that he had no knowledge of the content of those entries or whether any of the authors actually de-transitioned or regret their transitions. (Id. at 196:3-7, 201:12-25).

Kadel, 2022 WL 3226731, at *16.

Similarly, when asked in *Fain* about his opinion that there is "evidence that *a growing number* of young people regret transition and wish to reverse it," Dr. Levine admitted he lacked any scientific support for such an opinion. Charles Decl., Ex. C at 158:8-159:2; 160:25-161:9; 163:9-24. Dr. Levine did not point to his own

experience as a basis for this opinion and conceded three times that the sources he cited in his report did not provide relevant evidence. *Id.*

Given that these hypotheses about "rapid onset gender dysphoria" and ideas about "detransition" are unverified or unsupported, Dr. Levine cannot claim the use of reliable methodology. His reliance on his own *ipse dixit* fails to establish a basis upon which to assert these opinions. Indeed, case law establishes that "broad opinions [that] are based solely on … generalized views, anecdotal accounts, and speculation … are not reliable." *In re 3M Combat Arms Earplug Prod. Liab. Litig.*, 2021 WL 684183, at *3 (N.D. Fla. Feb. 11, 2021). And that opinions "based on mere conjecture, assumption, credibility calls, and amounting to no more than ipse dixit" are "neither reliable nor helpful." *Day v. Edenfield*, 2022 WL 972430, at *10 (N.D. Fla. Mar. 31, 2022).

C. Dr. Levine Is Not Qualified To Offer Opinions About Puberty-Delaying Treatment or the Treatment of Prepubertal Children Generally.

Dr. Levine has repeatedly admitted, most recently at the *Brandt* trial six months ago, and at depositions for the last several years, that he has virtually no experience administering psychiatric treatment to prepubertal children and no experience performing research or publishing studies about them. Charles Decl., Ex. A at ¶5; Ex. B at 887:5-8; Ex. C at 26:10-13; Ex. D at 23:1-8. When asked whether he has treated any children with gender dysphoria, he admitted, "I have only on rare

occasion personally treated or directly or indirectly treated a child." Charles Decl. Ex. C at 28:23-29:6; 62:6-14. Dr. Levine also confirmed his testimony from March 30, 2022, that over the course of his nearly 50-year career, he had only seen an estimated six prepubertal children, and not for more than one visit. Charles Decl., Ex. B at 887:5-8; Ex. R at 87:1-7. When asked if he had helped to develop guidelines for the treatment of prepubertal children or adolescents with gender identity issues he responded "the answer is no." Charles Decl., Ex. C at 51:10-16. Dr. Levine is not recognized as an expert in providing treatment to prepubertal children by his private employer who by his own admission does not refer children to him as patients, nor by the University Hospitals' LGBTQ and Gender Care Program--the Cleveland hospital affiliated with Case Western Reserve University Medical School where Dr. Levine is a clinical professor—which he previously admitted did not consult with him as part of its formation or their ongoing work. Charles Decl., Ex. R at 113:19-114:4. Nor does he write or research about providing treatment to prepubertal children or deliver any psychiatric care to them in his day-to-day practice.[9]

While lacking a reliable methodology for his proposed opinions about the

[9] Notably, the *Kadel* court held that "Levine's opinions on mental health approaches to social transition are irrelevant as well, as Defendants maintain that the Plan's exclusion of coverage for mental health treatments of gender dysphoria has never been given effect and is no longer part of the Plan. (*See* ECF Nos. 137 n.2; 137-4 ¶ 27.)" *Kadel,* 2022 WL 3226731, at *16. Dr. Levine has also testified that he has counseled some parents to support their minor child's social transition. Charles Decl., Ex. B at 896:23-25.

treatment of prepubertal children, Dr. Levine does not hesitate to offer his personal beliefs about their care. Dr. Levine would "consider banning puberty blocking hormones even for children who have been cross-gender identified for four years to give them a chance to desist." Charles Decl., Ex. D at 186:20-25. But Dr. Levine acknowledges the unscientific nature of this opinion, admitting he does not know where it comes from or "to what extent it's from my politics, or from my being a parent or a doctor, I don't know." Charles Decl., Ex. D at 187:20-24.

In short, given his proposed testimony and experience, Dr. Levine is not qualified under the *Daubert* standards to offer opinions on matters relating to the care of prepubertal children, and he cannot use his personal beliefs as reliable evidence. Nor is any of this testimony relevant. This case concerns coverage of gender-affirming medical care, and no clinical practice guideline recommends the provision of medical treatments, like puberty delaying medications or hormones, until after the onset of puberty.[10]

D. Dr. Levine's Report, Opinions, and Testimony Lack Probative Value and Are Thus Inadmissible Under Federal Rule Of Evidence 403.

Finally, the Court should exclude Dr. Levine's opinions because their

[10] The *Kadel* court also found that Dr. Levine's criticism of medical or surgical treatment of gender dysphoria in prepubescent children was not relevant because "Plaintiffs conceded that such treatments are not medically necessary until the onset of puberty. *See* Section II.B, *supra*." *Kadel*, 2022 WL 322673, at *16.

introduction will result in unfair prejudice, confusion of the issues, or in misleading testimony. Fed. R. Evid. 403. Most of Dr. Levine's opinions are unreliable and unhelpful. The testimony would also result in prejudice, as the testimony seeks to sow confusion about the veracity of Plaintiffs' gender identity, gender dysphoria diagnosis, and treatment they have been undergoing for years—issues unrelated to whether the Florida Medicaid Program can deny coverage of the same kinds of treatments to transgender people that it provides cisgender people.

IV. CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request the Court grant the instant motion and limit Dr. Levine's opinions and testimony, at a minimum, to his opinions (1) identifying risks associated with prescribing medication and surgery to adolescents, and (2) criticizing the quality of the research on treatments for gender dysphoria and that Dr. Levine's report, opinions, and his testimony be otherwise excluded in full.

Dated this 7th day of April 2023.

Respectfully Submitted,

/s/ Carl S. Charles

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CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ Carl S. Charles
Carl S. Charles
Counsel for Plaintiffs

CERTIFICATE OF WORD COUNT

As required by Local Rule 7.1(F), I certify that this Memorandum contains 7,636 words.

/s/ Carl S. Charles
Carl S. Charles
Counsel for Plaintiffs

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

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TAB 175-1

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, et al., *Plaintiffs*, v. JASON WEIDA[1], et al., *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

DEFENDANTS' RESPONSE TO PLAINTIFFS'
FIRST SET OF REQUESTS FOR ADMISSION

Pursuant to Federal Rule of Civil Procedure 36, Defendants Secretary Weida and the Agency for Health Care Administration ("Defendants") submit their response to Plaintiffs' First Set of Requests for Admission.

GENERAL OBJECTIONS

Defendants make the following general objections to Plaintiffs' Requests for Admission, which apply to each request regardless of whether the general objections are expressly incorporated into the specific objections below:

[1] Jason Weida has succeeded Simone Marstiller as Secretary of the Agency for Health Care Administration, as reflected in ECF 78.

Pl. Trial Ex. 001

PLAINTIFFS002191

1. Defendants object to the Requests for Admission to the extent they are overly broad, unduly burdensome, not reasonably calculated to lead to the discovery of admissible evidence, and not proportional to the needs of the case.

2. Defendants object to the Requests for Admission to the extent they seek to elicit information or evidence otherwise protected by the attorney-client privilege, the work-product privilege, the First Amendment associational privilege, the legislative privilege, or any other applicable privilege recognized under federal or Florida law.

3. Defendants object to the Requests for Admission to the extent they seek to elicit information that is in the public domain or already in Plaintiffs' possession, and therefore of no greater burden for Plaintiffs than for the Secretary to obtain.

4. Defendants object to the Requests for Admission to the extent they seek publicly available information, statements, or documents that speak for themselves and require neither an admission nor a denial from any party.

5. Only to the extent that Federal Rule of Civil Procedure 36(a)(4) would be construed as requiring an admission or denial and that an objection alone is not sufficient, the Secretary deny each Request for Admission. Otherwise, Defendants stand on the foregoing General Objections

and the below-stated specific objections without expressly admitting or denying any Request for Admission.

RESPONSES TO REQUESTS FOR ADMISSION

1. Admit that gender-affirming care can be medically necessary.

RESPONSE: Defendants object to the definition of gender-affirming care because it is contrary to the term's ordinary use. Subject to and without waiving such objection, Defendants admit that certain types of behavioral health services to treat gender dysphoria can be medically necessary, but other types of treatment are not.

2. Admit that the Challenged Exclusion prohibits Florida Medicaid coverage of gender affirming care that can be medically necessary for the treatment of Gender Dysphoria.

RESPONSE: Denied insofar as the Challenged Exclusion does not preclude the coverage of behavioral health services for gender dysphoria, and the services for which coverage is precluded are not medically necessary.

3. Admit that each of the Various Services can be medically necessary for the treatment of Gender Dysphoria.

RESPONSE: Denied.

4. Admit that each Plaintiff identifies as transgender.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

5. Admit that each Plaintiff has been diagnosed with Gender Dysphoria.

RESPONSE: Admitted that each Plaintiff has been diagnosed with

Gender Dysphoria, but Defendants reserve the right to challenge such diagnoses.

6. Admit that each Plaintiff receives health care coverage through Florida's Medicaid program.

RESPONSE: Admitted.

7. Admit that, prior to the enactment of the Challenged Exclusion, Florida Medicaid covered "services for the treatment of gender dysphoria," as that term is defined in the Challenged Exclusion, for each Plaintiff.

RESPONSE: Admitted that the Agency did not have a policy excluding coverage for such treatments prior to the adoption of the Challenged Exclusion.

8. Admit that Florida Medicaid covers each of the Various Services when necessary to treat at least one condition other than Gender Dysphoria.

RESPONSE: Admitted. However, these services not medically necessary for the treatment of gender dysphoria.

9. Admit that Florida Medicaid covers mastectomy, reduction mammoplasty, and breast reconstruction surgery when necessary to treat at least one condition other than Gender Dysphoria.

RESPONSE: Admitted. However, these services not medically necessary for the treatment of gender dysphoria.

10. Admit that Florida Medicaid covers hysterectomy and oophorectomy procedures when necessary to treat at least one condition other than Gender

Dysphoria.

RESPONSE: Admitted. However, these services not medically necessary for the treatment of gender dysphoria.

11. Admit that Florida Medicaid covers vaginoplasty procedures when necessary to treat at least one condition other than Gender Dysphoria.

RESPONSE: Admitted. However, these services not medically necessary for the treatment of gender dysphoria.

12. Admit that Florida Medicaid covers orchiectomy, penectomy, and/or phalloplasty procedures when medically necessary to treat at least one condition other than Gender Dysphoria.

RESPONSE: Admitted. However, these services not medically necessary for the treatment of gender dysphoria.

13. Admit that, prior to the enactment of the Challenged Exclusion, Florida Medicaid did not exclude coverage of prescribed hormones for the treatment of Gender Dysphoria.

RESPONSE: Admitted that the Agency did not have a policy categorically excluding coverage for such treatments prior to the adoption of the Challenged Exclusion.

14. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff August Dekker received coverage under Florida Medicaid for hormone therapy as treatment for his Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

15. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff August Dekker received coverage under Florida Medicaid for a double mastectomy as treatment for his Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

16. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff Brit Rothstein received coverage under Florida Medicaid for hormone therapy as treatment for his Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

17. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff Susan Doe received coverage under Florida Medicaid for a GnRH antagonist as treatment for her Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

18. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff K.F. received coverage under Florida Medicaid for a GnRH antagonist as treatment for his Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

19. Admit that, prior to the enactment of the Challenged Exclusion,

Florida Medicaid gave Plaintiff Brit Rothstein prior authorization for double mastectomy as treatment for his Gender Dysphoria.

RESPONSE: Admitted that such authorization was given by the relevant Health Plan, but was not given by the Agency.

20. Admit that, following the enactment of Challenged Exclusion, Plaintiffs have not received coverage under Florida Medicaid for the services described in Requests 14 to 19 above.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

21. Admit that if Plaintiff August Dekker does not continue to receive hormone therapy, he may undergo physical changes.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

22. Admit that if Plaintiff Brit Rothstein does not continue to receive hormone therapy, he may undergo physical changes.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

23. Admit that if Plaintiff Brit Rothstein does not receive the double mastectomy previously authorized by Defendants, he may experience exacerbated distress and chest dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

24. Admit that if Plaintiff Susan Doe does not continue to receive a GnRH antagonist, she will undergo endogenous puberty.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

25. Admit that if Plaintiff K.F. does not continue to receive a GnRH antagonist, he will undergo endogenous puberty.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

26. Admit that undergoing endogenous puberty causes development of secondary sex characteristics.

RESPONSE: Admitted.

27. Admit that undergoing endogenous puberty causes irreversible physical changes.

RESPONSE: Admitted.

28. Admit that you did not prepare any criteria for determining whether to grant a variance under Florida Statutes § 120.542 to permit Florida Medicaid coverage of any of the Various Services when used to treat Gender Dysphoria.

RESPONSE: Admitted that the Agency did not prepare any such criteria, but the Florida Legislature did as set forth in the cited statute.

29. Admit that you have no existing criteria for determining whether to grant a variance under Florida Statute § 120.542 to permit Florida Medicaid

coverage of any of the services excluded by the Challenged Exclusion.

RESPONSE: Denied.

30. Admit that you are not currently preparing any criteria for determining whether to grant a variance under Florida Statute § 120.542 to permit Florida Medicaid coverage of any of the services excluded by the Challenged Exclusion.

RESPONSE: Admitted. The criteria are set forth in the cited statute.

31. Admit that none of the Various Services are experimental when used to treat Gender Dysphoria.

RESPONSE: Denied.

32. Admit that none of the Various Services are investigational when used to treat Gender Dysphoria.

RESPONSE: Denied.

33. Admit that licensed medical professionals with experience treating Gender Dysphoria are in the best position to make medical determinations regarding the diagnosis and treatment of patients with Gender Dysphoria.

RESPONSE: Objection. The request is vague insofar as the term "best position" is not defined and could be interpreted in a number of ways.

34. Admit that, as recently as 2016, you did not consider puberty

suppression therapy for the treatment of Gender Dysphoria to be experimental.

RESPONSE: Denied.

35. Admit that, as recently as 2016, you did not consider puberty suppression therapy for the treatment of Gender Dysphoria to be investigational.

RESPONSE: Denied.

36. Admit that the individuals involved in the process of creating and implementing the Challenged Exclusion were not the same individuals who are typically involved in this process on your behalf.

RESPONSE: Denied.

37. Admit that, as recently as 2016, you did not consider any of the Various Services to be experimental.

RESPONSE: Denied.

38. Admit that, as recently as 2016, you did not consider any of the Various Services to be investigational.

RESPONSE: Denied.

39. Admit that you have criteria for determining whether to grant a variance under Florida Statutes § 120.542 for any service used to treat a healthcare condition besides Gender Dysphoria.

RESPONSE: Denied.

40. Admit that the Challenged Exclusion restricts coverage for gender-affirming care that has been the subject of decades of scholarly research.

RESPONSE: Objection. This request is vague insofar as the term "scholarly research" is not defined and could be interpreted in a number of ways.

41. Admit that no major medical organization recommends or supports prohibiting coverage of the Various Services when used to treat Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

42. Admit that transgender people have historically been subject to discrimination.

RESPONSE: Objection. This request is not relevant to any party's claim or defense and is not proportional to the needs of the case.

43. Admit that, prior to the enactment of the Challenged Exclusion, you were aware that transgender people have historically been subject to discrimination.

RESPONSE: Objection. This request is not relevant to any party's claim or defense and is not proportional to the needs of the case.

44. Admit that being transgender is immutable.

RESPONSE: Denied.

45. Admit that being transgender bears no relation to one's ability to contribute to society.

RESPONSE: Objection. This request calls for an opinion, not a matter of fact. Furthermore, the request is not relevant to any party's claim or defense and is not proportional to the needs of this case.

46. Admit that you provide Florida Medicaid coverage for some health care services that have not been studied through randomized clinical trials.

RESPONSE: Objection. This request is vague and overly burdensome. Each health service is unique, and such a broad statement does not apply. To fully answer, the Agency would incur an undue burden of having to assess thousands of individual health services and determine whether they lack randomized clinical trials.

47. Admit that you provide Florida Medicaid coverage for some health care services that have not been studied through long-term longitudinal studies.

RESPONSE: Objection. This request is vague and overly burdensome. Each health service is unique, and such a broad statement should not apply. To fully answer, the Agency would incur an undue burden of having to assess thousands of individual health services and determine whether they lack long-term longitudinal studies.

48. Admit that you provide Florida Medicaid coverage for some health care services that have a risk of producing unintended, irreversible consequences.

RESPONSE: Objection. This request is vague insofar as the terms "unintended" and "consequences" are undefined and could be interpreted in a number of ways.

49. Admit that the well-established medical consensus is that gender-affirming care should be provided to transgender people with Gender Dysphoria.

RESPONSE: Denied.

50. Admit that the WPATH Standards of Care are the most widely used standards in the United States for treating Gender Dysphoria.

RESPONSE: Denied.

51. Admit that the WPATH Standards of Care are the leading standards of care for the treatment of Gender Dysphoria.

RESPONSE: Denied.

52. Admit that the WPATH Standards of Care are authoritative standards of care for the treatment of Gender Dysphoria.

RESPONSE: Denied.

53. Admit that the WPATH Standards of Care are widely accepted as the leading standards of care for the treatment of Gender Dysphoria.

RESPONSE: Denied.

54. Admit that the WPATH Standards of Care are widely accepted as authoritative standards of care for the treatment of Gender Dysphoria.

RESPONSE: Denied.

55. Admit that the Endocrine Society's Clinical Practice Guidelines are widely accepted as authoritative standards of care for the treatment of Gender Dysphoria.

RESPOSNE: Denied.

56. Admit that the Endocrine Society's Clinical Practice Guidelines are authoritative standards of care for the treatment of Gender Dysphoria.

RESPOSNE: Denied.

57. Admit that Defendants are not aware of any other widely used standards of care to treat Gender Dysphoria other than the WPATH Standards of Care or the Endocrine Society's Clinical Practice Guidelines.

RESPONSE: Denied.

58. Admit that your coverage of medical care should be made pursuant to the standards of care for a particular condition.

RESPONSE: Objection. This request calls for an opinion not a matter of fact. Furthermore, it is overly broad and lacks specificity.

59. Admit that the treatment of a medical condition should be made pursuant to the standards of care for a particular condition.

RESPONSE: Objection. This request calls for an opinion not a matter of fact. Furthermore, it is overly broad and lacks specificity.

60. Admit that persons from the Office of the Governor Ronald DeSantis were involved in your decision to promulgate the Challenged Exclusion.

RESPONSE: Denied.

61. Admit that persons from the Florida Department of Health were involved in your decision to promulgate the Challenged Exclusion.

RESPONSE: Denied.

62. Admit that you caused Chloe Cole to be invited to the July 8 Hearing.

RESPONSE: Denied.

63. Admit that you caused Sophia Galvin to be invited to the July 8 Hearing.

RESPONSE: Denied.

64. Admit that you caused Anthony Verdugo to be invited to the July 8 Hearing.

RESPONSE: Denied.

65. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Christian Family Coalition.

RESPONSE: Denied.

66. Admit that you caused to be invited to the July 8 Hearing any persons

affiliated with the Florida Citizens Alliance.

RESPONSE: Denied.

67. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Warriors of Faith.

RESPONSE: Denied.

68. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Protect our Children Project.

RESPONSE: Denied.

69. Admit that, in promulgating the Challenged Exclusion, you did not consult "evidence-based clinical practice guidelines", as that term is used in 59G-1.035.

RESPONSE: Denied.

70. Admit that, in promulgating the Challenged Exclusion, you did not consult articles "published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty association", as that term is used in 59G-1.035.

RESPONSE: Denied.

71. Admit that, in promulgating the Challenged Exclusion, you did not consult "coverage policies by other creditable insurance payor sources", as that term is used in 59G-1.035.

RESPONSE: Denied.

72. Admit that only Dr. Andre Van Mol, Dr. Quentin Van Meter, and Dr. Miriam Grossman were included on the July 8 Hearing panel.

RESPONSE: Denied.

73. Admit that Dr. Andre Van Mol, Dr. Quentin Van Meter, and Dr. Miriam Grossman have all taken positions that support Defendants' promulgation of exclusions for coverage of treatment of Gender Dysphoria.

RESPONSE: Objection. This request is vague insofar as the term "positions" is not defined and could be interpreted in a number of ways.

74. Admit that you did not include anyone on the July 8 Hearing panel who has taken a position that opposes Defendants' promulgation of exclusions for coverage of Gender Dysphoria.

RESPONSE: Objection. This request is vague insofar as the term "positions" is not defined and could be interpreted in a number of ways.

75. Admit that you selected the authors of the GAPMS Memo reports because of their opposition to gender-affirming care.

RESPONSE: Denied.

76. Admit that each of the authors of the GAPMS Memo have publicly taken positions in opposition to gender-affirming care.

RESPONSE: Denied.

77. Admit that you selected the panel members for the July 8 Hearing because of their opposition to gender-affirming care.

RESPONSE: Denied.

78. Admit that, prior to the GAPMS Memo's drafting and promulgation, you determined that gender-affirming care was experimental or investigational.

RESPONSE: Defendants object to the definition of gender-affirming care because it is contrary to the term's ordinary use. Subject to and without waiving such objection, Defendants deny.

79. Admit that, regardless of what information was available to you, you intended to reach the conclusion in the GAPMS Memo that gender-affirming care was experimental or investigational.

RESPONSE: Defendants object to the definition of gender-affirming care because it is contrary to the term's ordinary use. Subject to and without waiving such objection, Defendants deny.

* * *

Dated: January 12, 2023

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I hereby certify that on January 12, 2023, a true and correct copy of the foregoing document was served upon all counsel of record via email, as follows:

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TAB 175-4

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
Tallahassee Division

AUGUST DEKKER, et al., *Plaintiffs*, v. SIMONE MARSTILLER, et al., *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' FIRST SET OF REQUESTS FOR ADMISSION TO DEFENDANTS FLORIDA AGENCY FOR HEALTHCARE ADMINISTRATION AND SECRETARY SIMONE MARSTILLER

Pursuant to Federal Rules of Civil Procedure 26 and 36, Plaintiffs propound this First Set of Requests for Admission to Defendants Florida Agency for Health Care Administration and Secretary Marstiller to be answered fully and within the timeframe required under the Federal Rules and the Local Rules of this Court.

DEFINITIONS

As used herein, the following terms shall have the meanings indicated below:

1. "Defendants," "you," and "your" mean both Defendant Simone Marstiller and the Florida Agency for Health Care Administration ("AHCA"), their agents, employees, administrators, attorneys, representatives, contractors,

consultants, investigators, and all other Persons and entities working or purporting to act on behalf of, or in concert with, or in participation with AHCA.

2. The "Challenged Exclusion" means Florida Administrative Code 59G-1.050(7), which was enacted on August 21, 2022, prohibiting coverage for "services for the treatment of gender dysphoria," including "puberty blockers," "hormones and hormone antagonists," "sex reassignment surgeries," and "any other procedures that alter primary or secondary sexual characteristics."

3. "Florida Medicaid" means the same as "Medicaid" defined at Fla. Stat. 409.901(14) & 409.962(11) and includes all contractors, including health insurance plans, engaged by Defendants for the administration of Florida's Medicaid program.

4. "Florida Medicaid program" means the same as "Medicaid program" defined at Fla. Stat. 409.901(16).

5. "GAPMS Memo" refers to Defendants' June 2022 publication titled "Florida Medicaid: Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria," including by reference all attachments and exhibits.

6. Unless otherwise specified, "gender-affirming care" means any health care, physical, mental, or otherwise, administered or prescribed for the treatment of Gender Dysphoria.

7. "Gender Dysphoria" refers to the clinically significant distress or impairment related to the incongruence between one's experienced/expressed gender and their assigned sex at birth, including their primary and/or secondary sex characteristics. For purposes of these Requests, "Gender Dysphoria" shall include: (a) the diagnoses for "Gender dysphoria in adolescents and adults" and "Gender dysphoria in children," as defined within *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (DSM-5-TR); (b) the diagnosis for "gender identity disorder," including any subcategories such as "Gender Identity Disorder in Adolescents and Adults," "Gender Identity Disorder in Children," and "Gender Identity Disorder Not Otherwise Specified," as defined within the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR); (c) the diagnosis for "gender identity disorder," including any subcategories such as "Gender Identity Disorder in Children," "Transsexualism," and "Gender Identity Disorder of Adolescence or Adulthood, Nontranssexual Type," and Gender Identity Disorder not Otherwise Specified," as defined within the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revision* (DSM-III-TR); (d) the diagnosis for "gender identity disorder," including any subcategories such as "Gender Identity Disorder

in Children," "Transsexualism," and "Atypical Gender Identity Disorder," as defined within the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III); and (e) the diagnoses for "gender incongruence of adolescence and adulthood" and "gender incongruence of childhood," as defined within the *International Classification of Diseases, Eleventh Revision* (ICD-11); and the diagnoses for "transsexualism" and "gender identity disorder," including any subcategories, as defined within the *International Classification of Diseases, Tenth Revision* (ICD-10) and *International Classification of Diseases, Ninth Revision* (ICD-9).

8. "July 8 Hearing" refers to the hearing that Defendants held on July 8, 2022 in Tallahassee, Florida regarding the Challenged Exclusion.

9. The term "major medical organization" shall mean the American Medical Association, the American Psychological Association, the American Psychiatric Association, Endocrine Society, the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the American Academy of Family Physicians.

10. "Medically necessary" shall have the same meaning as in 59G-1.010(166).

11. "Person" and "persons" mean any natural person, partnership, association, corporation, joint venture, trust, community group, government or

subdivision of any government (including any instrumentality, bureau, department, office, or agency of any government), not-for-profit enterprise, or other business entity, and all present and former officers, directors, agents, administrators, managers, representatives, contractors, consultants, employees, or other persons acting or purporting to act on behalf of such person.

12. "Plaintiffs" means the named plaintiffs in this action and any other plaintiff that is added in the future.

13. "Various Services" refers to the following procedures: penectomy, orchiectomy, vaginoplasty, feminizing genitoplasty, breast reconstruction, chondrolaryngoplasty, phalloplasty, metoidioplasty, masculinizing genitoplasty, single or double mastectomy, reduction mammoplasty, hysterectomy, oophorectomy, salpingo-oophorectomy, estradiol (in all forms, including oral/sublingual estradiol, transdermal estradiol, estradiol valerate IM, and estradiol cypionate IM), medroxyprogesterone acetate (Provera), micronized progesterone, spironolactone, finasteride, dutasteride, and testosterone (in all forms, including testosterone cypionate, testosterone enthanate, testosterone topical gel 1%, testosterone topical gel 1.62%, testosterone patches, testosterone cream, testosterone axillary gel 2%, testosterone undecanoate), and Gonadotropin-releasing hormone (GnRH) antagonists.

INSTRUCTIONS

1. These Requests are issued to each of the Defendants. Defendants' responses to these Requests shall be made within thirty (30) days of service of these Requests.

2. All responses to these Requests should be directed to: Jennifer Altman, Pillsbury Winthrop Shaw Pittman LLP, 600 Brickell Avenue, Suite 3100, Miami, FL 33131, Email: jennifer.altman@pillsbury.com, cc: soraya.garcia@pillsburylaw.com.

3. Unless otherwise specified, the time period covered by these Requests is January 1, 2015 to the present. If it is necessary to refer to periods of time prior to January 1, 2015 to respond to a Request, please do so.

4. These Requests are continuing in nature, up to and during the course of trial. Defendants' responses to these Requests are to be promptly supplemented or amended if, after the time of their initial responses, Defendants learn that any response is or has become in some material respect incomplete or incorrect, to the full extent provided for by Federal Rule of Civil Procedure 26(e). Plaintiffs will object to any attempt to introduce evidence to the Court that should have been but was not disclosed in the responses or supplementation of the responses.

5. If a Request cannot be complied with in full, it shall be complied with to the extent possible, and accompanied by an explanation of your objection to the request or other reasons you are unable to fully comply.

6. As to each Request, Defendants shall specifically admit or deny the statement contained therein. If denied, the denial must fairly meet the substance of the requested admission. If Defendants qualify their answer or deny any part of the matter for which admission is requested, Defendants shall admit so much of the statement as is true and qualify or deny the remainder.

7. If Defendants object that a term or phrase is vague or ambiguous, Defendants shall respond with their understanding of the term or phrase and specifically admit or deny the statement.

8. If Defendants object to any part of a Request, Defendants shall specify each part of the Request to which Defendants object; set forth with specificity the grounds for objecting to each such part of the Request, including the reasons, and otherwise respond to all parts of the Request to which Defendants do not object.

11. Responses to these Requests shall include all information within the custody, possession, or control of you, your employees, partners, contractors, accountants, attorneys, or other agents, or which are otherwise available to you.

12. When, after a reasonable and thorough investigation using due diligence, you are unable to admit or deny a Request or any part thereof, specify in

full the reason that you are unable to admit or deny the Request and the steps you have taken to locate information that would allow you to admit or deny the Request. If you deny any part of a matter for which admission is requested, you shall admit so much of the statement as is true.

13. For purposes of interpreting or construing the scope of these Requests, all terms shall be given their most expansive and inclusive interpretation. This includes, without limitation, the following:

a. Construing "and" as well as "or" in the disjunctive or conjunctive, as necessary to make the Request more inclusive;

b. Construing the singular form of the word to include the plural, and the plural form to include the singular;

c. Construing the masculine to include the feminine, and vice versa;

d. Construing the term "including" to mean "including but not limited to" and construing the term "all" to mean "any and all," and vice versa;

e. Construing the term "each" to include "every," and construing "every" to include "each";

f. Construing the use of a verb in any tense as applying to the use of the verb in all other tenses as is necessary to make any paragraph more, rather than less, inclusive;

g. Construing and interpreting all spelling, syntax, grammar, abbreviations, idioms, and proper nouns to give proper meaning and consistency to their context.

REQUESTS FOR ADMISSION

1. Admit that gender-affirming care can be medically necessary.

2. Admit that the Challenged Exclusion prohibits Florida Medicaid coverage of gender affirming care that can be medically necessary for the treatment of Gender Dysphoria.

3. Admit that each of the Various Services can be medically necessary for the treatment of Gender Dysphoria.

4. Admit that each Plaintiff identifies as transgender.

5. Admit that each Plaintiff has been diagnosed with Gender Dysphoria.

6. Admit that each Plaintiff receives health care coverage through Florida's Medicaid program.

7. Admit that, prior to the enactment of the Challenged Exclusion, Florida Medicaid covered "services for the treatment of gender dysphoria," as that term is defined in the Challenged Exclusion, for each Plaintiff.

8. Admit that Florida Medicaid covers each of the Various Services when necessary to treat at least one condition other than Gender Dysphoria.

9. Admit that Florida Medicaid covers mastectomy, reduction mammoplasty, and breast reconstruction surgery when necessary to treat at least one condition other than Gender Dysphoria.

10. Admit that Florida Medicaid covers hysterectomy and oophorectomy procedures when necessary to treat at least one condition other than Gender Dysphoria.

11. Admit that Florida Medicaid covers vaginoplasty procedures when necessary to treat at least one condition other than Gender Dysphoria.

12. Admit that Florida Medicaid covers orchiectomy, penectomy, and/or phalloplasty procedures when medically necessary to treat at least one condition other than Gender Dysphoria.

13. Admit that, prior to the enactment of the Challenged Exclusion, Florida Medicaid did not exclude coverage of prescribed hormones for the treatment of Gender Dysphoria.

14. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff August Dekker received coverage under Florida Medicaid for hormone therapy as treatment for his Gender Dysphoria.

15. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff August Dekker received coverage under Florida Medicaid for a double mastectomy as treatment for his Gender Dysphoria.

16. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff Brit Rothstein received coverage under Florida Medicaid for hormone therapy as treatment for his Gender Dysphoria.

17. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff Susan Doe received coverage under Florida Medicaid for a GnRH antagonist as treatment for her Gender Dysphoria.

18. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff K.F. received coverage under Florida Medicaid for a GnRH antagonist as treatment for his Gender Dysphoria.

19. Admit that, prior to the enactment of the Challenged Exclusion, Florida Medicaid gave Plaintiff Brit Rothstein prior authorization for double mastectomy as treatment for his Gender Dysphoria.

20. Admit that, following the enactment of Challenged Exclusion, Plaintiffs have not received coverage under Florida Medicaid for the services described in Requests 14 to 19 above.

21. Admit that if Plaintiff August Dekker does not continue to receive hormone therapy, he may undergo physical changes.

22. Admit that if Plaintiff Brit Rothstein does not continue to receive hormone therapy, he may undergo physical changes.

23. Admit that if Plaintiff Brit Rothstein does not receive the double mastectomy previously authorized by Defendants, he may experience exacerbated distress and chest dysphoria.

24. Admit that if Plaintiff Susan Doe does not continue to receive a GnRH antagonist, she will undergo endogenous puberty.

25. Admit that if Plaintiff K.F. does not continue to receive a GnRH antagonist, he will undergo endogenous puberty.

26. Admit that undergoing endogenous puberty causes development of secondary sex characteristics.

27. Admit that undergoing endogenous puberty causes irreversible physical changes.

28. Admit that you did not prepare any criteria for determining whether to grant a variance under Florida Statutes § 120.542 to permit Florida Medicaid coverage of any of the Various Services when used to treat Gender Dysphoria.

29. Admit that you have no existing criteria for determining whether to grant a variance under Florida Statute § 120.542 to permit Florida Medicaid coverage of any of the services excluded by the Challenged Exclusion.

30. Admit that you are not currently preparing any criteria for determining whether to grant a variance under Florida Statute § 120.542 to permit Florida Medicaid coverage of any of the services excluded by the Challenged Exclusion.

31. Admit that none of the Various Services are experimental when used to treat Gender Dysphoria.

32. Admit that none of the Various Services are investigational when used to treat Gender Dysphoria.

33. Admit that licensed medical professionals with experience treating Gender Dysphoria are in the best position to make medical determinations regarding the diagnosis and treatment of patients with Gender Dysphoria.

34. Admit that, as recently as 2016, you did not consider puberty suppression therapy for the treatment of Gender Dysphoria to be experimental.

35. Admit that, as recently as 2016, you did not consider puberty suppression therapy for the treatment of Gender Dysphoria to be investigational.

36. Admit that the individuals involved in the process of creating and implementing the Challenged Exclusion were not the same individuals who are typically involved in this process on your behalf.

37. Admit that, as recently as 2016, you did not consider any of the Various Services to be experimental.

38. Admit that, as recently as 2016, you did not consider any of the Various Services to be investigational.

39. Admit that you have criteria for determining whether to grant a variance under Florida Statutes § 120.542 for any service used to treat a healthcare condition besides Gender Dysphoria.

40. Admit that the Challenged Exclusion restricts coverage for gender-affirming care that has been the subject of decades of scholarly research.

41. Admit that no major medical organization recommends or supports prohibiting coverage of the Various Services when used to treat Gender Dysphoria.

42. Admit that transgender people have historically been subject to discrimination.

43. Admit that, prior to the enactment of the Challenged Exclusion, you were aware that transgender people have historically been subject to discrimination.

44. Admit that being transgender is immutable.

45. Admit that being transgender bears no relation to one's ability to contribute to society.

46. Admit that you provide Florida Medicaid coverage for some health care services that have not been studied through randomized clinical trials.

47. Admit that you provide Florida Medicaid coverage for some health care services that have not been studied through long-term longitudinal studies.

48. Admit that you provide Florida Medicaid coverage for some health care services that have a risk of producing unintended, irreversible consequences.

49. Admit that the well-established medical consensus is that gender-affirming care should be provided to transgender people with Gender Dysphoria.

50. Admit that the WPATH Standards of Care are the most widely used standards in the United States for treating Gender Dysphoria.

51. Admit that the WPATH Standards of Care are the leading standards of care for the treatment of Gender Dysphoria.

52. Admit that the WPATH Standards of Care are authoritative standards of care for the treatment of Gender Dysphoria.

53. Admit that the WPATH Standards of Care are widely accepted as the leading standards of care for the treatment of Gender Dysphoria.

54. Admit that the WPATH Standards of Care are widely accepted as authoritative standards of care for the treatment of Gender Dysphoria.

55. Admit that the Endocrine Society's Clinical Practice Guidelines are widely accepted as authoritative standards of care for the treatment of Gender Dysphoria.

56. Admit that the Endocrine Society's Clinical Practice Guidelines are authoritative standards of care for the treatment of Gender Dysphoria.

57. Admit that Defendants are not aware of any other widely used standards of care to treat Gender Dysphoria other than the WPATH Standards of Care or the Endocrine Society's Clinical Practice Guidelines.

58. Admit that your coverage of medical care should be made pursuant to the standards of care for a particular condition.

59. Admit that the treatment of a medical condition should be made pursuant to the standards of care for a particular condition.

60. Admit that persons from the Office of the Governor Ronald DeSantis were involved in your decision to promulgate the Challenged Exclusion.

61. Admit that persons from the Florida Department of Health were involved in your decision to promulgate the Challenged Exclusion.

62. Admit that you caused Chloe Cole to be invited to the July 8 Hearing.

63. Admit that you caused Sophia Galvin to be invited to the July 8 Hearing.

64. Admit that you caused Anthony Verdugo to be invited to the July 8 Hearing.

65. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Christian Family Coalition.

66. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Florida Citizens Alliance.

67. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Warriors of Faith.

68. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Protect our Children Project.

69. Admit that, in promulgating the Challenged Exclusion, you did not consult "evidence-based clinical practice guidelines", as that term is used in 59G-1.035.

70. Admit that, in promulgating the Challenged Exclusion, you did not consult articles "published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty association", as that term is used in 59G-1.035.

71. Admit that, in promulgating the Challenged Exclusion, you did not consult "coverage policies by other creditable insurance payor sources", as that term is used in 59G-1.035.

72. Admit that only Dr. Andre Van Mol, Dr. Quentin Van Meter, and Dr. Miriam Grossman were included on the July 8 Hearing panel.

73. Admit that Dr. Andre Van Mol, Dr. Quentin Van Meter, and Dr. Miriam Grossman have all taken positions that support Defendants' promulgation of exclusions for coverage of treatment of Gender Dysphoria.

74. Admit that you did not include anyone on the July 8 Hearing panel who has taken a position that opposes Defendants' promulgation of exclusions for coverage of Gender Dysphoria.

75. Admit that you selected the authors of the GAPMS Memo reports because of their opposition to gender-affirming care.

76. Admit that each of the authors of the GAPMS Memo have publicly taken positions in opposition to gender-affirming care.

77. Admit that you selected the panel members for the July 8 Hearing because of their opposition to gender-affirming care.

78. Admit that, prior to the GAPMS Memo's drafting and promulgation, you determined that gender-affirming care was experimental or investigational.

79. Admit that, regardless of what information was available to you, you intended to reach the conclusion in the GAPMS Memo that gender-affirming care was experimental or investigational.

* * *

Respectfully submitted this 12th day of December, 2022.

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* *Admitted pro hac vice.*

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing was served by email on December 12, 2022, on all counsel of record:

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COUNSEL FOR DEFENDANTS

/s/ Joe Little
Counsel for Plaintiffs

TAB 175-18

Florida Medicaid

Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria

June 2022

Pl. Trial Ex. 018

Ron DeSantis, Governor
Simone Marstiller, Secretary

Contents

Introductory Remarks and Abstract

Generally Accepted Professional Medical Standards

The Secretary of the Florida Agency for Health Care Administration requested that the Division of Florida Medicaid review the treatment of gender dysphoria for a coverage determination pursuant to Rule 59G-1.035, Florida Administrative Code (F.A.C.) (See Attachment A for the Secretary's Letter to Deputy Secretary Tom Wallace). The treatment reviewed within this report included "sex reassignment treatment," which refers to medical services used to obtain the primary and/or secondary physical sexual characteristics of a male or female. As a condition of coverage, sex reassignment treatment must be "consistent with generally accepted professional medical standards (GAPMS) and not experimental or investigational" (Rule 59G-1.035, F.A.C., see Attachment B for the complete rule text).

The determination process requires that "the Deputy Secretary for Medicaid will make the final determination as to whether the health service is consistent with GAPMS and not experimental or investigational" (Rule 59G-1.035, F.A.C.). In making that determination, Rule 59G-1.035, F.A.C., identifies several factors for consideration. Among other things, the rule contemplates the consideration of "recommendations or assessments by clinical or technical experts on the subject or field" (Rule 59G-1.035(4)(f), F.A.C.). Accordingly, this report attaches five assessments from subject-matter experts:

- **Attachment C:** Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.
- **Attachment D:** James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.
- **Attachment E:** Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.
- **Attachment F:** Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.
- **Attachment G:** G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

Abstract

Available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. Studies presenting the benefits to mental health, including those claiming that the services prevent suicide, are either low or very low quality and rely on unreliable methods such as surveys and retrospective analyses, both of which are cross-sectional and highly biased. Rather, the available evidence demonstrates that these treatments cause irreversible physical changes and side effects that can affect long-term health.

Five clinical and technical expert assessments attached to this report recommend against the use of such interventions to treat what is categorized as a mental health disorder (See attachments):

- **Health Care Research:** Brignardello-Petersen and Wiercioch performed a systematic review that graded a multitude of studies. They conclude

that evidence supporting sex reassignment treatments is low or very low quality.

- **Clinical Psychology:** Cantor provided a review of literature on all aspects of the subject, covering therapies, lack of research on suicidality, practice guidelines, and Western European coverage requirements.
- **Plastic Surgery:** Lappert provided an evaluation explaining how surgical interventions are cosmetic with little to no supporting evidence to improve mental health, particularly those altering the chest.
- **Pediatric Endocrinology:** Van Meter explains how children and adolescent brains are in continuous phases of development and how puberty suppression and cross-sex hormones can potentially affect appropriate neural maturation.
- **Bioethics:** Donovan provides additional insight on the bioethics of administering these treatments, asserting that children and adolescents cannot provide truly informed consent.

Following a review of available literature, clinical guidelines, and coverage by other insurers and nations, Florida Medicaid has determined that the research supporting sex reassignment treatment is insufficient to demonstrate efficacy and safety. In addition, numerous studies, including the reports provided by the clinical and technical experts listed above, identify poor methods and the certainty of irreversible physical changes. Considering the weak evidence supporting the use of puberty suppression, cross-sex hormones, and surgical procedures when compared to the stronger research demonstrating the permanent effects they cause, these treatments do not conform to GAPMS and are experimental and investigational.

Health Service Summary

Gender Dysphoria

Frequently used to describe individuals whose gender identity conflicts with their natural-born sex, the term gender dysphoria has a history of evolving definitions during the past decades (Note: This report uses the term "gender" in reference to the construct of male and female identities and the term "sex" when regarding biological characteristics). Prior to the publication of the *Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), the American Psychiatric Association (APA) used the diagnosis of gender identity disorder (GID) to describe individuals who sought to transition to the opposite gender. However, behavioral health clinicians sought a revision after determining that using GID created stigma for those who received the diagnosis. This is despite the APA having adopted GID to replace the previous diagnosis of transsexualism for the exact same reason (APA, 2017).[1]

When crafting its new definition and terminology, the APA sought to remove the stigma of classifying as a disorder the questioning of one's gender identity by focusing instead on the psychological distress that such questioning can evoke. This approach argues that individuals seeking behavioral health and transition services are doing so due to experiencing distress and that gender non-conformity by itself is not a mental health issue. This led to the adoption of gender dysphoria in 2013 when the APA released the DSM-V. In addition to using a new term, the APA also differentiated the diagnosis between children and adolescents and adults, listing different characteristics for the two age groups (APA, 2017).

According to the DSM-V, gender dysphoria is defined as "the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender." As for the criteria to receive the diagnosis, the APA issued stricter criteria for children than adolescents and adults. For the former, the APA states that a child must meet six out of eight behavioral characteristics such as having "a strong desire to be of the other gender or an insistence that one is the other gender" or "a strong preference for cross-gender roles in make-believe or fantasy play." The criteria for adults and adolescents are less stringent with individuals only having to meet two out of six characteristics that include "a strong desire to be the other gender" or "a strong desire to be rid of one's primary and/or secondary sexual characteristics." The APA further notes that these criteria can also apply to young adolescents (DSM-V, 2013).

In 2021, the Merck Manual released a slightly different definition for gender dysphoria, citing that the condition "is characterized by a strong, persistent cross-gender identification associated with anxiety, depression, irritability, and often a wish to live as a gender different from the one associated with the

[1] The concept of gender being part of identity and disconnected from biological sex originated during the mid-twentieth century and was publicized by psychologist John W. Money. His research asserted that gender was a complete social construct and separate from biology, meaning that parents and/or caregivers could imprint on a young child (under three years) the identity of a boy or girl. In 1967, Money's theories led to a failed experiment on twin boys where physicians surgically transitioned one to appear as a girl. The twin that underwent sex reassignment never fully identified as a female. However, Money never publicly acknowledged this and reported the experiment as a success. Furthermore, he promoted his conclusions across the scientific community, concealing what actually unfolded. As a result, Money's ideas on gender fluidity served as a basis for performing procedures on children with hermaphroditic features or genital abnormalities. The case reveals how the understanding of a concept (e.g., gender) at any given time can lead to incorrect medical decisions with irreversible consequences (Gaetano, 2015).

sex assigned at birth." Additionally, the Merck Manual further states that "gender dysphoria is a diagnosis requiring specific criteria but is sometimes used more loosely for people in whom symptoms do not reach a clinical threshold" (Merck Manual, 2021). This definition is largely consistent with the DSM-V but does not emphasize the distress component to the same extent.[2]

Like other behavioral health diagnoses classified in the DSM-V, gender dysphoria has the following subtypes:

- **Early-Onset Gender Dysphoria:** This subtype begins during childhood and persists through adolescence into adulthood. It can be interrupted by periods where the individual does not experience gender dysphoria signs and may classify as homosexual (DSM-V, 2013).
- **Late-Onset Gender Dysphoria:** Occurring after puberty or during adulthood, this subtype does not begin until late adolescence and can emerge following no previous signs of gender dysphoria. The APA attributes this partially to individuals who did not want to verbalize their desires to transition (DSM-V, 2013).

Further studies have identified additional subtypes of gender dysphoria. In 2018, Lisa Littman introduced the concept of a rapid-onset subtype. Classified as rapid-onset gender dysphoria (ROGD), it features characteristics such as sudden beginnings during or following puberty. However, it differs from the DSM-V definitions because ROGD is associated with other causes such as social influences (e.g., peer groups, authority figures, and media). In other words, adolescents who had no history of displaying typical gender dysphoria characteristics go through a sudden change in identity following intense exposure to peers and/or media that heavily promotes transgender lifestyles (Littman, 2018). While more long-term studies are needed to confirm whether ROGD is a temporary or long-term condition, Littman's study has initiated discussions regarding potential causes of gender dysphoria as well as introduced a potential subtype.

Additionally, the frequent use of gender dysphoria in clinical and lay discourse has led to a fracturing of the definition. Studies on the topic frequently do not apply the DSM-V's criteria for the diagnosis and overlook certain key features such as distress. In a 2018 review by Zowie Davy and Michael Toze, the authors evaluated 387 articles that examine gender dysphoria and noted stark departures from the APA's definition. They further asserted that the APA intended to "reduce pathologization" by establishing a new definition for gender dysphoria in the DSM-V. This in turn would reduce diagnoses, although as Davy and Toze note, the tendency for the literature to diverge from the APA's definition may result in increased numbers of individuals classified as having gender dysphoria when they do not meet the DSM-V's criteria (Davy and Toze, 2018). This further raises the question of whether individuals are receiving potentially irreversible treatments for the condition when they might not actually have it.

The current usage of gender dysphoria is the result of discussions spanning across decades as demonstrated in the past editions of the DSM. Until 2013, the APA considered having gender identity issues a mental disorder by itself regardless of the presence of psychological distress. That perspective has since shifted to only consider the adverse psychological effects of questioning one's gender as a disorder. In addition, the APA considers gender as part of one's identity, which is not subject to a diagnosis. Whether the APA has shifted its terminology and criteria for gender identity issues due to

[2] Following the release of the Florida Department of Health's guidelines for treating gender dysphoria, Merck removed its definition for "gender dysphoria" from the Merck Manual (Fox News, 2022).

emerging clinical data or cultural changes is another question. In 1994, the APA replaced transsexualism with gender identity disorder as part of the "effort to reduce stigma" (APA, 2017). This raises questions about what influences decisions to revise definitions and criteria; is it social trends or medical evidence?

Behavioral Health Issues Co-Occurring with Gender Dysphoria

Because gender dysphoria pertains directly to the distress experienced by an individual who desires to change gender identities, secondary behavioral health issues can co-occur such as depression and anxiety. If left untreated, these conditions can lead to the inability to function in daily activities, social isolation, and even suicidal ideation. Studies do confirm that adolescents and adults with gender dysphoria report higher levels of anxiety, depression, and poor peer relationships than the general population (Kuper et al, 2019). Other associated conditions include substance abuse, eating disorders, and compulsivity. A significant proportion of individuals with gender dysphoria also have autism spectrum disorder (ASD) (Saleem and Rizvi, 2017). Although the number reporting secondary issues is increased, individuals diagnosed with gender dysphoria do not necessarily constitute the entire population that is gender non-conforming (i.e., does not identify with natal sex), and no information is available breaking down the percentage of those who are non-conforming with gender dysphoria and those who are non-conforming with no distress. Additionally, available research raises questions as to whether the distress is secondary to pre-existing behavioral health disorders and not gender dysphoria. This is evident in the number of adolescents who reported anxiety and depression diagnoses prior to transitioning (Saleem and Rizvi, 2017).

Furthermore, conventional treatments for secondary behavioral health issues are available. These include cognitive behavioral therapy, medication, and inpatient services. The APA reports that treatments for these are highly effective with 80% to 90% of individuals diagnosed with depression responding positively (APA, 2020). In addition, a high percentage of adolescents diagnosed with gender dysphoria had received psychiatric treatment for a prior or co-occurring mental health issue. A 2015 study from Finland by Kaltiala-Heino et al noted that 75% of children seeking sex reassignment services had been treated by a behavioral health professional (Kaltiala-Heino et al, 2015).

Diagnosing Gender Dysphoria

Prior to the publication of the DSM-V, diagnosing individuals experiencing gender identity issues followed a different process. Behavioral health clinicians could assign the diagnosis based on gender non-conformance alone. That has changed since 2013. Today, non-conforming to one's gender is part of personal identity and not a disorder requiring treatment. This change has led professional associations to shift the diagnostic criteria for gender dysphoria to focus on the distress caused by shifting identities (DSM-V, 2013).

For adolescents, the APA identifies "a marked incongruence between one's experienced/expressed gender and natal sex, of at least 6 months' duration" as the core component of gender dysphoria (DSM-V, 2013). What the APA does not elucidate is the threshold for "marked." This raises questions as to whether practitioners exercise uniformity when applying the diagnostic criteria or if they do so subjectively. For example, the WPATH's *Standards of Care for the Health of Transsexual, Transgender, and Gender Non-Conforming People* provides guidance on the processes mental health practitioners should use when assessing for gender dysphoria but offers no benchmarks for meeting diagnostic criteria (WPATH, 2012).

Such processes include evaluating for gender non-conforming behaviors and other co-existing mental disorders like anxiety or depression. This involves not only interviewing the adolescent but also the family in addition to reviewing medical histories. WPATH also asserts that gender dysphoria assessments need to account for peer relationships, academic performance, and provide information of potential treatments. This last component is necessary because it might affect an individual's choices regarding transitioning, particularly if the information does not correspond to the desired outcome (WPATH, 2012).

The diagnosis of gender dysphoria is a relatively recent concept in mental health, being the product of decades of discussion and building upon previous definitions. Instead of treating gender non-conformity as a disorder, behavioral health professionals acknowledge it as part of one's identity and focus on addressing the associated distress. Considering the new criteria, this changes the dynamics of the population who would have qualified for a diagnosis before 2013 and those who would today. Given that desiring to transition into a gender different from natal sex no longer qualifies as a disorder, behavioral health professionals are treating distress and referring adolescents and adults to therapies that are used off-label and pose irreversible effects.

Current Available Treatments for Gender Dysphoria

At present, proposed treatment for gender dysphoria occurs in four stages, beginning with psychological services and ending with sex reassignment surgery. As an individual progresses through each stage, the treatments gradually become more irreversible with surgical changes being permanent. Because of the increasing effects, individuals must have attempted treatment at the previous stage before pursuing the next one (Note: late adolescents and adults have already completed puberty and do not require puberty blockers). Listed in order, the four stages are as follows:

- **Behavioral Health Services:** Psychologists and other mental health professionals are likely the first practitioners individuals with gender dysphoria will encounter. In accordance with clinical guidelines established by the World Professional Association for Transgender Health (WPATH)[3], behavioral health professionals are supposed to "find ways to maximize a person's overall psychological well-being, quality of life, and self-fulfillment." WPATH further discourages services for attempting to change someone's gender identity. Instead, it instructs practitioners to assess for the condition and readiness for puberty blockers or cross-sex hormones while offering guidance to function in a chosen gender. WPATH does assert that the clinicians do need to treat any other underlying mental health issues secondary or co-occurring with gender dysphoria (WPATH, 2012). However, the organization provides conflicting guidance because it also advises practitioners to prescribe cross-sex hormones on demand (Levine, 2018).
- **Puberty Suppression:** Used only on individuals in the earliest stages of puberty (Tanner stage 2), preventing pubertal onset provides additional time to explore gender identities before the physical characteristics of biological sex develop. This treatment is intended to reduce distress and anxiety related to the appearance of adult sexual physical features. To suppress puberty, pediatric endocrinologists inject gonadotropin releasing hormone (Gn-RH) at specific intervals (e.g., 4 weeks or 12 weeks). The Gn-RH suppresses gonadotropin receptors that allow for the

[3] The World Professional Association for Transgender Health asserts that it is a professional organization. However, it functions like an advocacy group by allowing open membership to non-clinicians (WPATH, 2022).

development of primary and secondary adult sexual characteristics. Prior to receiving puberty suppression therapy, individuals must have received a diagnosis of gender dysphoria and have undergone a mental health evaluation (Kyriakou et al, 2020).

- **Cross-Sex Hormones:** For adults and late adolescents (16 years or older), the next treatment phase recommended is taking cross-sex hormones (e.g., testosterone or estrogen) to create secondary sex characteristics. In men transitioning into women, these include breast development and widening around the pelvis. Women who transition into men experience deeper voices, redistribution of fat deposits, and growing facial hair. According to the Endocrine Society, late adolescents who qualify for cross-sex hormones must have a confirmed diagnosis of gender dysphoria from a mental health practitioner with experience treating that population. Some physical changes induced by these hormones are irreversible (Endocrine Society, 2017).
- **Sex Reassignment Surgery:** Sometimes referred to as "gender affirming" surgery, this treatment does not consist of just one procedure but several, depending on the desires of the transitioning individual. Primarily, sex reassignment procedures alter the primary and secondary sexual characteristics. Men transitioning into women (trans-females) undergo a penectomy (removal of the penis), orchiectomy (removal of the testes), and vulvoplasty (creation of female genitals). Other procedures trans-females may undergo include breast augmentation and facial feminization. For women that transition into men (trans-males), procedures include mastectomy (removal of the breasts), hysterectomy (removal of the uterus), oophorectomy (removal of the ovaries), and phalloplasty (creation of male genitals). Because of the complexities involved in phalloplasty, many trans-males do not opt for this procedure and limit themselves to mastectomies. Additionally, the effects of sex reassignment surgery, such as infertility, are permanent (WPATH, 2012).

While some clinical organizations assert that they are the standard of care for gender dysphoria, the U.S. Food and Drug Administration (FDA) currently has not approved any medication as clinically indicated for this condition (Unger, 2018). Although puberty blockers and cross-sex hormones are FDA approved, the FDA did not approve them for treating gender dysphoria, meaning that their use for anything other than the clinical indications listed is off-label (American Academy of Pediatrics, 2014). As for surgical procedures, the FDA does not evaluate or approve them, but it does review all surgical devices (FDA, 2021). In addition, the Endocrine Society concedes that its practice guidelines for sex reassignment treatment does *not* constitute a "standard of care" and that its grades for available services are low or very low (Endocrine Society, 2017).[4]

[4] Disagreement over how to treat gender dysphoria, gender identity disorder, and transsexualism has persisted since sex reassignment surgery first became available in the 1960s. In a 2006 counterargument, Paul McHugh highlights how individuals seeking surgery had other reasons that extended beyond gender identity, including sexual arousal and guilt over homosexuality. In addition, he asserts that undergoing sex reassignment procedures did not improve a patient's overall behavioral health and that providing a "surgical alteration to the body of these unfortunate people was to collaborate with a mental disorder rather than to treat it" (McHugh, 2006).

Literature Review: Introduction

Currently, an abundance of literature and studies on gender dysphoria is available through academic journals, clinical guidelines, and news articles. Similar to other mental health issues, the material addresses a broad range of topics consisting of available treatments, etiology (i.e., causes), risks, benefits, and side effects. Although most stories reported by the media indicate that treatments such as cross-sex hormones and sex reassignment surgery are the most effective, research reveals that numerous questions still exist. These include what are the long-term health effects of taking cross-sex hormones, what are the real causes of gender dysphoria, and how many individuals that transition will eventually want to revert to their natal sex. Additionally, much of the available research is inconclusive regarding the effectiveness of sex reassignment treatments with multiple studies lacking adequate sample sizes and relying on subjective questionnaires. While much of the scientific literature leans in favor of cross-sex hormones and surgery as options for improving the mental health of individuals with gender dysphoria, it does not conclusively demonstrate that the benefits outweigh the risks involved, either short or long-term. What studies do reveal with certainty is that sex reassignment surgery and cross-sex hormones pose permanent effects that can result in infertility, cardiovascular disease, and disfigurement. All of this indicates that further research is necessary to validate available treatments for gender dysphoria. Thus, physicians, who recommend sex reassignment treatment, are not adhering to an evidence-based medicine approach and are following an eminence-based model.

The following literature review addresses the multiple facets of this condition and presents areas of ongoing debate and persisting questions. Beginning with the condition's etiology and continuing with evaluations of puberty blockers, cross-sex hormones, and surgery, the review explains each area separately and in context of gender dysphoria at large. Additionally, the review provides an analysis on available research on mental health outcomes as well as the condition's persistence into adulthood. Taken as a whole, the available studies demonstrate that existing gender dysphoria research is inconclusive and that current treatments are used to achieve cosmetic benefits while posing risky side effects as well as irreversible changes.

Literature Review: Etiology of Gender Dysphoria

What causes gender dysphoria is an ongoing debate among experts in the scientific and behavioral health fields. Currently, the research indicates that diagnosed individuals have higher proportions of autism spectrum disorder (ASD), history of trauma or abuse, fetal hormone imbalances, and co-existing mental illnesses. Also, experts acknowledge that genetics may factor into gender dysphoria. Another potential cause is social factors such as peer and online media influence. At the moment, none of the studies provides a definite cause and offer only correlations and weakly supported hypotheses. In addition, evidence favoring a biological explanation is highly speculative. However, the research does raise questions about whether treatments with permanent effects are warranted in a population with disproportionately high percentages of ASD, behavioral health problems, and trauma.

In a 2017 literature review by Fatima Saleem and Syed Rizvi, the authors examine gender dysphoria's numerous potential causes and the remaining questions requiring further research. In conclusion, the pair indicate that associations exist between the condition and ASD, schizophrenia, childhood abuse, genetics, and endocrine disruption chemicals but that more research is needed to improve understanding of how these underlying issues factor into a diagnosis. Throughout the review, Saleem and Rizvi identify the following as potential contributing elements to the etiology of gender dysphoria:

- **Neuroanatomical Etiology:** During fetal development, the genitals and brain develop during different periods of a pregnancy, the first and second trimesters respectively. Because the processes are separate, misaligned development is possible where the brain may have features belonging to the opposite sex. The authors identify one study where trans-females presented with a "female-like putamen" (structure at the base of the brain) when undergoing magnetic resonance imaging (MRI) scans.[5]
- **Psychiatric Associations:** Saleem and Rizvi identify multiple studies reporting that individuals with gender dysphoria have high rates of anxiety and depressive disorders with results ranging as high as 70% having a mental health diagnosis. In addition, the pair note that schizophrenia may also influence desires to transition. However, the review does not assess whether the mental health conditions are secondary to gender dysphoria.
- **Autism Spectrum Disorder:** Evidence suggests a significant percentage of individuals diagnosed with gender dysphoria also have ASD. The authors note that the available studies only establish a correlation and do not identify mechanisms for causation.
- **Childhood Abuse:** Like the above causes, Saleem and Rizvi note that those with gender dysphoria tended to experience higher rates of child abuse across all categories, including neglect, emotional, physical, and sexual.
- **Endocrine Disruptors:** Although this cause still requires substantial research, it is a valid hypothesis regarding how phthalates found in plastics can create an imbalance of testosterone in fetuses during gestation, which can potentially lead to gender dysphoria. The authors point to one study that makes this suggestion.

[5] Research on neuroanatomical etiology for gender dysphoria remains highly speculative due to limitations of brain imaging (Mayer and McHugh, 2016). In addition, neuroscience demonstrates that exposures to certain environments and stimuli as well as behaviors can affect brain changes (Gu, 2014). Furthermore, available research indicates that male and female brains have different physical characteristics but cannot be placed in separate categories due to extensive overlap of white/grey matter and neural connections (Joel et al, 2015).

Saleem and Rizvi's review reveal that gender dysphoria's etiology can have multiple factors, most of which require treatments and therapies not consisting of cross-sex hormones or surgery. (Saleem and Rizvi, 2017).

Out of the research on the condition's etiology, a large portion focuses on the correlation with ASD. One of the more substantial studies by Van der Miesen et al published in 2018 evaluates 573 adolescents and 807 adults diagnosed with ASD and compares them to 1016 adolescents and 846 adults from the general population. The authors' findings note that adolescents and adults with ASD were approximately 2.5 times more likely to indicate a desire of becoming the opposite sex. Although the methodology used to reach this conclusion consisted of surveys where respondents had a choice of answering "never," "sometimes," or "often," the results correspond with those of similar studies. Van der Miesen et al also indicate that most responses favoring a change in gender responded with "sometimes." Additionally, the authors do not state how many in their sample group actually had a gender dysphoria diagnosis. (Van der Miesen et al, 2018).

Another study by Shumer et al from 2016 utilizes a smaller sample size (39 adolescents) referred to an American hospital's gender clinic. Unlike Van der Miesen et al's research, Shumer et al evaluate subjects with a diagnosis of gender dysphoria for possible signs of ASD or Asperger's syndrome. Their findings revealed that 23% of patients presenting at the clinic would likely have one of the two conditions. Possible explanations for the high percentage are the methods used to gather the data. Shumer et al requested a clinical psychologist to administer the Asperger Syndrome Diagnostic Scale to the parents of the sample patients, four of whom already had an ASD diagnosis. The authors conclude that the evidence to support high incidence of gender dysphoria in individuals with ASD is growing and that further research is needed to determine the specific cause (Shumer et al, 2016).

Research indicating a strong correlation between ASD and gender dysphoria is not the only area where new studies are emerging. Discussions about the effects of prenatal testosterone levels are also becoming more prevalent. One such example is Sadr et al's 2020 study that looks at the lengths of the index and ring fingers (2D:4D) of both left and right hands of 203 individuals diagnosed with gender dysphoria. The authors used this method because prenatal testosterone levels can affect the length ratios of 2D:4D. By comparing the ratios of a group with gender dysphoria to a cohort from the general population, Sadr et al could assess for any significant difference. Their results indicated a difference in trans-females who presented with more feminized hands. For trans-males, the difference was less pronounced. The results for both groups were slight, and the meta-analysis that accompanies the study notes no statistically significant differences in multiple groups from across cultures. However, Sadr et al further assert that the evidence strongly suggests elevated prenatal testosterone levels in girls and reduced amounts in boys may contribute to gender dysphoria, requiring additional research (Sadr et al, 2020).

In addition to biological factors and correlations with ASD, researchers are exploring psychological and social factors to assess their role in gender dysphoria etiology. This literature examines a range of potential causative agents, including child abuse, trauma, and peer group influences. One such study by Kozlowska et al from 2021 explores patterns in children with high-risk attachment issues who also had gender dysphoria. The authors wanted to assess whether past incidents of abuse, loss, or trauma are associated with higher rates of persons desiring to transition. As a basis, Kozlowska et al cite John Bowlby's research on childhood brain development, noting that the process is not linear and depends

heavily on lived experiences. The study further acknowledges that biological factors combined with life events serve as the foundation for the next developmental phase and that early poor-quality attachment issues increase the risk for psychological disorders in adolescence and adulthood. Such disorders include mood and affective disorders, suicidal ideations, and self-harm. Kozlowska et al also cite other studies that indicate a high correlation between gender dysphoria and "adverse childhood events" and further assert that the condition "needs to be conceptualized in the context of the child's lived experience, and the many different ways in which lived experience is biologically embedded to shape the developing brain and to steer each child along their developmental pathway" (Kozlowska et al, 2021).

For their study, Kozlowska et al recruited 70 children diagnosed with gender dysphoria and completed family assessments going back three generations. This in-depth level was necessary to ascertain any and all events that could affect a child's developmental phases. Additionally, the researchers individually assessed the diagnosed children. To establish comparisons, Kozlowska et al performed assessments on a non-clinical group and a mixed-psychiatric group. Their results demonstrate that children with gender dysphoria have significantly higher rates of attachment issues as well as increased reports of "adverse childhood events" such as trauma (e.g., domestic violence and physical abuse). Furthermore, the authors indicate that a high proportion of families reported "instability, conflict, parental psychiatric disorder, financial stress, maltreatment events, and relational ruptures." These results led Kozlowska et al to conclude that gender dysphoria can be "associated with developmental pathways – reflected in at-risk patterns of attachment and high rates of unresolved loss and trauma – that are shaped by disruptions to family stability and cohesion." The study also cites that treatment requires "a comprehensive biopsychosocial assessment with the child and family, followed by therapeutic interventions that address, insofar as possible, the breadth of factors that are interconnected with each particular child's presentation" (Kozlowska et al, 2021).

This recent study raises questions regarding the medical necessity of gender dysphoria treatments such as puberty blockers and cross-sex hormones for adolescents. If high percentages of children diagnosed with gender dysphoria also have histories of trauma and attachment issues, should conventional behavioral health services be utilized without proposing treatments that pose irreversible effects? Would that approach not provide additional time to address underlying issues before introducing therapies that pose permanent effects (i.e., the watchful waiting approach)?

Aside from the notion that childhood abuse and adversity can potentially cause gender dysphoria, other possible explanations such as social factors (e.g., peer influences and media) may be contributing factors. Research on rapid onset gender dysphoria (ROGD) links this phenomenon to peer and social elements. In an analysis utilizing parent surveys, Lisa Littman asserts that the rapid rise of ROGD is not associated with the traditional patterns of gender dysphoria onset (i.e., evidence of an individual's gravitation to the opposite sex documented over multiple years) but rather exposure to "social and peer contagion." Littman uses this term in the context of definitions cited in academic literature, stating that "social contagion is the spread of affect or behaviors through a population" and that "peer contagion is the process where an individual and peer mutually influence each other in a way that promotes emotions and behaviors that can potentially undermine their own development or harm others." Examples of the latter's negative effects include depression, eating disorders, and substance abuse. What prompted this study is a sudden increase of parents reporting their daughters declaring themselves to be transgender without any previous signs of gender dysphoria. Littman also indicates

that these parents cite that their daughters became immersed in peer groups and social media that emphasized transgender lifestyles (Littman, 2018).

In addition to identifying characteristics of ROGD, the study examines social media content that provides information to adolescents regarding how to obtain cross-sex hormones through deception of physicians, parents, and behavioral health professionals. Such guidance includes coaching on how to fit a description to correspond to the DSM-V and pressures to implement treatment during youth to avoid a potential lifetime of unhappiness in an undesirable body. Littman further states that "online content may encourage vulnerable individuals to believe that non-specific symptoms and vague feelings should be interpreted as gender dysphoria." The study also notes that none of the individuals assessed using the parental surveys qualified for a formal diagnosis using the DSM-V criteria (Littman, 2018).

The survey responses revealed similar data to Kozlowska et al's study with 62.5% of the adolescents having a mental health or neurodevelopmental disorder. Furthermore, the responses indicate a rapid desire to bypass behavioral health options and pursue cross-sex hormones. 28.1% of parents surveyed stated that their adolescents did not want psychiatric treatments. One parent even reported that their daughter stopped taking prescribed anti-depressants and sought advice only from a gender therapist. Littman's research further reveals that 21.2% of parents responded that their adolescent received a prescription for puberty blockers or cross-sex hormones at their first visit (Littman, 2018). These responses indicate that practitioners do not uniformly follow clinical guidelines when making diagnoses or prescribing treatment.

In the discussion, Littman proposes two hypotheses for the appearance of ROGD. The first states that social and peer contagion is one of the primary causes, and the second asserts that ROGD is a "maladaptive coping mechanism" for adolescents dealing with emotional and social issues. While the surveyed parents did not report early signs of gender dysphoria, a majority noted that their daughters had difficulty in handling negative emotions. Littman concludes that ROGD is distinct from gender dysphoria as described in the DSM-V and that further research is needed to assess whether the condition is short or long-term (Littman, 2018). What the study does not explore, but raises the question, is what proportion of those being treated for gender dysphoria are adolescents with ROGD.

Littman's study along with the others reveal that the causes of gender dysphoria are still a mystery and could have multiple biological and social elements. Because of this ongoing uncertainty, treatments that pose irreversible effects should not be utilized to address what is still categorized as a mental health issue. That allows adequate opportunity for individuals to receive treatment for co-existing mental disorders, establish their gender dysphoria diagnoses, and understand how cross-sex hormones and surgery will alter the appearance of their bodies as well as long-term health.

Literature Review: Desistance of Gender Dysphoria and Puberty Suppression

The World Professional Association for Transgender Health (WPATH) and the Endocrine Society both endorse the use of gonadotropin releasing hormones (Gn-RH) to suppress puberty in young adolescents who have gender dysphoria. Both organizations state that the treatment is safe and fully reversible. In addition, they state that delaying pubertal onset can provide extra time for adolescents to explore the gender in which they choose to live. The associations further state that puberty suppression is necessary to prevent the development of primary and secondary sexual characteristics that can inhibit successful transitions into adulthood (WPATH, 2012; Endocrine Society, 2017). Of the two groups, WPATH offers clinical criteria an individual should meet to qualify for puberty suppression such as addressing psychological co-morbidities and assessing whether gender dysphoria has intensified (WPATH, 2012).

Neither organization explains that the majority of young adolescents who exhibit signs of gender dysphoria eventually desist and conform to their natal sex and that the puberty suppression can have side effects. Both organizations neglect to mention that using Gn-RH for gender dysphoria by altering the appearance is not an FDA-approved clinical indication. Furthermore, the research used to justify puberty suppression is low or very-low quality and little information is available on long-term effects (Hruz, 2019). Additionally, in his assessment, Quentin Van Meter explained that physical differences between central precocious puberty and natural onset puberty demonstrate that Gn-RH does not have permanent adverse effects for those treated for the former but can for the latter such as insufficient bone-mineral density and neural development (Van Meter, 2022). Also, as recently as May 17, 2022, during a U.S. Senate Committee on Appropriations hearing, Lawrence Tabak, acting director of the National Institutes of Health, responded to Senator Marco Rubio, acknowledging that no long-term studies are available evaluating the effects of puberty blockers when used for gender dysphoria (U.S. Senate Committee on Appropriations, 2022).

Currently, some studies provide weak support for this treatment but leave too many questions as to its effectiveness and medical necessity, especially considering how many children decide against transitioning. In addition, puberty blockers halt development of primary and secondary sexual characteristics and deny opportunities for adolescents to adapt and become comfortable with their natal sex. Instead, puberty blockers can serve as a potential "gateway drug" for cross-sex hormones by denying them the experience of physically maturing (Laidlaw et al, 2018).

A 2013 study by Steensma et al offers data on the percentage of children who opt not to transition after experiencing gender dysphoria. The authors follow 127 adolescents (mean age of 15 during the evaluation period) for four years who had been referred to a Dutch gender dysphoria clinic. Out of this cohort, 47 (37%; 23 boys and 24 girls) continued experiencing the condition and applied for sex reassignment treatment. The other 80 adolescents never returned to the clinic. Because this clinic was the only one that treated gender dysphoria in the Netherlands, Steensma et al assumed that those who did not return no longer desired transitioning. The study indicates one of the key predictors for persisting gender dysphoria was the age of first presentation. Older adolescents that started going to the clinic were more likely to persist, while younger adolescents tended not to follow through. Steensma et al provide further insight into other predicting factors, particularly on how each individual views his or her gender identity. The authors note that adolescents who "wished they were the other sex" were more likely to become desisters and that those who "believed that they were the other sex" persisted

and later sought sex reassignment treatment (Steensma et al, 2013). While the study focuses on factors that contribute to the condition's persistence or desistance, it raises the question as to whether puberty suppression is necessary when age plays such an important role regarding the decision to transition.

WPATH and the Endocrine Society state that the primary reason for initiating pubertal suppression is not to treat a physical condition but to improve the mental health of adolescents with gender dysphoria. However, available research does not yield definitive results that this method is effective at addressing a mental health issue. The "gold standard" for medical studies is the randomized-controlled trial (RCT). Because RCTs utilize large sample sizes, have blind testing groups (i.e, placebos), and use objective controls, they can offer concrete conclusions and shape the array of established treatments. In addition, RCTs require comparisons between cohort outcomes and ensure that participants are randomly assigned to each group. These measures further reduce the potential for bias and subjectivity (Hariton and Locascio, 2018).

Presently, no RCTs that evaluate puberty suppression as a method to treat gender dysphoria are available. Instead, the limited number of published studies on the topic utilize small sample sizes and subjective methods (Hruz, 2019). A 2015 article by Costa et al is one such example. The study asserts that "psychological support and puberty suppression were both associated with an improved global psychological functioning in gender dysphoric adolescents." To reach this conclusion, the authors selected 201 children diagnosed with the condition and divided them into two groups, one to receive psychological support only and the other to get puberty blockers in addition to psychological support. Costa et al did not create a third group that lacked a gender dysphoria diagnosis to serve as a control. To assess whether puberty suppression is an effective treatment, the authors administered two self-assessments (Utrect Gender Dysphoria Scale and Children's Global Assessment Scale)[6] to the groups at 6-month intervals during a 12-month period. Because the study relies heavily on self-assessments, the conclusions are likely biased and invalid. Another problem that is also present and common throughout articles supporting puberty suppression is the short-term period of the study. Costa et al's conclusions may not be the same if additional follow-ups occurred three or five years later (Costa et al, 2015). This further raises the question whether low-quality studies like Costa et al's should serve as the basis for clinical guidelines advising clinicians to prescribe drugs for off-label purposes.

Aside from questionable research, information regarding the full physical effects of puberty suppression is incomplete. In a 2020 consensus parameter prepared by Chen et al, 44 experts in neurodevelopment, gender development, and puberty/adolescence reached a conclusion stating that "the effects of pubertal suppression warrant further study." The basis for this was that the "full consequences (both beneficial and adverse) of suppressing endogenous puberty are not yet understood." The participating experts emphasized that the treatment's impact on neurodevelopment in adolescents remains unknown. Chen et al explain that puberty-related hormones play a role in brain development as documented in animal studies and that stopping these hormones also prevents neurodevelopment in addition to sexual maturation. The authors further raise the question whether normal brain development resumes as if it had not been interrupted when puberty suppression ceases. Because this

[6] Behavioral health practitioners use the Children's Global Assessment Scale (CGAS) to measure child functioning during the evaluation process to determine diagnoses. Available evidence indicates that the CGAS is not effective for evaluating children who experienced trauma and presented with mental health symptoms (Blake et al, 2006).

question remains unanswered, it casts doubt on the veracity of organizations' assertions that puberty suppression is "fully reversible" (Chen et al, 2020).

In addition to the unanswered questions and low-quality research, puberty suppression causes side effects, some of which have the potential to be permanent. According to a 2019 literature review by De Sanctis et al, most side effects associated with Gn-RH are mild, consisting mostly of irritation around injection sites. However, clinicians have linked the drug to long-term conditions such as polycystic ovarian syndrome, obesity, hypertension, and reduced bone mineral density. While reports of these events are low and the authors indicate that Gn-RH is safe for treating central precocious puberty (Note: De Sanctis et al do not consider gender dysphoria in their analysis), the review raises questions about whether off-label use to treat a psychological condition is worth the risks (De Sanctis et al, 2019).

Furthermore, De Sanctis et al cite studies noting increased obesity rates in girls who take Gn-RH but that more research is needed to gauge the consistency. Additionally, the authors note that evidence is strong regarding reduced bone mineral density during puberty suppression but indicate that the literature suggests it is reversible following treatment (De Sanctis et al, 2019). While research leans toward the reversibility of effects on bone mineral density, the quantity of studies available on this subject are limited. Also, no long-term research has been completed on how puberty suppression affects bone growth. This is significant because puberty is when bone mass accumulates the most (Kyriakou et al, 2020). One example of a complication involving bone growth and Gn-RH is slipped capital femoral epiphysis. This condition occurs when the head of the femur (i.e., thighbone) can slip out of the pelvis, which can eventually lead to osteonecrosis (i.e., bone death) of the femoral head. Although the complication is rare, its link to puberty suppression indicates that the "lack of adequate sex hormone exposure" could be a cause (De Sanctis et al, 2019).

The current literature on puberty suppression indicates that using it to treat gender dysphoria is off-label, poses potentially permanent side effects, and has questionable mental health benefits. The limited research and lack of FDA approval for that clinical indication prompt questions about whether medications with physically altering effects should be used to treat a problem that most adolescents who experience it will later overcome by conforming to their natal sex. Additional evidence is required to establish puberty suppression as a standard treatment for gender dysphoria.

Literature Review: Cross-Sex Hormones as a Treatment for Gender Dysphoria

Currently, the debate surrounding the use of cross-sex hormones to treat gender dysphoria revolves around their ability to improve mental health without causing irreversible effects. It is not about whether taking cross-sex hormones can alter someone's appearance. The evidence demonstrating the effectiveness of cross-sex hormones in achieving the secondary sexual characteristics of the opposite sex is abundant. Also, the overall scientific consensus concludes that individuals who take cross-sex hormones will reduce the primary sexual function of his or her natal sex organs. What researchers continue evaluating are the short and long-term effects on mental health, impacts on overall physical health, and how the changes affect the ability to detransition. Of these, benefits to mental health overshadow the other discussions. Prescribers of cross-sex hormones focus so heavily on behavioral health outcomes that they de-emphasize that these drugs cause permanent physical changes and side effects that can lead to premature death (Hruz, 2020). Some clinical guidelines such as WPATH's do not even indicate that some of the changes are irreversible.

Like puberty suppression, the Endocrine Society and WPATH provide guidance on administering cross-sex hormones to individuals with gender dysphoria. Both organizations state that this treatment should not be administered without a confirmed diagnosis of gender dysphoria and only after a full psychosocial assessment. In addition, behavioral health practitioners must ensure that any mental comorbidities are not affecting the individual's desire to transition. WPATH and the Endocrine Society further state that clinicians should administer hormone replacements such as testosterone and Estradiol (estrogen) in gradual phases, where the dose increases over several months. For trans-females, the organizations state that progesterone (anti-androgen) is also necessary to block the effects of naturally produced testosterone (WPATH, 2012; Endocrine Society, 2017). When taking cross-sex hormones, trans-males need increased doses for the first six months. After that, the testosterone's effects are the same on lower doses. Once started, individuals cannot stop taking hormones unless they desire to detransition (Unger, 2016).

Although the two groups provide similar guidance, they vary on statements that can have significant impact on long-term outcomes, particularly regarding age. According to WPATH's standards, 16 years is the general age for initiating cross-sex hormones, but the organization acknowledges that the treatment can occur for younger individuals depending on circumstances (WPATH, 2012). This differs from the Endocrine Society, which states no specific age for appropriateness and explains the disagreements in assigning a number. The group highlights that most adolescents have attained sufficient competence by age 16 but may not have developed adequate abilities to assess risk (Endocrine Society, 2017). This raises the question whether adolescents can make sound decisions regarding their long-term health. Additionally, the varying guidance raises an issue with WPATH not only using age 16 as a standard but also indicating that younger adolescents are capable of making that choice.

WPATH's guidance also does not stress the irreversible nature of cross-sex hormones, citing the treatment as "partially reversible" and not indicating which changes are permanent. Furthermore, parts of WPATH's information are misleading and directly conflict with guidance issued by clinics and other sources. One such example consists of WPATH stating that "hormone therapy *may* (emphasis added) lead to irreversible changes." This statement is misleading in light of existing research, which indicates that multiple physical changes are permanent. In addition, WPATH claims that certain effects of cross-

sex hormones such as clitoral enlargement can last one to two years when it is actually irreversible (UCSF, 2020). WPATH also does not explain the risks to male fertility, noting that lowered sperm count or sterility is "variable." The University of California at San Francisco (UCSF) provides starkly different information by stating that trans-females should expect to become sterile within a few months of starting cross-sex hormones. UCSF also advises trans-females to consult a sperm bank if they may want to father children after transitioning (WPATH, 2012; UCSF, 2020). Below is a chart that outlines the effects of cross-sex hormones and identifies which ones are reversible or permanent.

Physical Changes Effectuated by Cross-Sex Hormones	
Physical Changes in Trans-Males (Female-to-Male Transitions)	
Physical Change	**Reversible or Irreversible**
Oily Skin or Acne	Reversible
Facial and Body Hair Growth	Irreversible
Male-Pattern Baldness	Irreversible
Increased Muscle Mass	Reversible
Body Fat Redistribution	Reversible
Ceasing of Menstruation	Reversible
Enlarged Clitoris	Irreversible
Vaginal Atrophy	Reversible
Deepening of Voice	Irreversible
Physical Changes in Trans-Females (Male-to-Female Transitions)	
Body Fat Redistribution	Reversible
Decreased Muscle Mass	Reversible
Skin Softening or Decrease in Oiliness	Reversible
Lower Libido	Reversible
Fewer Spontaneous Erections	Reversible
Male Sexual Dysfunction	Possibly Irreversible
Breast Growth	Irreversible
Decrease in Testicular Size	Reversible
Decrease in Sperm Production or Infertility	Likely Irreversible
Slower Facial and Body Hair Growth	Reversible

Sources: UCSF, 2020; WPATH, 2012; Endocrine Society, 2017[7]

The above chart demonstrates that trans-males and trans-females experience different effects from cross-sex hormones that can cause myriad issues in later life. For example, trans-males who opt to detransition may face challenges related to permanent disfigurement (e.g., facial hair and deepened voices). Trans-females, on the other hand, may not endure the same issues pertaining to visible physical changes but might become despondent over being unable to reproduce. This can occur regardless of whether the transitioning individual is satisfied with sex reassignment. Given that the clinical guidelines do not provide uniform information on the permanent effects of cross-sex hormones, clinicians are unable to make sound recommendations to patients. This treatment can supposedly alleviate symptoms

[7] This chart consists of conclusions regarding physical changes made by three different clinical organizations. If one organization determined that a physical change was irreversible, that was sufficient to meet the criteria to be listed as "irreversible" in the chart.

of distress. However, cross-sex hormones' permanent effects also have the potential to cause psychological issues.

Arguments favoring cross-sex hormones assert that the desired physical changes can alleviate mental health issues in individuals with gender dysphoria but do not consider that hormones used in this manner, like puberty blockers, are off-label. While the FDA has approved estrogen and testosterone for specific clinical indications (e.g., hypogonadism), it has not cleared these drugs for treating gender dysphoria. Additionally, these arguments do not acknowledge that the U.S. Drug Enforcement Administration (DEA) lists testosterone as a Schedule III controlled substance, meaning that it has a high probability of abuse (DEA, 2022). Furthermore, evidence of psychological benefit from cross-sex hormones is low-quality and relies heavily on self-assessments taken from small sample groups (Hruz, 2020).

A 2019 study by Kuper et al seeks to demonstrate that adolescents desiring cross-sex hormones have elevated rates of depression, anxiety, and challenges with peer relationships. To make their findings, the authors provided questionnaires to 149 adolescents who presented at a gender clinic in Dallas, Texas and concluded that half of the sample group experienced increased psychological issues. One problem with the study is that it relies on parent or self-assessments such as the Youth-Self Report, Body-Image Scale, and the Child Behavior Checklist. While these assessments have strong reliability, the sample is cross-sectional, consisting of gender dysphoric individuals who presented for an initial visit at the clinic. Also, Kuper et al do not directly link these psychological symptoms to gender dysphoria but rather insinuate a strong connection. Without an analysis of the longitudinal histories of the participants, the study cannot demonstrate whether gender dysphoria was a direct cause of the psychological issues, which could possibly result from trauma, abuse, or family dysfunction. Kuper et al's study only presents weak correlation between adolescents who report symptoms of distress and gender dysphoria. While the authors do not claim that the participants' psychological problems caused the condition, they fail to explicitly state that no demonstrable relationship exists and explain that their findings are "broadly consistent with the previous literature" (Kuper et al, 2019).

Additionally, a more comprehensive literature review from 2019 by Nguyen et al evaluates the effect of cross-sex hormones on mental health outcomes. Although the authors argue that the evidence supports the treatment, they do note that available studies use "uncontrolled observational methods" and "rely on self-report." The review also asserts that "future research should focus on applying more robust study designs with large sample sizes, such as controlled prospective cohort studies using clinician-administered ratings and longitudinal designs with appropriately matched control groups." All of these are characteristics of RCTs. While Nguyen et al highlight flaws in the studies in their conclusion, they do not emphasize them in their analysis, opting to focus primarily on results. Another problem with the studies selected for the review is the short-term periods for evaluation. Out of 11 studies Nguyen et al discuss, only one tracks its participants for 24 months. The others only follow their cohorts for 6 or 12 months (Nguyen et al, 2019). Without long-term data to support assertions that cross-sex hormones substantially improve the mental health of individuals with gender dysphoria, the review cannot make definitive conclusions on the treatment's benefits.

Basing their stances on this low-quality evidence, clinical associations such as the American Academy of Pediatrics (AAP) and the American Psychology Association endorse the use of cross-sex hormones as treatments for gender dysphoria. In particular, the AAP discourages use of the term "transition" and

asserts that medical treatments used to obtain secondary characteristics of the opposite sex are "gender affirming." This decision mirrors the DSM-V's interpretation of gender being part of identity. The AAP further states that taking cross-sex hormones is an "affirmation and acceptance of who they (i.e., patient) have always been" (AAP, 2018). The American Psychological Association also takes a similar stance in its *Resolution on Gender Identity Change Efforts* by asserting that medical treatments such as puberty suppression, cross-sex hormones, and surgery improve mental health and quality of life and reinforce the notion that transitioning and seeking sex reassignment therapies do not constitute a psychological disorder (American Psychological Association, 2021). Stances like these can substantially influence practitioners and their treatment recommendations. Given that low-quality evidence serves as the basis for supportive positions, this raises questions about whether clinicians can make informed decisions for their patients that will promote the best outcomes.

James Cantor published a critique in 2020 of the AAP's endorsement of "gender affirming" treatments, arguing that the organization did not base its recommendations on established medical evidence. He asserts that the AAP's position is based on research that does not support intervention but rather supports "watchful waiting" because most transgender youths desist and identify as their natal sex during puberty. Cantor further argues that the AAP not only disregards evidence but also cites "gender affirming" interventions as the only effective method. To conclude, he states the organization is "advocating for something far in excess of mainstream practice and medical consensus" (Cantor, 2020).

Given those evidentiary problems, those who rely on the AAP's endorsement as a basis for "gender affirming" treatments are practicing eminence-based medicine as opposed to evidence-based medicine. Eminence-based medicine refers to clinical decisions made by relying on the opinions of prominent health organizations rather than relying on critical appraisals of scientific evidence (Nhi Le, 2016). While it is true that the AAP has more knowledge than a lay person and a degree of credibility in the medical community, the opinions of such organizations are not valid unless they are based on quality evidence.

Research on sex reassignment also does not adequately address the reasons for and prevalence of detransitioning. Although no definite numbers are available regarding the percentage of transgender people who decide to detransition, research indicates that roughly 8% decide to return to their natal sex. The reasons range from treatment side effects to more self-exploration that provided insight on individuals' gender dysphoria. In a 2020 study by Lisa Littman, 101 people who had detransitioned provided their basis for doing so. Out of the sample group, 96% had taken cross-sex hormones and 33% had sex reassignment surgery. The average age for transitioning was 22 years, and the mean duration for the transition was 4 years. This indicates that even allowing additional time beyond the recommended age of 16 years can still lead to regrets. The study also raises the question as to whether individuals who transitioned at 16 or younger wanted to detransition in greater numbers. The author further offers reasons why these individuals sought cross-sex hormones and surgery, which include having endured trauma (mental or sexual), homophobia (challenged to accept oneself as a homosexual), peer and media influences, and misogyny (applicable only to trans-males). To obtain the results, the participants responded to a survey that asked about their backgrounds (e.g., reasons for transitioning, mental health comorbidities), and motivations for detransitioning. Littman noted that half of the women (former trans-males) had a mental health disorder and/or had experienced trauma within a year of deciding to transition. Men (former trans-females) reported much lower numbers of behavioral health issues and trauma after de-transitioning. Additionally, 77% of men surveyed identified as the opposite gender prior to transition, whereas just 58% of women had (Littman, 2020).

Of the reasons cited for detransitioning, the majority (60%) noted that they became more comfortable with their natal sex. Other reasons included concerns over complications from the treatments, primarily cross-sex hormones, and lack of improved mental health. Other less-cited explanations include concerns about workplace discrimination and worsening physical health. The study also notes that approximately 36% of participants experienced worse mental health symptoms. Based on the findings, Littman concludes that more research is needed in tracking the transgender population to obtain accurate percentages of those who decide to detransition and that men and women reported varying reasons for deciding to transition and later return to their natal sex. The author notes that higher rates of trauma and peer group influences might have contributed to women's decisions, which Littman attributes partially to rapid onset gender dysphoria (Littman, 2020). What the study also indicates is that cross-sex hormones are not a validated treatment for gender dysphoria. Nearly all of the participants had taken them and decided against maintaining the physical changes. Given that the majority of surveyed detransitioners cited that they were comfortable with their biological sex, the study indicates that gender dysphoria is not necessarily a lifelong issue. This necessarily raises doubts about whether cross-hormones, which cause permanent physical damage, is justified.

In addition to the psychological factors, cross-sex hormones pose significant long-term health risks to transitioning individuals. Currently, little information is available given that researchers have not had adequate time to study the effects in this population. However, use of hormones for other conditions has yielded data on how these drugs can affect the body and the cardiovascular system in particular. Because of the high dosages required to achieve physical change and the need to continuously take the drugs, cross-sex hormones can potentially harm quality of life and reduce life expectancy for transitioning individuals. According to Dutra et al, trans-females are three times more likely to die from a cardiovascular event than the general population. In their 2019 literature review, Dutra et al examined the results of over 50 studies evaluating the effects of cross-sex hormones on not only transgender individuals but those with menopause and other endocrine disorders, all of which indicate that use of estrogen or testosterone can increase risks for cardiovascular disease. Throughout their review, Dutra et al cite examples of trans-females having higher triglyceride levels after 24 months of cross-sex hormones and how researchers halted a study on estrogen due to an increase in heart attacks among participants. Another article the authors reference indicates a higher risk for thromboembolisms (i.e., blood clots) in trans-females. For trans-males, Dutra et al explain that research shows significant increased risk for hypertension, high cholesterol, obesity, and heart attacks. One study noted that trans-males have a four times greater risk of heart attack compared to women identifying as their natal sex. Dutra et al conclude that most transgender individuals are younger than 50 and that more studies are needed as this population ages. They do note that available studies indicate that cross-sex hormones pose dangers to long-term cardiovascular health (Dutra et al, 2019).

In sum, the literature reveals that the evidence for cross-sex hormones as a treatment for gender dysphoria is weak and insufficient. Between the permanent effects, off-label use, and consequences to long-term health, cross-sex hormones are a risky option that does not promise a cure but does guarantee irreversible changes to both male and female bodies. Additionally, the inadequate studies serving as the basis for recommendations by clinical associations can lead to providers making poorly informed decisions for their patients. Research asserting that taking cross-sex hormones improves mental health is subjective and short-term. More studies that utilize large sample sizes and appropriate

methods is required before the medical profession should consider cross-sex hormones as one of gender dysphoria's standard treatments.

Literature Review: Sex Reassignment Surgery

The final phase of treatment for gender dysphoria is sex reassignment surgery. This method consists of multiple procedures to alter the appearance of the body to resemble an individual's desired gender. Some procedures apply to the genitals (genital procedures) while others affect facial features and vocal cords (non-genital procedures). While the surgery creates aesthetical aspects, it does not fully transform someone into the opposite biological sex. Transgender persons who undergo the procedures must continue taking cross-sex hormones to maintain secondary sexual characteristics. Additionally, all physical changes are irreversible, and the success rate of a surgery varies depending on the procedure and the population. For example, surgeries for trans-females have much better results than those for trans-males. Complications such as post-operative infections can also arise with the urinary tract system. However, sex reassignment surgery supposedly can provide drastic, if not complete, relief from gender dysphoria (Endocrine Society, 2017). The following is a list of procedures (both genital and non-genital) for trans-females and trans-males that create physical features of the desired sex.

Procedures for Trans-Females

- **Genital Surgeries:** These consist of penectomy (removal of the penis), orchiectomy (removal of the testicles), vaginoplasty (construction of a neo-vagina), clitoroplasty (construction of a clitoris), and vulvoplasty (construction of a vulva and labia). To perform, a surgeon begins by deconstructing the penis and removing the testicles. The penile shaft and glans are repurposed to serve as a neo-vagina and artificial clitoris (Note: These are not actual female genitalia but tissue constructed to resemble female anatomy). If the shaft tissue is insufficient, the surgeon may opt to use a portion of intestine to build a neo-vagina. The scrotum serves as material for fashioning a vulva and labia. In addition to constructing female genitalia, the surgeon reroutes the urethra to align with the neo-vagina. Genital surgeries for trans-females result in permanent sterility (Bizic et al, 2014).
- **Chest Surgery:** To attain full breasts, trans-females can undergo enlargement. The procedure is similar to breast augmentation for women where a surgeon places implants underneath breast tissue. Prior to surgery, trans-females need to take cross-sex hormones for roughly 24 months to increase breast size to get maximum benefit from the procedure (Endocrine Society, 2017).
- **Cosmetic and Voice Surgeries:** Designed to create feminine facial features, fat deposits, and vocal sounds, these procedures are secondary to genital procedures and intended to alter trans-females' appearances to better integrate into society as a member of the desired gender (WPATH, 2012).

Procedures for Trans-Males

- **Mastectomy:** This is the most performed sex reassignment surgery on trans-males because cross-sex hormones and chest-binding garments are often insufficient at diminishing breasts. To remove this secondary sexual characteristic, trans-males can undergo a mastectomy where a surgeon removes breast tissue subcutaneously (i.e., under the skin) and reconstructs the nipples to appear masculine. The procedure can result in significant scarring (Monstrey et al, 2011).
- **Genital Surgeries:** Unlike the procedures for trans-females, genital surgeries for trans-males are more complex and have lower success rates. Consisting of hysterectomy, oophorectomy

(removal of the ovaries), vaginectomy (removal of the vagina), phalloplasty (construction of a penis), and scrotoplasty (construction of prosthetic testicles), a team of surgeons must manufacture a penis using skin from the patient (taken from an appendage) while removing the vagina and creating an extended urethra. The functionality of the artificial penis can vary based on how extensive the construction was. Attaining erections requires additional surgery to implant a prosthesis, and the ability to urinate while standing is often not achieved. Genital procedures for trans-males result in irreversible sterility (Monstrey et al, 2011).

- **Cosmetic Surgeries:** Similar to trans-females, these procedures create masculine facial features, fat deposits, and artificial pectoral muscles. They aid trans-males with socially integrating as their desired gender. Surgery to deepen voices is also available but rarely performed (WPATH, 2012).

Because sex reassignment surgery is irreversible, the criteria for receiving these procedures is the strictest of all gender dysphoria treatments. WPATH and the Endocrine Society suggest rigorous reviews of patient history and prior use of other therapies before approving. Furthermore, the two organizations recommend that only adults (18 years old) undergo sex reassignment surgery.[8] WPATH and the Endocrine Society also recommend ensuring a strongly documented diagnosis of gender dysphoria, addressing all medical and mental health issues, and at least 12 months of cross-sex hormones for genital surgeries. Although the organizations agree on most criteria, they differ on whether hormones should be taken prior to mastectomies. WPATH asserts that hormones should not be a requirement, whereas the Endocrine Society advises up to 2 years of cross-sex hormones before undergoing the procedure (WPATH, 2012; Endocrine Society, 2017). What this indicates is that trans-males might undergo breast removal without having first pursued all options if their clinician adheres to WPATH's guidelines, which can lead to possible regret over irreversible effects.

As with cross-sex hormones, sex reassignment surgery's irreversible physical changes can potentially show marked mental health improvements and prevent suicidality in people diagnosed with gender dysphoria. In April 2022, the chair of the University of Florida's pediatric endocrinology department, Dr. Michael Haller, advocated for the benefits of "gender affirming" treatments (WUSF, 2020). However, the available evidence calls such statements into question. Recent research assessing both cross-sex hormones and sex reassignment surgery indicate that the effects on "long-term mental health are largely unknown." In studies regarding the benefits of surgery, the results have the same weaknesses as the research for the effectiveness of cross-sex hormones. These include small sample sizes, self-report surveys, and short evaluation periods, all of which are insufficient to justify recommendations for irreversible treatments (Bränström et al, 2020).

Two studies conducted in Sweden provide insight on the effectiveness of sex reassignment surgery in improving the behavioral health of transgender persons. Because Sweden has a nationalized health system that collects data on all residents, this country can serve as a resource to assess service utilization and inpatient admissions. Both studies, one by Dhejne et al from 2011 and another by Bränström et al published in 2020, assessed individuals who had received sex reassignment surgery and examined outcomes over several decades. Dhejne et al's findings indicate that sex reassignment

[8] Although practice guidelines indicate the minimum age to undergo sex reassignment surgery is 18, available evidence demonstrates that mastectomies have been performed on adolescent girls as young as 13 who experience "chest dysphoria" (Olson-Kennedy et al, 2018).

procedures do not reduce suicidality. The authors explained that individuals who underwent sex reassignment surgery were still more likely to attempt or commit suicide than those in the general population. This study is unique because it monitored the subjects over a long period of time. Dhejne et al note that the transgender persons tracked for the study did not show an elevated suicide risk until ten years after surgery (Dhejne et al, 2011). Given that a high proportion of research follows sex reassignment patients for much shorter timeframes, this evidence indicates that surgery might have little to no effect in preventing suicides in gender dysphoric individuals over the long run.

In addition to having an increased suicide risk, Dhejne et al discuss how individuals who underwent sex reassignment procedures also had higher mortality due to cardiovascular disease. The authors do not list the specific causes but establish the correlation. Given that cross-sex hormones can damage the heart, the increased risk could be related to the drugs and not the surgery. Furthermore, the study explains that the tracked population had higher rates of psychiatric inpatient admissions following sex reassignment. Dhejne et al established this by examining the rates of psychiatric hospitalizations in these individuals prior to surgery and noted higher utilization in the years following the procedures. These results are in comparison to the Swedish population at large. While the study contradicts other research emphasizing improvements in mental health issues, it has its limitations. For example, the sample size is small. Dhejne et al identified only 324 individuals who had undergone sex reassignment surgery between 1973 and 2003. In addition, the authors noted that while the tracked population had increased suicide risks when compared to individuals identifying as their natal sex, the rates could have been much higher if the procedures were not available (Dhejne et al 2011). What this study postulates is that sex reassignment surgery does not necessarily serve as a "cure" to the distress resulting from gender dysphoria and that ongoing behavioral health care may still be required even after a complete transition.

Bränström et al's study evaluating the Swedish population used a larger sample (1,018 individuals who had received sex reassignment surgery) but tracked them for just a ten-year period (2005 to 2015).[9] Unlike Dhejne et al, the authors did not track suicides and focused primarily on mood or anxiety disorder treatment utilization. Their results indicate that transgender persons who had undergone surgery utilized psychiatric outpatient services at lower rates and were prescribed medications for behavioral health issues at an annual decrease rate of 8%. Bränström et al also did not limit comparisons to Sweden's overall population and factored in transgender persons who take cross-sex hormones but have not elected to have surgery. Those results still presented a decrease in outpatient mental health services. However, Bränström et al note that individuals only on cross-sex hormones showed no significant reduction in that category, which calls into question claims regarding effectiveness of cross-sex hormones in ameliorating behavioral issues.

The Bränström et al study prompted numerous responses questioning its methodology. The study lacked a prospective cohort or RCT design, and it did not track all participants for a full ten-year period (Van Mol et al, 2020). These criticisms resulted in a retraction, asserting that Bränström et al's conclusions were "too strong" and that further analysis by the authors revealed that the new "results demonstrated no advantage of surgery in relation to subsequent mood or anxiety disorder-related

[9] Although Bränström et al claim to follow individuals for a ten-year period, peer reviews of the research revealed that this was not the case, noting the authors had varying periods of tracking, ranging from one to ten years (Van Mol et al, 2020).

health care visits or prescriptions or hospitalizations following suicide attempts in that comparison" (Kalin, 2020).

There are multiple explanations for why the Bränström et al study reached different results than the Dhejne et al study. For starters, Bränström et al tracked a larger sample group over a later period (2005 to 2015 as opposed to 1973 to 2003) during which gender dysphoria underwent a dramatic shift in definition. Also, Dhejne et al did not see elevated suicides until after ten years, raising the question as to whether sex reassignment surgery has temporary benefits on mental health rather than long-term or permanent benefits. Like the other Swedish study, Bränström et al's findings are a correlation and do not specifically state that the procedures cause reduced psychiatric service utilization (Bränström et al, 2020).

A 2014 study by Hess et al in Germany evaluated satisfaction with sex reassignment procedures by attempting to survey 254 trans-females on their quality of life, appearance, and functionality as women. Out of the participants selected, only 119 (47%) returned completed questionnaires, which Hess et al indicate is problematic because dissatisfied trans-females might not have wanted to provide input. The results from the collected responses noted that 65.7% of participants reported satisfaction with their lives following surgery and that 90.2% indicated that the procedures fulfilled their expectations for life as women. While these results led Hess et al to conclude that sex reassignment surgery generally benefits individuals with gender dysphoria, the information is limited and raises questions (Hess et al, 2014). Such questions include whether the participants had mental health issues before or after surgery and did their satisfaction wane over time. Hess et al only sent out one questionnaire and not several to ascertain consistency over multiple years. Questions like these raise doubts about the validity of the study. Although Hess et al's research is just one study, numerous others utilize the same subjective methods to reach their conclusions (Hruz, 2018).

In his assessment, Patrick Lappert contributes additional insight on the appropriate clinical indications for mastectomies, noting that removal of breast tissue is necessary following the diagnosis of breast cancer or as a prophylactic against that disease. He cites that this basis is verifiable through definitive laboratory testing and imaging, making it an objective diagnosis, whereas gender dysphoria has no such empirical methods to assess and depends heavily on the patient's perspective. Also, Lappert notes that trans-males who make such decisions are doing so on the idea that the procedure will reduce their dysphoria and suicide risk. However, they are making an irreversible choice based on anticipated outcomes supported only by weak evidence, and thus cannot provide informed consent (Lappert, 2022).

The literature is inconclusive on whether sex reassignment surgery can improve mental health for gender dysphoric individuals. Higher quality research is needed to validate this method as an effective treatment. This includes studies that obtain detailed participant histories (e.g., behavioral diagnoses) and track participants for longer periods of time. These are necessary to evaluate the full effects of treatments that cause irreversible physical changes. In addition, sex reassignment procedures can result in severe complications such as infections in trans-females and urethral blockage in trans-males. Health issues related to natal sex can also persist. For example, trans-males who undergo mastectomy can still develop breast cancer and should receive the same recommended screenings (Trum et al, 2015). Until more definitive evidence becomes available, sex reassignment surgery should not qualify as a standard treatment for gender dysphoria.

Literature Review: Quality of Available Evidence and Bioethical Questions

Quality of Available Evidence

Clinical organizations that have endorsed puberty suppression, cross-sex hormones, and sex reassignment surgery frequently state that these treatments have the potential to save lives by preventing suicide and suicidal ideation. The evidence, however, does not support these conclusions. James Cantor notes that actual suicides (defined as killing oneself) are low, occur at higher rates for men, and that interpretations of available research indicate a blurring of numbers between those with gender dysphoria and homosexuals (Cantor, 2022). Although information exists that contradicts certain arguments, media outlets continue to report stories emphasizing the "lifesaving" potential of sex reassignment treatment. A May 2022 story by NBC announced survey results under the headline "Almost half of LGBTQ youths 'seriously considered suicide in the past year'" (NBC, 2022). This is a significant claim that can have a sensational effect on patients and providers alike, but how strong is the evidence supporting it? Almost all of the data backing this assertion are based on surveys and cross-studies, which tend to yield low-quality results (Hruz, 2018). In addition, how many gender dysphoric individuals are seeing stories in the media and not questioning the narrative? Because research on the effectiveness of treatments is ongoing, a debate persists regarding their use in the adolescent and young-adult populations, and much of it is due to the low-quality studies serving as evidence.

In their assessment, Romina Brignardello-Petersen and Wojtek Wiercioch examined the quality of 61 articles published between 2020 and 2022 (Note: See Attachment A for the full study). They identified research on the effectiveness of puberty blockers, cross-sex hormones, and sex reassignment surgery and assigned a grade (high, moderate, low, or very low) in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Out of the articles reviewed, all with a few exceptions received grades of low or very low quality when demonstrating outcomes regarding improvements in mental health and overall satisfaction with transitioning. For puberty blockers, Brignardello-Petersen and Wiercioch identified low quality evidence for alleviating gender dysphoria and very low quality for reducing suicidal ideation. The authors also had nearly identical findings for cross-sex hormones. However, they noted moderate quality evidence for the likelihood of cardiovascular side effects. Regarding surgery, Brignardello-Petersen and Wiercioch graded articles that examined overall satisfaction and complication rates. None of the studies received grades higher than low quality. These findings led the authors to conclude that "there is great uncertainty about the effects" of sex reassignment treatments and that the "evidence alone is not sufficient to support" using such treatments. Among the studies graded was one the U.S. Department of Health and Human Services cited in its information on "gender affirming" treatments. The authors noted this research had a "critical risk of bias" and was of low quality (Brignardello-Petersen and Wiercioch, 2022).

For his part, James Cantor provided a review of available literature, which addresses studies on etiology, desistance, effectiveness of puberty blockers and cross-sex hormones, suicidal behaviors, and clinical association and international guidelines. Throughout his analysis, Cantor cites weak evidence, poor methodologies (e.g., retrospective versus prospective studies), and lack of professional endorsements in research that indicates the benefits of sex reassignment treatment. Additionally, he notes that improvements in the behavioral health of adolescents who take cross-sex hormones can be attributed to the counseling they receive concurrently and that suicidality is not likely to result from gender

dysphoria but from co-occurring mental disorders. The reasoning behind the third point is based on the blending of suicide and suicidality, which are two distinct concepts. The former refers specifically to killing oneself, and the second regards ideation and threats in attempts to receive help. Cantor specifically notes that actual suicides are highly unlikely among gender dysphoric individuals, particularly trans-males. His other conclusions indicate that young children who experience gender identity issues will most likely desist by puberty, that multiple phenomena can cause the condition, and that Western European health services are not recommending medical intervention for minors. The basis for these statements is the paucity of high to moderate quality evidence on the effectiveness of sex reassignment treatments and numerous studies demonstrating desistance (Cantor, 2022).

Despite the need for stronger studies that provide definitive conclusions, many practitioners stand by the recommendations of the AAP, Endocrine Society, and WPATH. This is evident in a letter submitted to the *Tampa Bay Times*, which was a rebuttal to the Florida Department of Health's (DOH) guidance on treatment for gender dysphoria (Note: The guidance recommends against using puberty blockers, cross-sex hormones, or surgery for minors) (DOH, 2022). The authors, led by six professors at the University of Florida's College of Medicine, state that recommendations by clinical organizations are based on "careful deliberation and examination of the evidence by experts." However, evaluations of these studies show otherwise. Not only does the available research use cross-sectional methods such as surveys, but it provides insufficient evidence based on momentary snapshots regarding mental health benefits. These weak studies are the foundation for the clinical organizations' guidelines that the University of Florida professors tout as a gold standard. In addition, the letter's authors state that DOH's guidance is based on a "non-representative sample of small studies and reviews, editorials, opinion pieces, and commentary" (Tampa Bay Times, 2022). That statement misses the point when it comes to evidence demonstrating whether treatments with irreversible effects are beneficial because the burden of proof is on those advocating for this treatment, not on those acknowledging the need for further research. This raises the question concerning how much academic rigor these professors are applying to practice guidelines released by clinical organizations and whether they also apply the same level of rigor to novel treatments for other conditions (e.g., drugs, medical devices).

Another example of a lack of rigor is a 2019 article by Herman et al from the University of California at Los Angeles (UCLA) that evaluated responses to a 2015 national survey on transgender individuals and suicide. Unlike other studies, this one utilized a large cohort with 28,000 participants from across the U.S. responding. However, the researchers used no screening criteria and did not randomly select individuals. In addition, responses consisted entirely of self-reports with no supporting evidence to even prove a diagnosis of gender dysphoria. Although Herman et al conclude that the U.S. transgender population is at higher risk for suicidal behaviors, the authors' supporting evidence is subjective and serves as a weak basis. Additionally, the survey results do not establish gender dysphoria as a direct cause of suicide or suicidal ideation. The questions required participants to respond about their overall physical and mental health. Out of those that indicated "poor" health, 77.7% reported suicidal thoughts or attempts during the previous year, whereas just 29.1% of participants in "excellent" health had. These percentages indicate that causes beyond gender dysphoria could be affecting suicidal behaviors. Other reasons cited include rejection by family or religious organizations and discrimination. The authors also acknowledge that their findings are broad, not nationally representative, and should serve as a basis for pursuing future research (Herman et al, 2019).

Yet another example is a study published in 2022 by Olson et al tracks 300 young children that identify as transgender over a 5-year period, and asserts low probabilities for detransitioning, while supporting interventions such as puberty blockers. The authors found that children (median age of 8 years) who identified as a gender that differed from their natal sex were unlikely to desist at a rate of 94% and conclude that "transgender youth who socially transitioned at early ages" will continue "to identify that way." While this appears to contradict earlier studies that demonstrate most young adolescents who change gender identities return to their "assigned gender at birth," the authors note differences and limitations with the results. For example, Olson et al notes that they did not verify whether the participants met the DSM-V's diagnostic criteria for gender dysphoria and that the children's families supported the decisions to transition. Instead, the authors relied on a child's chosen pronouns to classify as transgender. Also, Olson et al acknowledged that roughly 66% of the sample was biologically male. This is particularly significant considering that the majority of transitioning adolescents in recent years were natal females. Another issue with the study includes the median age at the end of follow-up (13 years), which is when boys begin puberty. Furthermore, the authors cite that the participants received strong parental support regarding the transitions, which constitutes positive reinforcement (Olson et al, 2022). Other research demonstrates that such feedback on social transitioning from parents and peers can prevent desistance following pubertal onset (Zucker, 2019). Despite these limitations, the New York Times announced the study's publication under the headline "Few Transgender Children Change Their Minds After 5 Years" (New York Times, 2022). Such a title can add to the public's perception that gender dysphoria requires early medical intervention to address.

Bioethical Questions

The irreversible physical changes and potential side effects of sex reassignment treatment raise significant ethical questions. These questions concern multiple bioethical principles including patient autonomy, informed consent, and beneficence. In a 2019 article, Michael Laidlaw, Michelle Cretella, and Kevin Donovan argue that prescribing puberty blockers or cross-sex hormones on the basis that they will alleviate psychological symptoms should not be the standard of care for children with gender dysphoria. Additionally, the three authors assert that such treatments "constitute an unmonitored, experimental intervention in children without sufficient evidence of efficacy or safety." The primary ethical question Laidlaw, Cretella, and Donovan pose is whether pushing physical transitioning, particularly without parental consent, violates fully informed consent (Laidlaw et al, 2019).

In accordance with principles of bioethics, several factors must be present to obtain informed consent from a patient. These consist of being able to understand and comprehend the service and potential risks, receiving complete disclosure from the physician, and voluntarily providing consent. Bioethicists generally do not afford the ability of giving informed consent to children who lack the competence to make decisions that pose permanent consequences (Varkey, 2021). Laidlaw, Cretella, and Donovan reinforce this point regarding sex reassignment treatment when they state that "children and adolescents have neither the cognitive nor the emotional maturity to comprehend the consequences of receiving a treatment for which the end result is sterility and organs devoid of sexual function" (Laidlaw et al, 2019). This further raises the question whether clinicians who make such treatment recommendations are providing full disclosure about the irreversible effects and truly obtaining informed consent.

Another issue is the conflict between consumerism and the practitioner's ability to provide appropriate care. Consumerism refers to patients learning about treatments through media/marketing and requesting their health care provider to prescribe it, regardless of medical necessity. Considering that social media is rife with individuals promoting "gender affirmative" drugs and surgeries, children are making self-assessments based on feelings they may not understand and that can lead to deep regret in the future (Littman, 2018). This can contribute to patients applying pressure on their doctors to prescribe medications not proven safe or effective for the condition. Consumerism can also affect bioethical compliance because it constrains clinicians from using their full "knowledge and skills to benefit the patient," which is "tantamount to a form of patient abandonment and therefore is ethically indefensible" (Varkey, 2021).

In his assessment, G. Kevin Donovan explains the bioethical challenges related to sex reassignment treatment, emphasizing the lack of informed consent when administering these services. He asserts that gender dysphoria is largely a self-diagnosis practitioners cannot verify with empirical tests (e.g., labs and imaging) and that providing such treatments is experimental. Because of the lack of consent and off-label use of puberty blockers and cross-sex hormones, Donovan raises the question as to how "experienced and ethical physicians so mislead others or be so misled themselves?" He further attributes this phenomenon to societal and peer pressures that influence self-diagnosis and confirm decisions to transition. As a result, these pressures lead to individuals wanting puberty blockers, cross-sex hormones, and surgery. Donovan goes on to identify several news stories where embracing sex reassignment treatment is a "cult-like" behavior. To conclude, he links these factors back to the failure to obtain informed consent from transgender patients and how that violates basic bioethical principles (Donovan, 2022).

Coverage Policies of the U.S. and Western Europe

U.S. Federal Level Coverage Policies

Medicare: In 2016, the Centers for Medicare and Medicaid Services (CMS) published a decision memo announcing that Medicare Administrative Contractors (MACs) can evaluate sex reassignment surgery coverage on a "case-by-case" basis.[10] CMS specifically noted that the decision memo is not a National Coverage Determination and that "no national policy will be put in place for the Medicare program" (CMS, 2016). This memo was the result of CMS reviewing over 500 studies, reports, and articles to the validity of the procedures. Following its evaluation, CMS determined that "the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding . . . small sample sizes, lack of validated assessment tools, and considerable (number of participants in the studies) lost to follow up." In 2017, CMS reinforced this position with a policy transmittal that repeated the 2016 memo's criteria (CMS, 2017).

The basis for Medicare's decision is that the "clinical evidence is inconclusive" and that "robust" studies are "needed to ensure that patients achieve improved health outcomes." In its review of available literature, CMS sought to answer whether there is "sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria." After evaluating 33 studies that met inclusion criteria, CMS's review concludes that "not enough high-quality evidence" is available "to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively." Additionally, out of the 33 studies, just 6 provided "useful information" on the procedures' effectiveness, revealing that their authors "assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies" that "did not demonstrate clinically significant changes or differences in psychometric test results" following sex reassignment surgery (CMS, 2016).

U.S. Department of Defense – Tricare: Tricare does not cover sex reassignment surgery, but it will cover psychological services such as counseling for individuals diagnosed with gender dysphoria and cross-sex hormones when medically necessary (Tricare, 2022).[11]

U.S. Department of Veterans Affairs: The U.S. Department of Veterans Affairs (VA) does not cover sex reassignment surgery, although it will reimburse for cross-sex hormones and pre- and post-operative care related to transitioning. Because the VA only provides services to veterans of the U.S. armed forces, it cannot offer sex reassignment treatment to children (VA, 2020).[12]

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[10] The Centers for Medicare and Medicaid Services is part of the U.S. Department of Health and Human Services. Its primary functions are to administer the entire Medicare system and oversee federal compliance of state Medicaid programs. In addition, CMS sets reimbursement rates and coverage criteria for the Medicare program.
[11] Tricare is the insurance program that covers members of the U.S. armed forces and their families. This includes children of all ages.
[12] The U.S. Department of Veterans Affairs oversees the Veterans Health Administration (VHA), which consists of over 1,000 hospitals, clinics, and long-term care facilities. As the largest health care network in the U.S., the VHA provides services to veterans of the U.S. armed forces.

State-Level Coverage Policies

Florida: In April 2022, DOH issued guidance for the treatment of gender dysphoria, recommending that minors not receive puberty blockers, cross-sex hormones, or sex reassignment surgery. [13] The justification offered for recommending against these treatments is that available evidence is low-quality and that European countries also have similar guidelines. Accordingly, DOH provided the following guidelines:

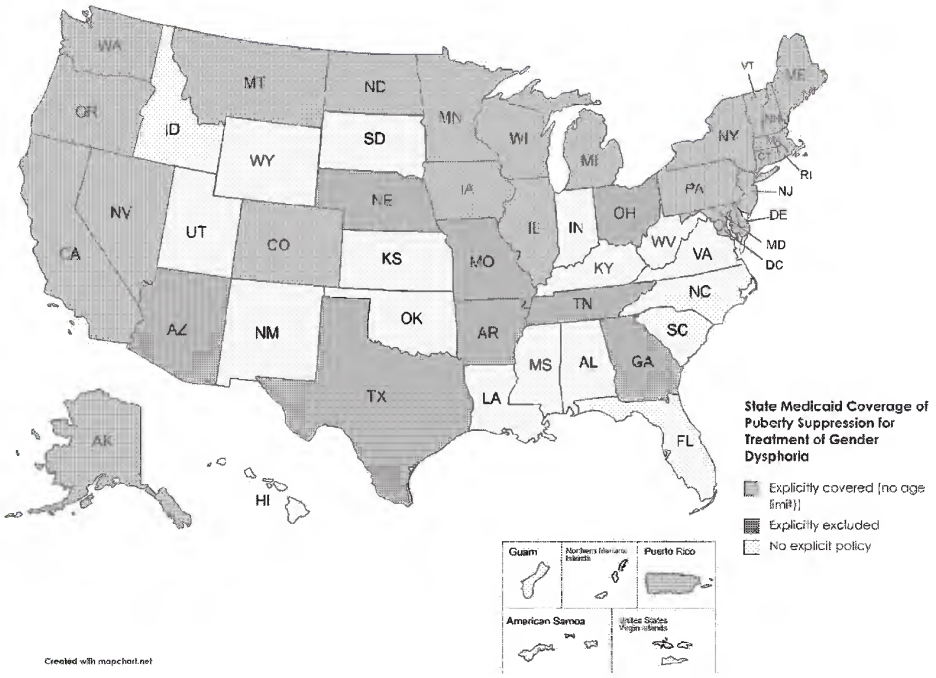
- "Social gender transition should not be a treatment option for children or adolescents."
- "Anyone under 18 should not be prescribed puberty blockers or hormone therapy."
- "Gender reassignment surgery should not be a treatment option for children or adolescents."
- "Children and adolescents should be provided social support by peers and family and seek counseling from a licensed provider."

In a separate fact sheet released simultaneously with the guidance, DOH further asserts that the evidence cited by the federal government cannot establish sex reassignment treatment's ability to improve mental health (DOH, 2022).

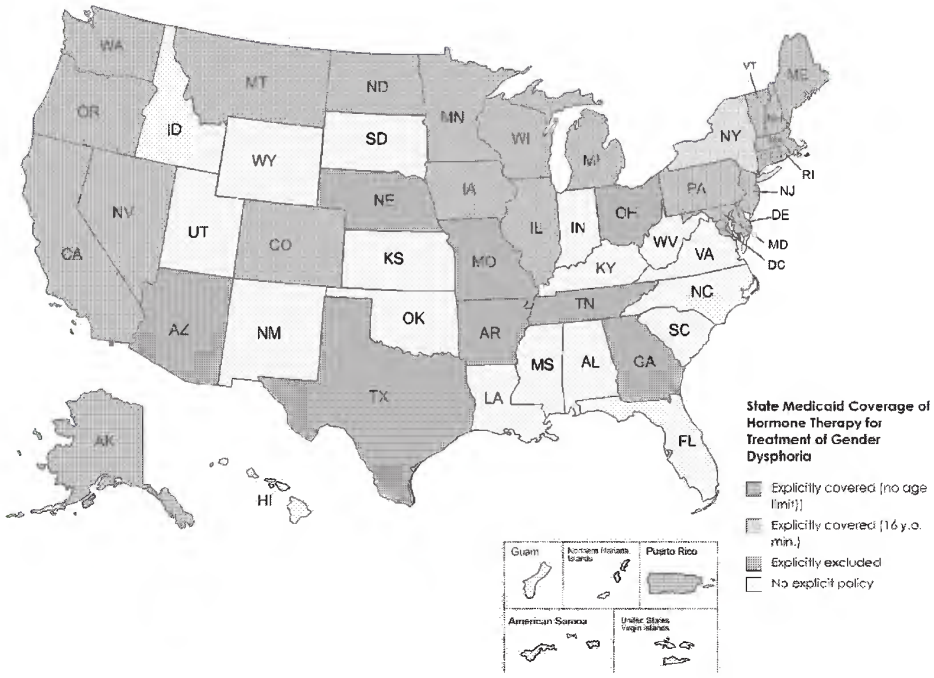
State Medicaid Programs: Because individual states differ in health services offered, Medicaid programs vary in their coverage of sex reassignment treatments. The following maps identify states that cover sex reassignment treatments, states that have no policy, and states that do not cover such treatments.

[13] Unlike the federal government, the State of Florida delegates responsibilities for Medicaid and health care services to five separate agencies (Agency for Health Care Administration, Department of Health, Department of Children and Families, Department of Elder Affairs, and Agency for Persons with Disabilities). Each agency has its own separate head (secretary or surgeon general), which reports directly to the Executive Office of the Governor. As Florida's public health agency, DOH oversees all county health departments, medical professional boards, and numerous health and welfare programs (e.g., Early Steps and Women, Infants, and Children). Because it oversees the boards, DOH has authority to release practice guidelines.

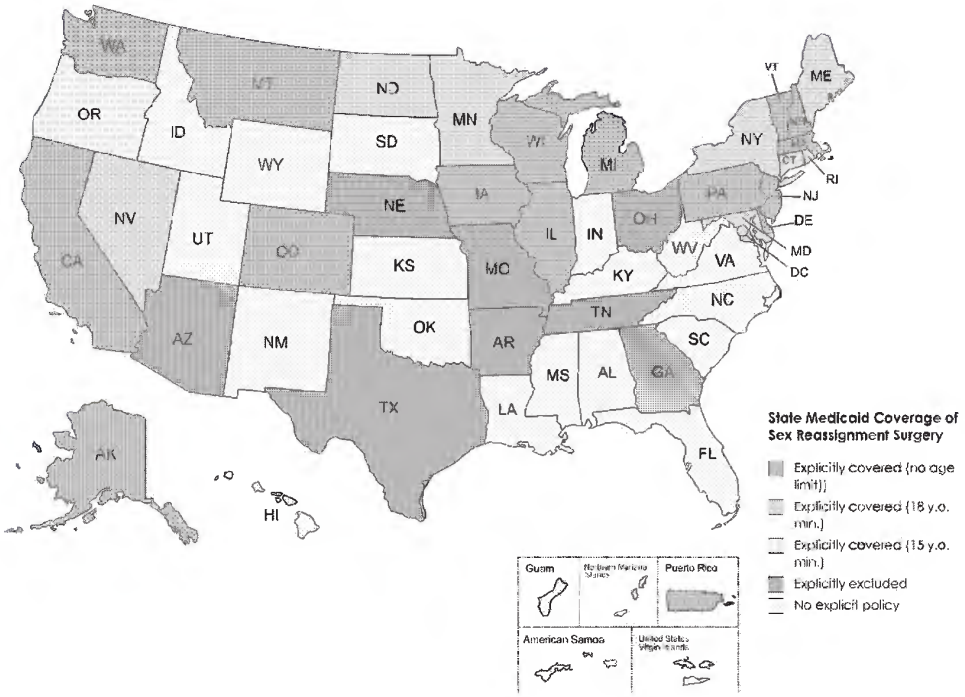
State Medicaid programs with coverage decisions regarding puberty blockers:



State Medicaid programs with coverage decisions regarding cross-sex hormones:



State Medicaid programs with coverage decisions regarding sex reassignment surgery:



Western Europe

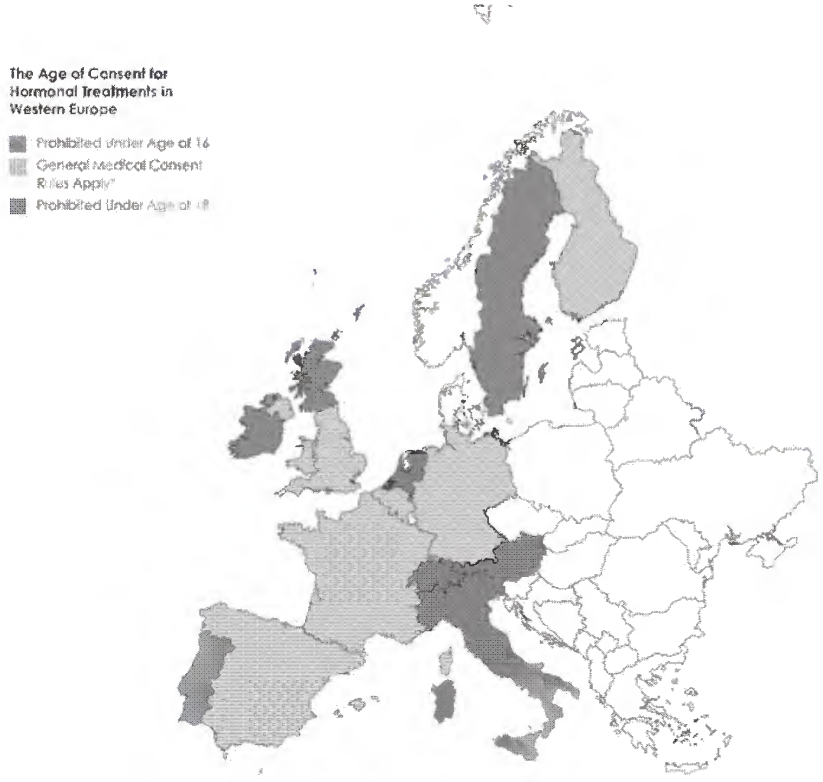
Scandinavian countries such as Sweden and Finland have released new guidelines on sex reassignment treatment for children. In 2022, the Swedish National Board of Health stated that "the risks of hormonal interventions for gender dysphoric youth outweigh the potential benefits." With the exception of youths who exhibited "classic" signs of gender identity issues, adolescents who present with the condition will receive behavioral health services and gender-exploratory therapy (Society for Evidence Based Gender Medicine, 2022).

In Finland, the Palveluvalikoima issued guidelines in 2020 stating that sex reassignment in minors "is an experimental practice" and that "no irreversible treatment should be initiated." The guidelines further assert that youths diagnosed with gender dysphoria often have co-occurring psychiatric disorders that must be stabilized prior to prescribing any cross-sex hormones or undergoing sex reassignment surgery (Palveluvalikoima, 2020).

The United Kingdom (U.K.) is also reassessing the use of irreversible treatments for gender dysphoria due the long-term effects on mental and physical health. In 2022, an independent interim report commissioned by the U.K.'s National Health Service (NHS) indicates that additional research and systematic changes are necessary to ensure the safe treatment of gender dysphoric youths. These include reinforcing the diagnosis process to assess all areas of physical and behavioral health, additional training for pediatric endocrinologists, and informing parents about the uncertainties regarding puberty blockers. The interim report is serving as a benchmark until the research is completed for final guidelines (The Cass Report, 2022).

Like state Medicaid programs, health systems across Western Europe also vary in their coverage of sex reassignment treatment.

Western European nations' requirements for cross-sex hormones:



In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Western European nations' requirements for sex reassignment surgery:

In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Generally Accepted Professional Medical Standards Recommendation

This report does not recommend sex reassignment treatment as a health service that is consistent with generally accepted professional medical standards. Available evidence indicates that the services are not proven safe or effective treatments for gender dysphoria.

Rationale

The available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. As this report demonstrates, the evidence favoring "gender affirming" treatments, including evidence regarding suicidality, is either low or very low quality:

- **Puberty Blockers:** Evidence does not prove that puberty blockers are safe for treatment of gender dysphoria. Evidence that they improve mental health and reduce suicidality is low or very low quality.
- **Cross-Sex Hormones:** Evidence suggesting that cross-sex hormones provide benefits to mental health and prevents suicidality is low or very low quality. Rather, evidence shows that cross-sex hormones cause multiple irreversible physical consequences as well as infertility.
- **Sex Reassignment Surgery:** Evidence of improvement in mental health and reduction in suicidality is low or very low quality. Sex reassignment surgery results in irreversible physical changes, including sterility.

While clinical organizations like the AAP endorse the above treatments, none of those organizations relies on high quality evidence. Their eminence in the medical community alone does not validate their views in the absence of quality, supporting evidence. To the contrary, the evidence shows that the above treatments pose irreversible consequences, exacerbate or fail to alleviate existing mental health conditions, and cause infertility or sterility. Given the current state of the evidence, the above treatments do not conform to GAPMS and are experimental and investigational.

✓ **Concur** ____ **Do not Concur**

Comments:

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_____ 6/2/22

Deputy Secretary for Medicaid (or designee) *Date*

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Attachments

Attachment A: Secretary for the Florida Agency for Health Care Administration's Letter to Deputy Secretary Thomas Wallace. 20 April 2022.

Attachment B: Complete text of Rule 59G-1.035, F.A.C.

Attachment C: Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.

Attachment D: James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.

Attachment E: Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.

Attachment F: Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.

Attachment G: G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

TAB 175-19

ATTACHMENT A

RON DESANTIS
GOVERNOR

SIMONE MARSTILLER
SECRETARY

April 20, 2022

Tom Wallace
Deputy Secretary for Medicaid
Agency for Health Care Administration
2727 Mahan Drive
Tallahassee, FL 32308

Dear Deputy Secretary Wallace:

On April 20, 2022, the Florida Department of Health released guidance on the treatment of gender dysphoria for children and adolescents.[1] The Florida Medicaid program does not have a policy on whether to cover such treatments for Medicaid recipients diagnosed with gender dysphoria. Please determine, under the process described in Florida Administrative Code Rule 59G-1035, whether such treatments are consistent with generally accepted professional medical standards and not experimental or investigational. Pursuant to Rule 59G-1035(5), I look forward to receiving your final determination.

Sincerely,

Simone Marstiller
Secretary

[1] *See* https://www.floridahealth.gov/newsroom/2022/04/20220420-gender-dysphoria-press-release.pr.html (last visited Apr. 20, 2022).

TAB 175-25

Pl. Trial Ex. 025

TESTOSTERONE

DRUGDEX Evaluations

DOSING/ADMINISTRATION

Adult Dosing

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

Hypogonadism, Male

1) FDA Dosage, Striant(R)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [17].

b) Usual dose: One 30-mg buccal system applied to the gum approximately every 12 hours, applying to opposite sides of the mouth with each dose; monitor testosterone levels at 4 to 12 weeks after initiation, and discontinue if levels are consistently outside normal range [23]

c) Dosing notes: If the system fails to adhere or falls off within 8 hours of application, a new system may be applied and continued for a total of 12 hours from the placement of the first system; however, if it is within 8 hours of the next scheduled dose, apply the new system for 12 hours and then continue with the next dose. Remove system prior to oral care and apply a new system after [23].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Striant(R) testosterone buccal system is not indicated for use in women [23].

Nasal route

Hypogonadism, Male

1) FDA Dosage, Natesto(TM)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [16].

b) Usual dose: 1 actuation per nostril (2 pump actuations, 11 mg) intranasally 3 times a day (morning, afternoon, and evening, 6 to 8 hours apart) at the same time each day for a total daily dose of 33 mg; after 1 month check testosterone levels periodically [22]

c) If total testosterone level usually below 300 nanograms/dL, consider alternative therapy [22].

d) If total testosterone level generally greater than 1050 nanograms/dL, discontinue treatment with testosterone nasal gel [22].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Natesto(TM) testosterone nasal gel is not indicated for use in women [22].
There is insufficient evidence of long-term safety (ie, cardiovascular and prostate cancer risks) for Natesto(TM) testosterone gel treatment in geriatric patients [22].
The safety and efficacy of Natesto(TM) testosterone gel treatment have not been established in patients with a BMI greater than 35 kg/m(2) [22].

Topical application

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [5][15][1][3][2][18].

2) FDA Dosage, Axiron(R)

a) Initial dose: 60 mg (1 pump or twist actuation of 30 mg to each axilla) applied once daily at the same time each morning to clean, dry, intact skin of the axilla; do not apply to any other parts of the body; obtain serum testosterone concentration at least 14 days after initiation; draw 2 to 8 hours after application [20]

b) Dose titration: decrease or increase dose by 30-mg increments based on serum testosterone concentration from a single blood draw 2 to 8 hours after application and at least 14 days after starting treatment or following dose adjustment, according to the following recommendation [20][20]:

Serum testosterone concentration below 300 nanogram/deciliter (ng/dL): Increase daily dose from 60 to 90 mg or from 90 mg to 120 mg

Serum testosterone concentration exceeds 1050 ng/dL: Decrease daily dose from 60 mg to 30 mg, or discontinue therapy if at the lowest daily dose of 30 mg

3) FDA Dosage, AndroGel(R) 1%

a) Initial dosage: 50 mg topically once daily (4 pump actuations, or 5 g of gel) preferably in the morning to clean, dry, intact skin on shoulders and upper arms and/or abdomen [5]

b) Dose titration: May increase once-daily dose to 75 mg (6 pump actuations, or 7.5 g of gel) and further to 100 mg (8 pump actuations, or 10 g of gel) if testosterone concentration below normal physiologic level [5]

c) Discontinue use if serum testosterone concentrations consistently exceed the normal range at a daily dose of 50 mg [5]

4) FDA Dosage, AndroGel(R) 1.62%

a) Initial dosage: 40.5 mg (2 pump actuations or 2.5 g of gel) applied topically once daily in the morning to clean, dry, intact skin of the shoulders and upper arms; measure predose morning serum testosterone concentration at approximately 14 and 28 days [15]

b) Dosage titration: Decrease or increase dose to minimum of 20.25 mg/day (1 pump actuation or 1.25 g of gel) up to 81 mg/day (4 pump actuations, or 5 g of gel), based on predose morning serum testosterone concentration drawn approximately 14 and 28 days after starting treatment or following dose adjustment, according to the following recommendation [15]:

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Key: ng = nanograms	

c) The application site and dose of AndroGel(R) 1.62% are not interchangeable with other topical testosterone products [15]

5) FDA Dosage, Fortesta(TM)

a) Initial dose: 40 mg (4 pump actuations) applied once daily to clean, dry, intact skin of the front and inner thighs in the morning; measure serum testosterone level at approximately 14 and 35 days, draw 2 hours post-application [21]

b) Dose titration: decrease or increase dose to a minimum of 10 mg/day or maximum of 70 mg/day, based on serum testosterone concentrations, drawn 2 hours after application at approximately 14 days and 35 days after treatment initiation or following dose adjustments, according to the following recommendation [21]:

Total Serum Testosterone Concentrations 2 hours Post Fortesta(TM) Application	Dose Titration
Equal to or greater than 2500 ng/dL	Decrease daily dose by 20 mg (2 pump actuations)
Equal to or greater than 1250 and less than 2500 ng/dL	Decrease daily dose by 10 mg (1 pump actuation)
Equal to or greater than 500 and less than 1250 ng/dL	No change: continue current dose
Less than 500 ng/dL	Increase daily dose by 10 mg (1 pump actuation)
Key: ng = nanograms	

c) The application site and dose of Fortesta(TM) are not interchangeable with other topical testosterone products [21].

6) FDA Dosage, Testim(R) 1% Gel

a) Initial dose: one 5 g tube applied once daily (preferably in morning) to clean, dry, intact skin on the shoulder and/or upper arms; measure morning testosterone level 2 weeks after initiation [24].

b) Dose titration: increase dose to 10 g/day (2 tubes) if serum testosterone concentration is below the normal physiologic range or if desired clinical

response is not observed [24]

7) FDA Dosage, Vogelxo(TM)

a) Initial dose: 50 mg (1 tube or packet or 4 pump actuations) applied topically to clean, dry, intact skin of shoulders or upper arms once daily; measure morning predose testosterone level after approximately 14 days [25]

b) Dose titration: may increase to 100 mg (2 tubes or packets or 8 pump actuations) once daily if morning predose testosterone level remains below normal (ie, 300 to 1000 nanograms/dL) [25]

c) Maximum dose: 100 mg/day [25]

8) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (1.6% gel): 50 to 100 mg applied topically once daily. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used). Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

AndroGel(R), 1%, Androgel(R) 1.62%, Natesto(TM), Striant(R), Testim(R), and Vogelxo(TM) topical testosterone gel products are not indicated for use in women [25][22][49][27][24][23]

Transdermal route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (patch): 2.5 to 7.5 mg/day. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions (guideline dosage) [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage, Androderm(R) 2 mg/day and 4 mg/day System

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [14].

b) Initial dose: One 4 mg/day transdermal system (not two 2 mg/day systems) applied every 24 hours at night; measure early morning serum testosterone level 2 weeks later [19]

c) Dose titration: Increase dose to 6 mg daily at night (one 4 mg/day plus one 2 mg/day system) or decrease dose to 2 mg daily at night (one 2 mg/day system) if early morning serum testosterone level drawn 2 weeks after starting therapy is outside the target range (400 to 930 nanograms/dL) [19].

2) FDA Dosage, Switching from Androderm(R) 2.5 mg/day, 5 mg/day, and 7.5 mg/day System to Androderm(R) 2 mg/day, 4 mg/day, and 6 mg/day System

At next scheduled dose, make switch according to following recommendation [19]:

patients currently on the 2.5 mg/day system may switch to the 2 mg/day system [19]

patients currently on the 5 mg/day system may switch to the 4 mg/day system [19]

patients currently on the 7.5 mg/day system may switch to the 6 mg/day system [19]

Two weeks after switching therapy, measure an early morning serum testosterone level [19]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks. Base dosage (initial, maintenance, and adjustments) on patient response and presence of adverse reactions [82].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks as replacement therapy; dose based on diagnosis, response to treatment, and presence of adverse effects. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Metastatic breast cancer, Female

1) Usual dosage (women): 200 to 400 mg IM every 2 to 4 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg subQ every 2 weeks or 50% of the dose subQ once weekly [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Prior to initiation: Confirm the diagnosis of hypogonadism with serum testosterone concentration below the normal range when measured in the morning on at least 2 separate days [74].

b) Initial dosage: 75 mg subQ in the abdominal region once a week [74]

c) Dosage titration: Measure total testosterone trough concentration (Ctrough) 7 days after the most recent dose after 6 weeks of dosing, following 6 weeks after dose adjustment, and periodically while on treatment. If Ctrough is 650 nanograms (ng)/dL or higher, decrease the dose by 25 mg. If Ctrough is less than 350 ng/dL, increase the dose by 25 mg. If Ctrough is 350 to less than 650 ng/dL, maintain the same dose [74].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Initial dosage: 1000 mg IM at 0 and 6 weeks and then every 12 weeks to maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [58].

b) Usual dosage: 750 mg IM, and then 750 mg IM 4 weeks later, and then 750 mg IM every 10 weeks thereafter [59]

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

3) Off-label Dosage

a) Off-Label Dosage: 1000 mg IM, and then 1000 mg IM at week 6, and then 1000 mg IM every 12 weeks [60]

Oral route

Hypogonadism, Male

1) Tlando(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [53].

b) Dosage: 225 mg (2 capsules) orally twice daily in the morning and evening with food; do not adjust dosage [53].

c) Measure serum testosterone following 3 to 4 weeks of treatment and periodically thereafter; draw level 8 to 9 hours after the morning dose [53].

d) Continue treatment if serum testosterone is 300 to 1080 ng/dL, otherwise discontinue treatment [53].

2) Jatenzo(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [57].

b) Initial dosage: 237 mg twice daily in the morning and evening with food [57]

c) Adjust dose based on serum testosterone concentrations measured 6 hours after the morning dose in plain tubes, clotted at room temperature for 30 minutes prior to centrifugation. Wait seven days after starting treatment or adjusting the dose before checking the serum testosterone concentration. Thereafter, periodically monitor serum testosterone concentrations 6 hours after the morning dose. Administer the same dose in the morning and evening according to the following table [57]:

Testosterone Concentration in Serum From Plain Tube Drawn 6 hours After Morning Dose	Current dose (mg, twice daily)	New dose (mg, twice daily)
Less than 425 nanograms/dL	158	198
	198	237
	237	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	396 (two 198 mg capsules)
425 to 970 nanograms/dL	No dose change	
More than 970 nanograms/dL	396 (two 198 mg capsules)	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	237
	237	198
	198	158
	158	Discontinue therapy

d) Maximum dosage: 396 mg (two 198 mg capsules) twice daily [57]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Dosage in Renal Failure

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Hepatic Insufficiency

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Other Disease States

A) Testosterone Enanthate

1) In patients who develop edema with or without congestive heart failure, discontinue testosterone enanthate and restart at a lower dose [73].

Pediatric Dosing

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

a) The safety and effectiveness of Striant(R) testosterone buccal system have not been established in males younger than 18 years [23].

Nasal route

a) The safety and efficacy of Natesto(TM) testosterone gel have not been established in patients younger than 18 years [22].

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Off-label Dosage, Adolescent

a) Dosage (gel): 50 mg applied topically once daily [8]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

The safety and efficacy of AndroGel(R) 1%, AndroGel(R) 1.62%, Axiron(R), Fortesta(TM), Testim(R) 1%, and Vogelxo(TM) have not been established in males younger than 18 years [20][25][27][24][49][21]. Acceleration of bone age and premature closure of epiphyses may occur with improper use [21].

Transdermal route

a) Safety and efficacy of testosterone transdermal system have not been established in males younger than 18 years. Acceleration of bone age and premature closure of epiphyses may occur with improper use [19].

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) Usual dosage (12 years or older): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Base dosage (initial, maintenance, and adjustments) on patient response, presence of adverse reactions, age, and skeletal age. Some regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses [82].

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Delayed puberty, Male

1) Usual dosage (adolescent males): 50 to 200 mg IM every 2 to 4 weeks for a limited duration, such as 4 to 6 months. Some dosage regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses. Although various dosing regimens may be used, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses in addition to patient response and adverse effects [73].

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) Usual dosage (adolescent males): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Although various dosing regimens may be used to induce pubertal changes in hypogonadal males, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) subQ every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg subQ every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years [59].

Oral route

a) General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years. Improper use may result in acceleration of bone age and premature closure of epiphyses [53][57].

FDA Uses

Testosterone

Hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Replacement therapy in congenital or acquired conditions associated with a deficiency or absence of endogenous testosterone, as follows:

Primary hypogonadism (congenital or acquired): Testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals [20][22][23][25][19][27][28][24][21]
Hypogonadotropic hypogonadism (congenital or acquired): Idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation [20][22][23][25][19][27][28][24][21]

Limitations of Use

The safety and efficacy of testosterone therapy have not been established in men with late-onset (age-related) hypogonadism [14][5][15][1][3][16][17][2][18].

Evidence (Topical Gel)

In several randomized clinical trials in men with hypogonadism, 75% or more achieved normal serum testosterone levels with administration of testosterone gel for 2 to 3 months [29][21], with effects sustained for 6 months [30] and up to 3 years [31] in several extension studies.

Lean body mass (LBM) significantly increased with testosterone 1% gel compared with placebo at 6 months in symptomatic men 50 to 80 years old with low to low-normal testosterone levels (LBM change, 1.28 vs 0.02 kg; N=362). Fat mass decreased 1.16 kg with testosterone versus 0.14 kg with placebo, an effect that was more pronounced in patients with a BMI of 30 kg/m(2) or greater. Fat mass progressively decreased during 12 additional months of testosterone therapy, but LBM was not further affected [32].

Evidence (Buccal)

During a randomized, 12-week trial in men with hypogonadism, 86.6% of 82 evaluable patients treated with buccal testosterone twice daily had mean serum testosterone concentrations within the physiologic range [23].

Evidence (Intranasal)

In an open-label trial in hypogonadal men, 90% of 73 subjects treated with testosterone nasal gel 3 times daily had an average testosterone level within normal range after 90 days of treatment; no patients had levels above the normal range (N=306) [22].

Testosterone Cypionate

Primary hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years or older)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone cypionate is indicated for replacement therapy for congenital or acquired deficiency or absence of endogenous testosterone.

Primary hypogonadism: Testicular failure caused by cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy [82]
Hypogonadotropic hypogonadism: Deficiency of gonadotropin or luteinizing hormone-

releasing hormone (LHRH); pituitary-hypothalamic injury from tumors, trauma, or radiation [82]

Limitations of Use

Safety and efficacy not established in men with late-onset (age-related) hypogonadism [82].

Use androgens cautiously in the pediatric population because of adverse effects on bone maturation. The risk of compromising final mature height increases as age decreases. Assess bone age in the wrist and hand every 6 months [83].

Testosterone Enanthate

Delayed puberty, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (adolescent males, IM only)

Efficacy: Pediatric, Evidence favors efficacy

Recommendation: Pediatric, Class IIb

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone enanthate IM injection is indicated to stimulate puberty in select male patients with delayed puberty [73].

Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater the younger the child. Assessment of bone age in the wrist and hand every 6 months is recommended [73].

c) Pediatric:

1) Only carefully selected males should receive testosterone for the treatment of delayed puberty. Delayed puberty should not be secondary to a pathological disorder. Most patients have a familial pattern of delayed puberty and are expected to attain puberty spontaneously at a relatively late date. For patients unresponsive to psychological support, a brief treatment with conservative doses may occasionally be justified [73].

Hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (adolescent males, IM only)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone enanthate is indicated for testosterone replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone, such as:

Primary hypogonadism (congenital or acquired), including testicular failure from conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy [74][75], Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicular-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range [74].
Hypogonadotropic hypogonadism (congenital or acquired), including gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation [74][75]. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range [74].

Limitations of Use

Safety and efficacy of subQ testosterone enanthate in male patients less than 18 years old have not been established [76]

Evidence (Adult)

In a single-arm study of men with hypogonadism who received subQ testosterone enanthate, 90% achieved normal serum testosterone levels at week 12 [74].

c) Adult:

1) IM Preparation

a) Replacement therapy needed prior to puberty will be needed during adolescence for secondary sexual characteristic development. Replacement therapy needed following puberty will require prolonged duration of therapy to maintain sexual characteristics [73].

b) Several dosage regimens of IM testosterone enanthate were compared in the treatment of primary hypogonadism in 23 men. Patients received testosterone enanthate 100 mg weekly, 200 mg every 2 weeks, 300 mg every 3 weeks, or 400 mg every 4 weeks for 12 to 16 weeks. The 200 and 300 mg regimens appeared to be the most effective in terms of suppression of the serum luteinizing hormone (LH) concentration and infrequency of administration [77].

2) SubQ Preparation

a) In a 52-week, single-arm study of men with hypogonadism (N=150), 90% of testosterone enanthate-treated patients achieved a time-averaged serum total testosterone concentration over 7 days within the normal range (300 to 1100 nanograms (ng)/dL) at week 12. No patient had a maximum total testosterone concentration greater than 1500 ng/dL at week 12. The initial self-administered dose of 75 mg subQ once weekly was increased by 25 mg at week 7 if the week 6 total testosterone concentration at the end of the dosing interval (trough concentration [Ctrough]) was less than 350 ng/dL ,and was decreased by 25 mg if Ctrough was 650 ng/dL or greater [74].

d) Pediatric:

1) Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater the younger the child. Assessment of bone age in the wrist and hand every 6 months is recommended [73].

Metastatic breast cancer, Female

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (IM only); Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

IM testosterone enanthate is indicated for palliation of inoperable metastatic (skeletal) mammary cancer in women who are 1 to 5 years postmenopausal [73].

c) Adult:

1) May be used in the palliative treatment of advancing, inoperable metastatic (skeletal) mammary cancer in women who are 1 to 5 years postmenopausal with the primary goal of ovary ablation. Therapy may also be used in premenopausal women who have benefited from oophorectomy with hormone-responsive tumors. Androgen therapy may accelerate metastatic breast carcinoma; therefore, these patients should be monitored closely [73].

Testosterone Undecanoate

Hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone undecanoate is indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone, such as

Primary hypogonadism (congenital or acquired): Testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals; in these conditions, men have low serum testosterone concentrations and gonadotropins above the normal range [53][57][59].

Hypogonadotropic hypogonadism (congenital or acquired): Idiopathic gonadotropin deficiency, luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation; in these conditions, men have low serum testosterone concentrations and gonadotropins in the normal or low range [53][57][59].

Testosterone undecanoate IM should be used only in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis [59].

Limitations of Use

Safety and efficacy of testosterone capsules in males less than 18 years old have not been established [53][57]

The safety and efficacy of testosterone undecanoate IM therapy has not been established in men with late-onset (age-related) hypogonadism [58].

Evidence

Testosterone undecanoate therapy increases testosterone levels in hypogonadal male patients [61][57][62][60][59].

c) Adult:

1) Oral Capsules - Tlando(R)

a) In an open-label, single-arm study enrolling hypogonadal men, a mean 24-hour serum testosterone level within normal range (eugonadal, 300 to 1080 nanograms[ng]/dL) was achieved in 80% (95% CI, 72% to 88%) of patients receiving testosterone undecanoate capsules 225 mg twice daily with food for 24 days (N=95); no dosage adjustments were permitted. Around 19% (n=18) of subjects, majority of whom were obese, did not achieve a eugonadal range. Cmax of testosterone throughout the studied interval did not exceed 1.5 x ULN (1620 ng/dL) in 82% of patients, while 5% experienced levels between 1.8 x ULN (1944 ng/mL) and 2.5 x ULN (2700 ng/dL); no patients experienced testosterone Cmax over 2.5 x ULN. Mild to moderate adverse events were reported in 20% of the treatment population. The most frequently reported treatment-emergent adverse events were blood prolactin increase (6.3%), headache (2.1%), weight increase (2.1%), and musculoskeletal pain (2.1%). Mean age was 56 years, 16.8% were over 65 years, 69.5% had a BMI of 30 kg/m(2) or greater, and baseline total testosterone on average was 202 +/- 74 ng/dL [61].

2) Oral Capsules - Jatenzo(R)

a) Mean plasma total testosterone over 24 hours was within the normal eugonadal range in 87% of patients in a 4-month study of adult hypogonadal males who received testosterone undecanoate capsules (N=166). The percentage of patients who had Cmax 1500 nanograms (ng)/dL or less, between 1800 and 2500 ng/dL, and greater than 2500 ng/dL at the final visit were 83%, 3%, and 3%, respectively Testosterone undecanoate was taken orally at a starting dose of 237 mg twice per day with meals. The dose was adjusted on Days 21 and 56 between a minimum of 158 mg twice per day and a maximum of 396 mg twice per day on the basis of the average testosterone concentration obtained over 24 hours post-morning dose [57].

3) Intramuscular

a) In 3 studies, testosterone undecanoate therapy significantly increased testosterone levels in hypogonadal male patients [62][60][59] with injection site reactions [62][60] occurring in less than 1% in 1 study [62] and 25.9% in another study [60]

Non-FDA Uses

Testosterone

Antineoplastic adverse reaction - Leydig cell failure in adult

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone therapy did not result in significant changes in bone mineral density, body composition, lipids, or quality of life in one study conducted in men [33].

c) Adult:

1) Testosterone was not effective in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. Men (n=35) aged 40 to 49 years with the diagnosis of mild Leydig cell dysfunction due to chemotherapy were randomized to 2.5 to 5 mg transdermal testosterone daily or placebo for 1 year. Upon completion of the study, total and calculated free testosterone increased significantly with the testosterone group compared with the placebo group (p=0.05 and p=0.02, respectively). Mean total and calculated free testosterone levels increased from 13.3 nanomoles/liter (nmol/L) and 342.9 nmol/L at baseline to 17.3 nmol/L and 454.8 nmol/L during the study. No significant changes in testosterone levels were observed in the placebo group. There were no significant changes in bone mineral density or in body mass in either group.

There was a significant reduction in fatigue and a moderate improvement in activity score compared with the placebo group (p=0.008 and p=0.05, respectively). Mood or sexual function did not change with either group and only a small reduction in low density lipoprotein was reported in the testosterone treated group [33].

Congenital hypoplasia of penis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Successful penile enlargement to normal size for age was reported following the administration of topically applied testosterone [34][35].

c) Pediatric:

1) Eight cases of micropenis from childhood through adulthood (age range, 22 to 31 years) were followed. Diagnosis included 4 patients with hypogonadism, 2 patients with genetic or familial adiposogenital dystrophy, and 2 with miscellaneous types of endocrine abnormalities. In 5 cases, the micropenis was treated with testosterone propionate 2% in a stearin-lanolin base for a variable period of time in infancy or childhood. Topical treatment caused an increase in penis size that was disproportionate to the rest of the body. However, in adolescence and adulthood, patients with a prior history of treatment with topical testosterone during childhood had no size advantage over untreated patients. The authors felt topical testosterone only postponed the age at which an individual had to cope with a micropenis [34].

2) Parenteral (testosterone enanthate 25 mg given IM monthly for a total of 3 doses) and topical testosterone cream (2% to 10%) have been used short term to induce temporary enlargement of a micropenis prior to surgical repair [36][37][38].

3) Successful penile enlargement to normal size for age following the administration of topically applied testosterone 5% cream for 21 days was reported in 5 boys with normal XY karyotype who had microphallus and hypopituitarism. The cream was applied to the penis in 4 of the patients and to the right axilla in one. The investigators concluded that topical testosterone acted systemically to produce phallic growth; serum testosterone levels were equivalent to normal adult levels on the last day of therapy [35].

Coronary arteriosclerosis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Supplementation of low-dose testosterone effectively reduced exercise-induced myocardial ischemia in men with stable angina [10].

c) Adult:

1) Low-dose (5 mg/day) testosterone supplementation was effective in reducing exercise-induced myocardial ischemia in men diagnosed with stable angina. Forty-six men were randomized to transdermal testosterone or placebo for 12 weeks. Treatment with testosterone was associated with an increase in time to 1 mm ST-segment depression from 309 seconds at baseline to 343 seconds at 4 weeks and 361 seconds at 12 weeks, as measured by treadmill exercise testing. The changes were statistically

significant when compared with placebo (p=0.02). Additionally, the treatment group reported significant improvements in pain perception (p=0.026) and role limitation resulting from physical problems (p=0.024) compared with placebo [10].

Deficiency of testosterone biosynthesis, Female

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone transdermal patch demonstrated favorable results in bone density, body composition, and neurobehavioral function in women with androgen deficiency due to hypopituitarism [12].

Testosterone improved well-being, mood, and sexual function in premenopausal women with low libido and low testosterone [13].

c) Adult:

1) Transdermal testosterone application resulted in increased bone mineral density at the hip and radius, increased mean fat-free mass, increased thigh muscle area, and improved mood and sexual function in women with androgen deficiency due to hypopituitarism. The study participants (n=51, aged 19 to 50 years) had a serum free testosterone level of less than 3.1 picograms/milliliter (pg/mL) at the time of screening and were estrogen replete for at least 1 year prior to the study. Of the women participating, 59% were depressed at baseline and 46% and 68% had sexual function scores that were more than 2 or more than 1 standard deviation(s), respectively, below the normal mean (as measured by the Derogatis Interview for Sexual Function-Female Version). Participants were randomized to transdermal testosterone patches which delivered 300 mcg (in the form of 150 mcg patches) daily or placebo patches for 12 months. Study visits occurred at 1, 3, 6, 9, and 12 months after the baseline visit. At baseline, mean free testosterone was below normal for women of reproductive age, and 55% of women had undetectable levels, which increased into the normal range during testosterone administration. The dose of testosterone was decreased to 150 mcg daily in 37.8% of participants randomized to testosterone due to free testosterone levels being above the ULN for females of reproductive age. There were no changes in estradiol, insulin-like growth factor I, and sex hormone binding globulin levels with either testosterone or placebo administration. Bone density at the hip and radius increased significantly (p=0.023 and p=0.007, respectively) with mean percent changes at the hip being 0.9 +/- 0.5 and -1.2 +/- 0.6% for testosterone and placebo, respectively, and 0.8 +/- 0.2 and -0.5 +/- 0.4%, respectively, at the radius. Testosterone was associated with a 3.4 +/- 0.9% mean increase in fat-free mass compared with a 0.6 +/- 0.9% increase for placebo (p=0.04). There was a significant increase in muscle area of the thigh associated with testosterone administration compared with placebo (p=0.038). The mean increase in the testosterone and placebo groups was 6.6 +/- 1.4% and 1.5 +/-1.3%, respectively. Compared with placebo, mood significantly improved in patients receiving testosterone (p=0.029) as did sexual function (p=0.044). In women receiving testosterone, quality of life improved in the following areas: self-control (p=0.005), energy/fatigue (p=0.017), general health (p=0.026), and sleep (p=0.038). When compared with placebo, there was no improvement in spatial function or any other changes in cognitive function. Testosterone was well tolerated with increased acne being reported in one-third of patients. A mean increase in total cholesterol of 6% was reported in the testosterone group. Mild local irritation at patch site was reported in 65% of participants; the reactions were distributed equally between the testosterone and placebo groups [12].

2) Testosterone cream was effective in improving well-being, mood, and sexual function in premenopausal women in a randomized, placebo-controlled, crossover, double-blind trial. Thirty-four women completed the trial, with 31 women (mean age 39.7 years and mean serum testosterone 1.07 nanomoles/L) providing complete data. The trial

consisted of two 12-week treatment periods, separated by a 4-week washout period, in which the women were randomized to 10 mg testosterone 1% cream daily or placebo. The women using testosterone demonstrated significant improvements in scores of general well being (+12.9; 95% CI, +4.6 to +21.2; p=0.003) and of sexual self-rating (+15.7; 95% CI, +6.5 to +25; p=0.001) compared with placebo. Mean total testosterone levels during treatment were at the high end of normal and estradiol levels were unchanged. Testosterone was well tolerated with no adverse effects reported [13].

Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone gel supplementation may produce antidepressant effects in depressed men with low testosterone levels [11].

c) Adult:

1) Testosterone 1% topical gel produced antidepressant effects in a small study involving 22 depressed men with low or borderline testosterone levels (morning serum levels of 350 nanograms/dL or less. The men were randomized to 1% testosterone gel (10 g/day) or placebo gel for 8 weeks. Each subject continued his existing antidepressant regimen. Testosterone-treated patients had a significantly greater rate of decrease in scores on the Hamilton Depression Rating Scale compared with placebo (p=0.0004). This improvement was noted on both the vegetative and affective subscales of the Hamilton Depression Rating Scale (p=0.01 and p=0.05, respectively). In addition, testosterone gel was associated with a significantly greater rate of decrease in the Clinical Global Impression severity scores (p=0.04). There were no significant differences between the 2 groups regarding changes in body fat percentages or changes in muscle mass. One subject receiving testosterone reported increased nocturia and difficulty initiating urination. No other subject reported adverse effects attributable to testosterone [11].

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Testosterone in 3 different formulations, including transdermal gel, significantly increased testosterone levels from the physiological range for women to the normal male range by week 30 of treatment in an observational study in female-to-male transsexual individuals [9]. Hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8].

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving

hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) Testosterone in 3 different formulations significantly increased total testosterone levels from the physiological range for women to the normal male range by week 30 of treatment with no significant differences among formulations in an observational study in female-to-male transsexual individuals (N=45). At week 54, testosterone remained elevated and sex hormone-binding globulin, prolactin, and estradiol levels were significantly decreased from baseline while body weight and body mass index (BMI) were significantly increased in all groups. Results for selected hormonal and anthropometric outcomes are shown in the table below. Amenorrhea occurred at a mean 29.8 to 41 weeks. Significant changes from baseline were observed in HDL-C (decreased) and LDL-C (increased), but not total cholesterol. Fasting glucose increased significantly, but insulin and homeostasis model assessment for fasting insulin resistance (HOMA-IR) were similar to baseline. Hematocrit and hemoglobin increased from baseline. No significant changes were detected in liver enzymes, renal function, or bone mineral density. Patients were randomly assigned to testosterone enanthate 100 mg IM every 10 days, testosterone gel 50 mg once every evening, or testosterone undecanoate 1000 mg IM at week 0, week 6, and every 12 weeks thereafter. No subject had undergone sexual reassignment surgery [9].

Selected Hormonal and Anthropometric Parameters at Baseline and Week 54 Posttreatment		
Parameter	Baseline Range *	Week 54 Posttreatment Range*
Testosterone (ng/mL)	0.44 to 0.54	5.89 to 7.39 **
Estradiol (pg/mL)	102.9 to 167.3	70.6 to 81.9 **
Luteinizing hormone (international units/L)	5.8 to 12.8	5.1 to 9.2
Follicle stimulating hormone (international units/L)	4.6 to 6.2	5.1 to 5.6
Prolactin (ng/mL)	15.7 to 18.2	9.8 to 15.6 **
Sex hormone-binding globulin (nmol/L)	60.3 to 65.4	31.6 to 34.3 **
Body weight (kg)	57.8 to 67.3	60.5 to 68.7 **
BMI (kg/m(2))	22.1 to 23.9	22.4 to 24.3 **

Fat (%)	26.7 to 30.1	22.4 to 27.6 **
KEY: BMI=body mass index; ng=nanograms; pg=picograms		
* Range is among the 3 different testosterone formulations with no significant difference among the formulations at baseline or week 54.		
** Significant difference between baseline and week 54 values.		

2) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **
KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus no-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

d) Pediatric:

1) Adolescents

a) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible

symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
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KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus no-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

Osteoporosis, Male

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone therapy in men with osteoporosis significantly increased bone mineral density [40].

See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy
See Drug Consult reference: Canadian: Management of Osteoporosis in Men and Women

c) Adult:

1) Transdermal testosterone gel was associated with a small but significant increase in bone mineral density (BMD) in a prospective, multicenter study involving 227 men with hypogonadism. The men were randomized to testosterone gel delivering 5 to 10 mg/day or 2 testosterone patches delivering 5 mg/day. After 90 days, the gel dose was adjusted to 75 mg/day for another 3 months. At completion of the study, the 10 mg/day gel was associated with a 1.4 and 1.9-fold higher serum testosterone concentration than the 5 mg/day gel and the patch groups. The 10 mg/day gel group was also associated with a decreased bone resorption and with small but significant increases in BMD of the hip and spine (1.1% and 2.2%, respectively; p=0.0001) [40].

Postmenopausal osteoporosis; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The addition of testosterone to estradiol is not associated with increased benefits on bone mineral density [39].

c) Adult:

1) Testosterone 100 mg implants added to estradiol 50 mg implants had no significant effects on bone markers and may not be necessary for prevention of osteoporosis if adequate estradiol levels are maintained. Women (n=25) were given estradiol after a total hysterectomy with bilateral salpingo-oophorectomy. At 16 weeks, testosterone 100 mg was added to the treatment regimen. The bone formation marker, PICP was associated with a significant increase after estradiol alone (p=0.0032) but the addition of testosterone had no significant effects on bone markers when measured at 32 weeks. These biochemical changes confirm previous studies [39].

Sexual disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Improvements in sexual function have been reported in both female and male patients [41][42][43].

c) Adult:

1) Transdermal testosterone improved sexual function and psychological well-being in women with sexual dysfunction following oophorectomy and hysterectomy. A 36-week trial enrolled 75 women, ages 31 to 56 years old, who had reported impaired sexual functioning after surgically-induced menopause, despite estrogen replacement. The 75 women received at least 0.625 mg of conjugated equine estrogens orally per day. Randomly selected, the women also received placebo, 150 micrograms (mcg) of testosterone, or 300 mcg of testosterone per day transdermally for 12 weeks each. The mean serum free testosterone concentration increased during each treatment regimen. The higher testosterone dose resulted in the greatest physical and psychological improvement [41].

2) In one 16-month, open-label, multicenter study with 4 consecutive periods, 37 men with hypogonadism received intramuscular and transdermal testosterone (nonscrotal). Period 1 consisted of 3 weeks and patients were monitored following an IM testosterone injection. During period 2, patients received no replacement testosterone for 8 weeks. During period 3, single-dose pharmacokinetic studies were performed for 3 to 4 weeks. During period 4 (12 months) efficacy and safety of the transdermal system were compared with the results obtained during periods 1 and 2. Along with other symptoms, decreased libido, impotence, fatigue, depression, and hot flushes were evaluated. After one month of transdermal treatment, the prevalence of decreased libido and fatigue had decreased to levels seen during IM treatment and remained so for the duration of transdermal treatment [42]. Similar results were found in another study [43].

Weight gain

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone did not increase weight, body cell mass, or quality of life in patients with HIV infection [44].

Testosterone has produced an increase in fat free mass, muscle size, and strength [45] [46].

A significant increase in weight was observed in female patients with AIDS who received 1 active testosterone patch and 1 placebo patch versus 2 placebo skin patches but did not increase significantly in patients who received 2 active testosterone patches [47].

c) Adult:

1) Transscrotal testosterone did not increase weight, body cell mass, or quality of life in patients with HIV infection. In a multicenter, randomized, double-blinded, placebo-controlled study, men infected with HIV used transdermal scrotal testosterone patches (6 mg/day) (n=67) or placebo (n=66) for 12 weeks. Patches were applied and worn for 22 to 24 hours each day. Testosterone patches were effective in increasing serum testosterone levels [44].

2) There was 1.35 kg gain in lean body mass, increased red cell count, and improvements in the subcategory of role limitation due to emotional problems in HIV-infected men treated with transdermal testosterone [45]. In a double-blind, placebo-controlled randomized study, 41 HIV-infected men received 2 placebo patches or 2 testosterone transdermal system patches applied to the abdomen, back, arms, or thighs every 24 hours (total testosterone dose 5 mg/24 hr) for 12 weeks.

3) Androgen deficiency has been shown to be prevalent among women with AIDS wasting syndrome. It may result from undernutrition generalized illness, or more direct effects of HIV on the hypothalamic-pituitary-gonadal axis. Forty-five out of 53 women with AIDS wasting syndrome finished the study. Patients were randomized into 1 of 3 groups: 2 placebo skin patches (PP group); 1 active/1 placebo patch (AP group); or 2 active patches (AA group) which were applied twice weekly for 12 weeks. The delivery rates of testosterone were 150 and 300 mcg/day for the AP and AA groups, respectively. Therapy was well tolerated with no adverse effects with regard to hirsutism, lipid profiles, or liver function tests. A significant increase in weight was observed in the AP group (1.9 +/- 0.7 kg) versus the PP group (0.6 kg +/- 0.8 kg; p=0.043), but did not increase significantly in the AA group (0.9 +/- 0.4 kg) versus the PP group [47].

4) Testosterone increased lean body mass and improved quality of life in androgen-deficient men with AIDS wasting syndrome. In a randomized, double-blind, placebo-controlled trial, patients received testosterone enanthate 300 mg intramuscularly weekly for 6 months (n=26) or placebo (n=25). In the testosterone-treated group, 22 patients completed the trial and 19 patients in the placebo group completed the trial. Compared to placebo, testosterone-treated patients demonstrated a gain in fat free mass, lean body mass, and muscle mass (change, -0.6 kg and 2 kg; change, 0 kg and 1.9 kg; and change, -0.8 kg and 2.4 kg, respectively) [46].

5) Sublingual testosterone 5 mg three times daily for 6 months was administered to 67 men with hypogonadism which resulted in an increase in total body (p=0.0104) and lean body mass (p=0.007), mainly in the legs. There was no significant change in bone mineral density throughout the study. Longer studies are needed in this population [48].

Testosterone Cypionate

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8]. In a prospective study, significant changes in several domains of psychological functioning were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls [66]. Male physical characteristics were effectively achieved in an open-label time-series trial [81].

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) Significant changes in several domains of psychological functioning, as assessed using the Minnesota Multiphasic Personality Inventory second edition (MMPI-2), were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls (N=163; 48 transgender men, 53 male controls, 62 female controls). The MMPI-2 contains 10 clinical scales. Transgender men were compared with female controls using the female template of MMPI-2 and compared with male controls using the male template. Higher scores on each scale equate with lower levels of psychological functioning. Relative to female controls, transgender men had a significant change from baseline on the Hypochondria (-3.14), Depression (-3.28), Hysteria (-3.66), Paranoia (-4.62), and Masculinity-femininity (+5.05) scales after 3 months of therapy. No significant differences were observed after therapy versus female controls on the Psychopathic Deviate, Psychasthenia, Schizophrenia, Hypomania, or Social Inversion

scales or on any of the 10 scales relative to male controls. Testosterone was administered as 50 to 400 mg IM every 10 to 14 days (or 50% weekly) for most participants (n=32) [66].

2) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy

Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **

KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale

* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.

** Significant difference versus without-hormone-therapy group

^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.

3) Testosterone cypionate was effective in suppressing menses and increasing clitoral size and body hair in an open-label time-series trial that examined the effects of cross-sex hormones on both female-to-male and male-to-female transsexuals. Eleven of the 28 (31%) enrolled female-to-male transsexuals had previously been on testosterone in various formulations for a median duration of 24 months (range, 6 to 240 months). All previous treatment was discontinued and patients were started on testosterone cypionate (Depo-testosterone(R)) IM at doses of 50 to 200 mg every 2 weeks, with doses increased until cessation of menstruation or suppression of luteinizing hormone (LH) or follicle-stimulating hormone (FSH) in castrated patients. Some patients self-administered doses up to 400 mg per week against medical advice. Mean duration of follow-up was 16.6 +/- 15 months. Of patients who had never had any previous hormonal treatment or hysterectomy (n=12), all had reported previous normal menstrual histories. These patients all had cessation of menses by 4 months of treatment with testosterone cypionate 200 mg every 2 weeks. The mean total cholesterol level (n=28) at baseline was 209 +/- 46 mg/dL. At doses of 100 to 300 mg per month after a duration of 27 patient-months, the mean cholesterol level increased to 288 +/- 53 mg/dL, while at doses of 400 mg per month after a duration of 217 patient-months, the mean cholesterol level was 212 +/- 53 mg/dL. Significance (p less than 0.05) was reported for the change in cholesterol (all doses) from baseline. Triglycerides

were also significantly (p less than 0.05) increased to just over the ULN (normal range, 10 to 160 mg/dL). SGPT significantly (p less than 0.05) increased, but remained within the normal range. No significant changes were found in blood pressure, SGOT, bilirubin, or glucose. The amount and coarseness of hair on the chest, abdomen, and face were reported to be "strikingly" increased. No significant changes were reported for breast size, body weight, estradiol levels, or androstenedione levels. LH and FSH levels were suppressed to prepubertal levels only when the patient's testosterone level was over 1000 nanograms/deciliter or until the dose was greater than 800 mg per month. Clitoris growth increased rapidly over 1 year, with the longest clitoris measuring 6 cm [81].

d) Pediatric:

1) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy

Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **

KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale

* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.

** Significant difference versus without-hormone-therapy group

^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.

Testosterone Enanthate

Anemia

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in combination with other androgens for increasing the hematocrit in anemic patients who are receiving hemodialysis [67]

c) Adult:

1) A randomized clinical trial was conducted to compare the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis . Patients received either testosterone enanthate 4 mg/kg IM weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 mg/kg orally daily, oxymetholone 1 mg/kg orally daily, or nandrolone decanoate 3 mg/kg intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; 3 courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had an increase of at least 5 percentage points in hematocrit following the administration of either injectable androgen [67].

Burn, Severe; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Administration of testosterone enanthate can ameliorate muscle catabolism in severe burns [78].

c) Adult:

1) Testosterone enanthate 200 mg IM per week for 2 weeks restored serum testosterone levels and ameliorated the muscle catabolism in 6 severely burned (greater than 70% total body surface area) male patients. After the second injection, protein synthetic efficiency increased 2-fold (p less than 0.01) and protein breakdown decreased almost 2-fold (p less than 0.05) [78].

Congenital hypoplasia of penis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

IM testosterone enanthate and topical testosterone cream have been used short term to induce temporary enlargement of a micropenis prior to surgical repair [36][37][38].

c) Pediatric:

1) Testosterone enanthate 25 mg IM given monthly for a total of 3 doses and topical testosterone cream (2% to 10%) have been used short term to induce temporary

enlargement of a micropenis prior to surgical repair [36][37][38].

Contraception, Male

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

IM testosterone enanthate plus oral desogestrel was an effective and safe regimen for suppression of spermatogenesis [68].

Testosterone enanthate and cyproterone induced azoospermia more effectively than testosterone alone [69].

Testosterone enanthate plus levonorgestrel was more effective in producing azoospermia than testosterone enanthate alone [70].

Weekly injections effectively induced azoospermia in healthy fertile men [71].

Approximately 50% of healthy males become azoospermic and the other 50% become severely oligospermic following administration during clinical trials [72].

c) Adult:

1) Testosterone Enanthate and Desogestrel

a) IM testosterone enanthate plus oral desogestrel was an effective and safe regimen for suppression of spermatogenesis in a study of 24 healthy men aged 20 to 49 years. The men were randomized to 50 mg testosterone enanthate plus 150 mcg desogestrel (n=9), 100 mg testosterone enanthate plus 150 mcg desogestrel (n=7), or 100 mg testosterone enanthate plus 300 mcg desogestrel (n=8). Additionally, these 3 groups were compared with 2 control groups receiving 100 mg testosterone enanthate alone (n=18) or 100 mg testosterone enanthate plus 125 mcg oral levonorgestrel (n=18). At the end of 6 months, azoospermia was achieved in 100% of men receiving testosterone enanthate 100 mg plus desogestrel 150 mcg, 88% of men receiving testosterone enanthate 100 mg plus desogestrel 300 mcg, and 57% of men receiving testosterone enanthate 50 mg and desogestrel 150 mcg. This was compared with 61% for testosterone enanthate 100 mg plus levonorgestrel 125 mcg and 33% for testosterone enanthate 100 mg alone. All groups tended to gain weight compared with baseline and serum HDL was moderately suppressed in all groups [68].

2) Testosterone Enanthate and Cyproterone

a) In a smaller study, all men who received testosterone and cyproterone became azoospermic compared with 3 of 5 men receiving testosterone only. Fifteen men were randomized to receive cyproterone 50 mg orally twice daily plus testosterone enanthate 100 mg IM weekly; cyproterone 25 mg orally twice daily plus testosterone 100 mg IM weekly; or testosterone 100 mg IM weekly alone for 16 weeks. Patients in the cyproterone 100 mg, cyproterone 50 mg, and testosterone only groups achieved azoospermia at mean times of 6.8, 8.4, and 14 weeks, respectively. After treatment, baseline sperm counts were achieved in all men. Lipoprotein profiles nor liver function tests were detected in any patient. No significant differences in sexual behavior were reported among the 3 groups [69].

3) Testosterone Enanthate and Levonorgestrel

a) Testosterone enanthate 100 mg IM weekly plus levonorgestrel 500 mcg orally daily was more effective in producing azoospermia than testosterone enanthate alone at 6 months (67% vs 33%; p=0.06). A pregnancy rate was not mentioned [70].

4) Clinical trials have indicated that approximately 50% of healthy males become azoospermic and the other 50% become severely oligospermic following administration

of testosterone enanthate. Additionally, severe oligospermia appears to be associated with effective contraception [72].

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Voice deepening, facial hair increase, cessation of menses, and significant increases in testosterone levels were achieved within 6 months of initiating IM testosterone replacement therapy in individuals with female-to-male gender dysphoria in a retrospective study [65]. Hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8]. In a prospective study, significant changes in several domains of psychological functioning were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls [66]

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) Significant changes in several domains of psychological functioning, as assessed using the Minnesota Multiphasic Personality Inventory second edition (MMPI-2), were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls (N=163; 48 transgender men, 53 male controls, 62 female

controls). The MMPI-2 contains 10 clinical scales. Transgender men were compared with female controls using the female template of MMPI-2 and compared with male controls using the male template. Higher scores on each scale equate with lower levels of psychological functioning. Relative to female controls, transgender men had a significant change from baseline on the Hypochondria (-3.14), Depression (-3.28), Hysteria (-3.66), Paranoia (-4.62), and Masculinity-femininity (+5.05) scales after 3 months of therapy. No significant differences were observed after therapy versus female controls on the Psychopathic Deviate, Psychasthenia, Schizophrenia, Hypomania, or Social Inversion scales or on any of the 10 scales relative to male controls. Testosterone was administered as 50 to 400 mg IM every 10 to 14 days (or 50% weekly) for most participants (n=32) [66].

2) Therapeutic effects of voice deepening, facial hair increase, and cessation of menses were achieved with 3 different dosages of testosterone enanthate by 6 months after initiation of therapy in individuals with female to male gender dysphoria undergoing testosterone replacement therapy in a retrospective study (N=138). At 1 month, onset of treatment effects occurred in more patients with higher doses. However, no dose dependent effects were evident at 6 months, and 96.3% to 100% of patients achieved deepening of voice, 72.7% to 97.4% achieved increase in facial hair, and 85.7% to 96.6% achieved cessation of menses. Serum testosterone levels were significantly increased to around 700 nanograms/dL and serum estradiol levels were significantly decreased from baseline to month 6, with no significant differences among the different dosages of testosterone. No significant adverse events were reported in any group and there were no clinically relevant changes in liver enzymes, coagulation parameters, or urinalysis results. Testosterone enanthate was administered as 250 mg IM every 2 weeks (n=30), 250 mg IM every 3 weeks (n=50), or 125 mg every 2 weeks (n=58) based on patient preference relating to frequency of administration and cost [65].

3) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy

Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **

KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale

* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.

** Significant difference versus without-hormone-therapy group

^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.

d) Pediatric:

1) Adolescent

a) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
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KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus without-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

Sexual disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone enanthate prevented the loss of potency in patients receiving concomitant luteinizing hormone-releasing hormone (LHRH) agonist therapy [79].

c) Adult:

1) Reversible oligospermia without impotence in male patients treated with an luteinizing hormone-releasing hormone (LHRH) agonist plus testosterone was reported. When an LHRH agonist is used to produce reversible oligospermia, a reduction in plasma testosterone, libido, and potency occurs. Testosterone enanthate 100 mg IM every 2 weeks prevented the loss of potency in 6 patients receiving concomitant LHRH agonist therapy [79].

Weight gain

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone has produced an increase in fat-free mass, muscle size, and strength [45] [46][80].

c) Adult:

1) Testosterone increased lean body mass and improved quality of life in androgen-deficient men with AIDS wasting syndrome. In a randomized, double-blind, placebo-controlled trial, patients received testosterone enanthate 300 mg IM weekly for 6 months (n=26) or placebo (n=25). In the testosterone-treated group, 22 patients completed the trial and 19 patients in the placebo group completed the trial. Compared with placebo, testosterone-treated patients demonstrated a gain in fat-free mass, lean body mass, and muscle mass (change, -0.6 kg and 2 kg; change, 0 kg and 1.9 kg; and change, -0.8 kg and 2.4 kg, respectively) [46].

2) Testosterone enanthate 600 mg weekly for 10 weeks produced an increase in fat-free mass, muscle size, and strength in males. A standardized exercise program was additive to the effects of testosterone. Because anabolic steroids have potentially serious adverse effects, their use in athletics is not justified; however, it is postulated that short-term administration of androgens may be advantageous for immobilized, cachectic, AIDS patients, or those with chronic wasting disease [80].

Testosterone Undecanoate

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Testosterone undecanoate significantly increased testosterone levels in transsexual men (ie, female-to-male) from the physiological range for women to the normal male range in observational [9] and prospective studies [54]. Significant physical changes including body weight, lean body mass, body fat redistribution [55], and facial and body hair growth occurred during the first year of therapy [56]. Additionally, hormonal sex

reassignment therapy significantly reduced symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8]. Major adverse events have not been observed, but changes in lipid profiles, hematocrit, liver enzymes [54], and fasting plasma glucose have been reported during 1-year studies [9]. Regular monitoring for adverse effects of hormone therapy is recommended [7].

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) During the first year of treatment, body weight and lean body mass (LBM) were significantly increased by 3% and 10%, respectively, in transsexual men undergoing cross-sex hormonal therapy with testosterone during an observational study (n=162 transsexual men). Total body fat was decreased by a significant 9%, with redistribution of body fat significant in the leg (-16%) and gynoid (-14%), but not android regions. LBM was increased in all body parts by between 9% and 19%. Hip circumference was significantly changed by -1.9 cm, but there was no significant difference for waist circumference or the waist-to-hip ratio. Testosterone was administered as testosterone gel 50 mg/day, testosterone undecanoate 1000 mg IM once every 12 weeks, or testosterone esters 250 mg IM once every 2 weeks (not an FDA-approved product). Mean follow-up was 380 days [55].

2) Testosterone undecanoate injections significantly increased testosterone levels to the normal male range in 100% of hormone-naïve transgender men (female-to-male) in a 1-year prospective study (n=53 trans men). At baseline, serum testosterone levels were 30.2 nanograms/dL (ng/dL) and increased to a mean 595.8 ng/dL. Body weight was significantly increased from 68.4 to 70.6 kg, with an increase in lean body mass and decrease in total body fat. Waist-to-hip ratio was significantly increased (0.82 to 0.84) due to decreased hip circumference. Small, but significant, changes in total cholesterol (171.9 to 178.2 mg/dL), LDL-C (98.4 to 116.1 mg/dL), triglycerides (69 to 81.1 mg/dL), and HDL-C (56.3 to 47.8 mg/dL) occurred. Erythrocytosis was present in 2 men based on the male reference range (Hct level above 52%) and 20.1% had Hct levels above the female reference range of 48%. Liver enzyme elevations greater than 2 x ULN were reported with respect to the female reference range (1.9%), but none were 2 x the ULN of the male reference range. No cardiovascular events, venous thromboses, pulmonary

embolisms, deaths, or osteoporotic fractures were reported. Testosterone undecanoate was administered as 1000 mg IM at initiation, at 6 weeks, and then every 12 weeks thereafter. In cases of intolerance, participants could switch to testosterone esters 250 mg (not an FDA-approved product) every 2 weeks [54].

3) Testosterone in 3 different formulations significantly increased total testosterone levels from the physiological range for women to the normal male range by week 30 of treatment with no significant differences among formulations in an observational study in female-to-male transsexual individuals (N=45). At week 54, testosterone remained elevated and sex hormone-binding globulin, prolactin, and estradiol levels were significantly decreased from baseline while body weight and body mass index (BMI) were significantly increased in all groups. Results for selected hormonal and anthropometric outcomes are shown in the table below. Amenorrhea occurred at a mean 29.8 to 41 weeks. Significant changes from baseline were observed in HDL-C (decreased) and LDL-C (increased), but not total cholesterol. Fasting glucose increased significantly, but insulin and homeostasis model assessment for fasting insulin resistance (HOMA-IR) were similar to baseline. Hematocrit and hemoglobin increased from baseline. No significant changes were detected in liver enzymes, renal function, or bone mineral density. Patients were randomly assigned to testosterone enanthate 100 mg IM every 10 days, testosterone gel 50 mg once every evening, or testosterone undecanoate 1000 mg IM at week 0, week 6, and every 12 weeks thereafter. No subject had undergone sexual reassignment surgery [9].

Selected Hormonal and Anthropometric Parameters at Baseline and Week 54 Posttreatment

Parameter	Baseline Range *	Week 54 Posttreatment Range*
Testosterone (ng/mL)	0.44 to 0.54	5.89 to 7.39 **
Estradiol (pg/mL)	102.9 to 167.3	70.6 to 81.9 **
Luteinizing hormone (international units/L)	5.8 to 12.8	5.1 to 9.2
Follicle stimulating hormone (international units/L)	4.6 to 6.2	5.1 to 5.6
Prolactin (ng/mL)	15.7 to 18.2	9.8 to 15.6 **
Sex hormone-binding globulin (nmol/L)	60.3 to 65.4	31.6 to 34.3 **
Body weight (kg)	57.8 to 67.3	60.5 to 68.7 **
BMI (kg/m(2))	22.1 to 23.9	22.4 to 24.3 **
Fat (%)	26.7 to 30.1	22.4 to 27.6 **

KEY: BMI=body mass index; ng=nanograms; pg=picograms

* Range is among the 3 different testosterone formulations with no significant difference among the formulations at baseline or week 54.

** Significant difference between baseline and week 54 values.

4) Facial and body hair growth was significantly increased over time with testosterone undecanoate administration in hormone-naïve transsexual men in a prospective study (N=20). The Ferriman and Gallway score (FG; 0 to 36 scale with a score of greater than 8 in an androgen-dependent area indicating hirsutism) was a median 0.5 at baseline and increased to 12 after 12 months of therapy, but there was wide interindividual variability (range, 2 to 25). In an associated cross-sectional study in transgender men who had undergone sexual reassignment surgery and had been using testosterone for an average of 9.9 years (N=50), the median PG score was 24 with a range of 6 to 34. Moderate to severe alopecia was reported in 31%. Neither the FG score nor alopecia was positively correlated with duration or type of testosterone therapy in the cross-sectional group. Alopecia was correlated with age. In the prospective study group, all participants received testosterone undecanoate 1000 mg IM every 3 months. In the cross-sectional study group, testosterone was administered as testosterone esters 250 mg (not an FDA-approved product) IM every 2 or 3 weeks (n=35), testosterone undecanoate 1000 mg

IM every 12 weeks (n=7), or transdermal testosterone 50 mg/day (n=8); one participant used an oral and transdermal formulation together [56].

5) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

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* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.

** Significant difference versus no-hormone-therapy group

^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.

d) Pediatric:

1) Adolescent

a) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and

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Dose Adjustments

Adult Dosage

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

Hypogonadism, Male

1) FDA Dosage, Striant(R)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [17].

b) Usual dose: One 30-mg buccal system applied to the gum approximately every 12 hours, applying to opposite sides of the mouth with each dose; monitor testosterone levels at 4 to 12 weeks after initiation, and discontinue if levels are consistently outside normal range [23]

c) Dosing notes: If the system fails to adhere or falls off within 8 hours of application, a new system may be applied and continued for a total of 12 hours from the placement of the first system; however, if it is within 8 hours of the next scheduled dose, apply the new system for 12 hours and then continue with the next dose. Remove system prior to oral care and apply a new system after [23].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Striant(R) testosterone buccal system is not indicated for use in women [23].

Nasal route

Hypogonadism, Male

1) FDA Dosage, Natesto(TM)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [16].

b) Usual dose: 1 actuation per nostril (2 pump actuations, 11 mg) intranasally 3 times a day (morning, afternoon, and evening, 6 to 8 hours apart) at the same time each day for a total daily dose of 33 mg; after 1 month check testosterone levels periodically [22]

c) If total testosterone level usually below 300 nanograms/dL, consider alternative therapy [22].

d) If total testosterone level generally greater than 1050 nanograms/dL, discontinue treatment with testosterone nasal gel [22].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Natesto(TM) testosterone nasal gel is not indicated for use in women [22].
There is insufficient evidence of long-term safety (ie, cardiovascular and prostate cancer risks) for Natesto(TM) testosterone gel treatment in geriatric patients [22].
The safety and efficacy of Natesto(TM) testosterone gel treatment have not been established in patients with a BMI greater than 35 kg/m(2) [22].

Topical application

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [5][15][1][3][2][18].

2) FDA Dosage, Axiron(R)

a) Initial dose: 60 mg (1 pump or twist actuation of 30 mg to each axilla) applied once daily at the same time each morning to clean, dry, intact skin of the axilla; do not apply to any other parts of the body; obtain serum testosterone concentration at least 14 days after initiation; draw 2 to 8 hours after application [20]

b) Dose titration: decrease or increase dose by 30-mg increments based on serum testosterone concentration from a single blood draw 2 to 8 hours after application and at least 14 days after starting treatment or following dose adjustment, according to the following recommendation [20][20]:

Serum testosterone concentration below 300 nanogram/deciliter (ng/dL): Increase daily dose from 60 to 90 mg or from 90 mg to 120 mg

Serum testosterone concentration exceeds 1050 ng/dL: Decrease daily dose from 60 mg to 30 mg, or discontinue therapy if at the lowest daily dose of 30 mg

3) FDA Dosage, AndroGel(R) 1%

a) Initial dosage: 50 mg topically once daily (4 pump actuations, or 5 g of gel) preferably in the morning to clean, dry, intact skin on shoulders and upper arms and/or abdomen [5]

b) Dose titration: May increase once-daily dose to 75 mg (6 pump actuations, or 7.5 g of gel) and further to 100 mg (8 pump actuations, or 10 g of gel) if testosterone concentration below normal physiologic level [5]

c) Discontinue use if serum testosterone concentrations consistently exceed the normal range at a daily dose of 50 mg [5]

4) FDA Dosage, AndroGel(R) 1.62%

a) Initial dosage: 40.5 mg (2 pump actuations or 2.5 g of gel) applied topically once daily in the morning to clean, dry, intact skin of the shoulders and upper arms; measure predose morning serum testosterone concentration at approximately 14 and 28 days [15]

b) Dosage titration: Decrease or increase dose to minimum of 20.25 mg/day (1 pump actuation or 1.25 g of gel) up to 81 mg/day (4 pump actuations, or 5 g of gel), based on predose morning serum testosterone concentration drawn approximately 14 and 28 days after starting treatment or following dose adjustment, according to the following recommendation [15]:

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Key: ng = nanograms	

c) The application site and dose of AndroGel(R) 1.62% are not interchangeable with other topical testosterone products [15]

5) FDA Dosage, Fortesta(TM)

a) Initial dose: 40 mg (4 pump actuations) applied once daily to clean, dry, intact skin of the front and inner thighs in the morning; measure serum testosterone level at approximately 14 and 35 days, draw 2 hours post-application [21]

b) Dose titration: decrease or increase dose to a minimum of 10 mg/day or maximum of 70 mg/day, based on serum testosterone concentrations, drawn 2 hours after application at approximately 14 days and 35 days after treatment initiation or following dose adjustments, according to the following recommendation [21]:

Total Serum Testosterone Concentrations 2 hours Post Fortesta(TM) Application	Dose Titration

Equal to or greater than 2500 ng/dL	Decrease daily dose by 20 mg (2 pump actuations)
Equal to or greater than 1250 and less than 2500 ng/dL	Decrease daily dose by 10 mg (1 pump actuation)
Equal to or greater than 500 and less than 1250 ng/dL	No change: continue current dose
Less than 500 ng/dL	Increase daily dose by 10 mg (1 pump actuation)
Key: ng = nanograms	

c) The application site and dose of Fortesta(TM) are not interchangeable with other topical testosterone products [21].

6) FDA Dosage, Testim(R) 1% Gel

a) Initial dose: one 5 g tube applied once daily (preferably in morning) to clean, dry, intact skin on the shoulder and/or upper arms; measure morning testosterone level 2 weeks after initiation [24].

b) Dose titration: increase dose to 10 g/day (2 tubes) if serum testosterone concentration is below the normal physiologic range or if desired clinical response is not observed [24]

7) FDA Dosage, Vogelxo(TM)

a) Initial dose: 50 mg (1 tube or packet or 4 pump actuations) applied topically to clean, dry, intact skin of shoulders or upper arms once daily; measure morning predose testosterone level after approximately 14 days [25]

b) Dose titration: may increase to 100 mg (2 tubes or packets or 8 pump actuations) once daily if morning predose testosterone level remains below normal (ie, 300 to 1000 nanograms/dL) [25]

c) Maximum dose: 100 mg/day [25]

8) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (1.6% gel): 50 to 100 mg applied topically once daily. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used). Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

AndroGel(R), 1%, Androgel(R) 1.62%, Natesto(TM), Striant(R), Testim(R), and Vogelxo(TM) topical testosterone gel products are not indicated for use in women [25][22][49][27][24][23]

Transdermal route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (patch): 2.5 to 7.5 mg/day. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions (guideline dosage) [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage, Androderm(R) 2 mg/day and 4 mg/day System

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [14].

b) Initial dose: One 4 mg/day transdermal system (not two 2 mg/day systems) applied every 24 hours at night; measure early morning serum testosterone level 2 weeks later [19]

c) Dose titration: Increase dose to 6 mg daily at night (one 4 mg/day plus one 2 mg/day system) or decrease dose to 2 mg daily at night (one 2 mg/day system) if early morning serum testosterone level drawn 2 weeks after starting therapy is outside the target range (400 to 930 nanograms/dL) [19].

2) FDA Dosage, Switching from Androderm(R) 2.5 mg/day, 5 mg/day, and 7.5 mg/day System to Androderm(R) 2 mg/day, 4 mg/day, and 6 mg/day System

At next scheduled dose, make switch according to following recommendation [19]:

patients currently on the 2.5 mg/day system may switch to the 2 mg/day system [19]
patients currently on the 5 mg/day system may switch to the 4 mg/day system [19]
patients currently on the 7.5 mg/day system may switch to the 6 mg/day system [19]

Two weeks after switching therapy, measure an early morning serum testosterone level [19]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks. Base dosage (initial, maintenance, and adjustments) on patient response and presence of adverse reactions [82].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks as replacement therapy; dose based on diagnosis, response to treatment, and presence of adverse effects. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Metastatic breast cancer, Female

1) Usual dosage (women): 200 to 400 mg IM every 2 to 4 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg subQ every 2 weeks or 50% of the dose subQ once weekly [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Prior to initiation: Confirm the diagnosis of hypogonadism with serum testosterone concentration below the normal range when measured in the morning on at least 2 separate days [74].

b) Initial dosage: 75 mg subQ in the abdominal region once a week [74]

c) Dosage titration: Measure total testosterone trough concentration (Ctrough) 7 days after the most recent dose after 6 weeks of dosing, following 6 weeks after dose adjustment, and periodically while on treatment. If Ctrough is 650 nanograms (ng)/dL or higher, decrease the dose by 25 mg. If Ctrough is less than 350 ng/dL, increase the dose by 25 mg. If Ctrough is 350 to less than 650 ng/dL, maintain the same dose [74].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Initial dosage: 1000 mg IM at 0 and 6 weeks and then every 12 weeks to maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [58].

b) Usual dosage: 750 mg IM, and then 750 mg IM 4 weeks later, and then 750 mg IM every 10 weeks thereafter [59]

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

3) Off-label Dosage

a) Off-Label Dosage: 1000 mg IM, and then 1000 mg IM at week 6, and then 1000 mg IM every 12 weeks [60]

Oral route

Hypogonadism, Male

1) Tlando(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [53].

b) Dosage: 225 mg (2 capsules) orally twice daily in the morning and evening with food; do not adjust dosage [53].

c) Measure serum testosterone following 3 to 4 weeks of treatment and periodically thereafter; draw level 8 to 9 hours after the morning dose [53].

d) Continue treatment if serum testosterone is 300 to 1080 ng/dL, otherwise discontinue treatment [53].

2) Jatenzo(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [57].

b) Initial dosage: 237 mg twice daily in the morning and evening with food [57]

c) Adjust dose based on serum testosterone concentrations measured 6 hours after the morning dose in plain tubes, clotted at room temperature for 30 minutes prior to centrifugation. Wait seven days after starting treatment or adjusting the dose before checking the serum testosterone concentration. Thereafter, periodically monitor serum testosterone concentrations 6 hours after the morning dose. Administer the same dose in the morning and evening according to the following table [57]:

Testosterone Concentration in Serum From Plain Tube Drawn 6 hours After Morning Dose	Current dose (mg, twice daily)	New dose (mg, twice daily)
Less than 425 nanograms/dL	158	198
	198	237
	237	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	396 (two 198 mg capsules)
425 to 970 nanograms/dL	No dose change	
More than 970 nanograms/dL	396 (two 198 mg capsules)	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	237
	237	198
	198	158
	158	Discontinue therapy

d) Maximum dosage: 396 mg (two 198 mg capsules) twice daily [57]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Dosage in Renal Failure

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Hepatic Insufficiency

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Other Disease States

A) Testosterone Enanthate

1) In patients who develop edema with or without congestive heart failure, discontinue testosterone enanthate and restart at a lower dose [73].

Pediatric Dosage

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

a) The safety and effectiveness of Striant(R) testosterone buccal system have not been established in males younger than 18 years [23].

Nasal route

a) The safety and efficacy of Natesto(TM) testosterone gel have not been established in patients younger than 18 years [22].

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Off-label Dosage, Adolescent

a) Dosage (gel): 50 mg applied topically once daily [8]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

The safety and efficacy of AndroGel(R) 1%, AndroGel(R) 1.62%, Axiron(R), Fortesta(TM), Testim(R) 1%, and Vogelxo(TM) have not been established in males younger than 18 years [20][25][27][24][49][21]. Acceleration of bone age and premature closure of epiphyses may occur with improper use [21].

Transdermal route

a) Safety and efficacy of testosterone transdermal system have not been established in males younger than 18 years. Acceleration of bone age and premature closure of epiphyses may occur with improper use [19].

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) Usual dosage (12 years or older): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Base dosage (initial, maintenance, and adjustments) on patient response, presence of adverse reactions, age, and skeletal age. Some regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses [82].

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Delayed puberty, Male

1) Usual dosage (adolescent males): 50 to 200 mg IM every 2 to 4 weeks for a limited duration, such as 4 to 6 months. Some dosage regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses. Although various dosing regimens may be used, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses in addition to patient response and adverse effects [73].

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) Usual dosage (adolescent males): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Although various dosing regimens may be used to induce pubertal changes in hypogonadal males, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) subQ every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg subQ every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years [59].

Oral route

a) General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years. Improper use may result in acceleration of bone age and premature closure of epiphyses [53][57].

Administration

A) Testosterone

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the compounding and administration of a hazardous topical drug, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator, and use eye/face and respiratory protection if not prepared in a control device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection, and if there is inhalation potential use respiratory protection [50].

b) Buccal mucosa route

1) Administration

a) The rounded side of the buccal system surface should be placed against the gum and held firmly in place with a finger over the lip for 30 seconds to ensure adhesion [23].

b) If the buccal system falls off during the first 8 hours after application, replace with a new system that should be retained until a total of 12 hours have elapsed from placement of the first system; then continue usual dosing schedule. If the buccal system falls off 8 or more hours after application, apply a new buccal system that may be retained for 12 hours; then continue usual dosing schedule [23].

c) The buccal system should not be chewed or swallowed. Remove system prior to oral care and apply a new system after [23].

c) Nasal route

1) Preparation

a) Prime the pump prior to the first use by depressing the pump 10 times, discarding initial drug delivered. Wash off the gel with warm water then wipe tip with clean, dry tissue. If the product comes into contact with hands, wash hands with soap and water [22].

2) Administration

a) Completely depress the pump 1 time in each nostril; do not apply to any other part of the body. To administer, blow nose, uncap pump, and place the finger on the actuator. Then insert pump until the finger reaches the bottom of the nose. Apply gel to lateral nasal wall and remove pump once fully depressed, wiping the tip along the inside of the lateral nostril. Press on the nostrils just below the bridge of the nose and lightly massage the applied product. Do not blow nose or sniff for 1 hour [22].

d) Topical application route

1) Axiron(R)

a) If using antiperspirant or deodorant stick, roll-on, or spray, apply these 2 minutes prior to the application of testosterone topical solution as part of a normal, consistent, daily routine [20].

b) When using for the first time, prime the pump by depressing the pump-actuated or by twisting the dose dial 3 times; discard product dispensed directly into a basin, sink, or toilet and then wash the liquid away thoroughly [20].

c) Pump actuated: After priming, depress the pump completely only 1 time each time (1 pump actuation equals 30 mg) [20].

d) Pump actuated: Apply using the applicator provided. Position the nozzle over the applicator cup and depress the pump fully once. Do not fill the cup with more than 30 mg (1 pump actuation) [20].

e) Twist actuated: After priming, completely twist (180 degree turn) the dose dial 1 time (1 twist actuation equals 30 mg). The applicator should be filled with no more than 30 mg (1 twist

actuation). Dosing that requires greater than 1 twist actuation must be applied in increments of 30 mg [20]

f) Keep the applicator upright. Place it up into the axilla and wipe steadily down and up into the axilla. If the solution drips or runs, wipe it back up with the applicator cup. Do not rub the solution into the skin with fingers or hand [20].

g) Apply each morning to clean, dry, intact skin of the axilla. Do not apply to any other parts of the body. Allow each application site to dry completely prior to the next application (for higher doses) or dressing [20].

h) 30 mg, 1 pump or twist actuation: Apply once to 1 axilla only (left or right) [20].

i) 60 mg, 2 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla [20].

j) 90 mg, 3 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left or right axilla [20].

k) 120 mg, 4 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left axilla and 1 actuation to the right axilla [20].

l) After use, rinse the applicator under room temperature, running water, and then pat dry with a tissue. Place the applicator and cap on the bottle for storage [20].

m) Wash hands thoroughly with soap and water after applying testosterone topical solution [20].

n) Cover the application site with clothing or dressing after the solution has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [20].

o) Wait at minimum 2 hours prior to washing the application site or swimming [20].

p) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [20].

2) AndroGel(R)

a) Prime the AndroGel(R) pump by depressing the actuator 3 times while canister is in upright position. Safely discard the gel dispensed from the first 3 actuations. Priming is only necessary before the first dose [27][49].

b) Apply to clean, dry, intact skin of shoulder or upper arm that will be covered by clothing. For the 40.5 mg (2.5-g packets), squeeze a portion of the gel from the packet into the palm of hand and apply to application sites (as this size packet needs to be split between the left and right shoulder) and repeat until entire contents have been applied. The gel may be delivered from the actuator into the palm of one hand, then applied to the intended site, or may be applied directly from the pump to the intended application site [24][27][49].

c) Apply AndroGel(R) 1.62%, to the shoulder or upper arm (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to any other part of the body, including abdomen or genitals. Wait a minimum of 2 hours prior to washing the application site or swimming [49].

d) AndroGel(R) 1%, apply to the shoulder and upper arm and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to genitals. Avoid swimming or showering for at least 5 hours after application [51].

e) Patients should wash hands thoroughly with soap and water immediately after applying testosterone topical gel [27][49].

f) Cover the application site with clothing or dressing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [27][49].

g) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [27][49].

h) Children and women should avoid contact with unwashed or unclothed application site [27][49].

i) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [27][49].

j) Application recommendations for AndroGel(R) 1.62% for pump or packets are in the table below [15]:

AndroGel(R) 1.62%						
Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Upper Arm and Shoulder		Total Packets *	Gel Applications per Upper Arm and Shoulder *	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0	One 1.25-g packet	One 1.25-g packet	0
40.5 mg	2	1	1	One 2.5-g packet	Half the contents of one 2.5-g packet	Half the contents of one 2.5-g packet
60.75 mg	3	2	1	One 1.25-g AND one 2.5-g packet	One 2.5-g packet	One 1.25-g packet
81 mg	4	2	2	Two 2.5-g packets	One 2.5-g packet	One 2.5-g packet
* Weight given as gel content of packet.						

k) Application recommendations for AndroGel(R) 1% 75-g pump are in the table below [5]:

Dosing Guidelines for the AndroGel(R) 1% 75-g Multi-Dose Pump	
Prescribed Testosterone Dose	Number of Pump Actuations
50 mg daily	4 pumps once daily
75 mg daily	6 pumps once daily
100 mg daily	8 pumps once daily

3) Fortesta(TM)

a) Prime the pump by depressing the actuator 8 times while canister is in upright position; safely discard the gel dispensed from the first 8 actuations; only necessary to prime pump before the first dose [21].

b) Apply to clean, dry, intact skin of the front and inner thighs; do not apply to genitals or other parts of the body; use one finger to apply gel [21].

c) After the application site is dry, site should be covered with clothing (with sufficient length to cover application site); wash hands thoroughly with soap and water after applying gel [21].

d) Children and women should avoid contact with unwashed or unclothed application site [21].

e) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [21].

f) If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [21].

g) Application recommendations for Fortesta(TM) are in the table below [21]:

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Thigh	
		Thigh #1	Thigh #2
10 mg	1	1	0
20 mg	2	1	1

30 mg	3	2	1
40 mg	4	2	2
50 mg	5	3	2
60 mg	6	3	3
70 mg	7	4	3

4) Testim(R)

a) Apply to clean, dry, intact skin of shoulder or upper arm; do not apply to genitals or abdomen. Wash hands thoroughly with soap and water immediately after applying [24].

b) Do not wash application site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [24].

c) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [24].

d) Children and women should avoid contact with unwashed or unclothed application site [24].

e) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [24].

5) Vogelxo(TM)

a) With multidose bottle, prime the pump 3 times before first use (discard any product released). Depress pump 4 times or empty entire contents of 1 unit-dose tube or packet into palm of the hand and immediately apply to clean, dry, intact skin of shoulder and upper arm. When the daily dosage is 100 mg, repeat on the opposite shoulder [25].

b) Do not apply to abdomen or genitals. Wash hands thoroughly with soap and water immediately after applying [25].

c) Do not wash site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [25].

d) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [25].

e) Children and women should avoid contact with unwashed or unclothed application site [25].

f) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [25].

e) Transdermal route

1) Administration

a) Immediately after opening the pouch, apply the adhesive side of the Androderm(R) system to the back, abdomen, upper arm, or thigh in a clean, dry area of the skin. Press system firmly in place, ensuring good contact with the skin, especially around the edges. Avoid application to oily, damaged, or irritated skin. Do not apply to the scrotum, and avoid bony prominences or areas of prolonged pressure during sitting or sleeping [19].

b) Avoid swimming, showering, or washing the administration site for at least 3 hours after application [19].

c) Rotate application sites, with at least 7 days between applications to the same site [19].

B) Testosterone Cypionate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due

to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle; it is not for IV injection [83].

b) If crystals formed because product was stored at lower than recommended temperatures, they can be dissolved by warming or shaking the vial [83].

C) Testosterone Enanthate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle, avoiding intravascular injection. Crystals formed during storage at lower than recommended temperatures can be dissolved by warming or shaking the vial. A wet syringe or wet needle may turn the solution cloudy but does not affect product potency [73].

c) Subcutaneous route

1) Administration

a) Xyosted(TM) is for subQ injection in the abdominal region only. Avoid IM or intravascular injection. Do not use if the liquid in the syringe is cloudy or if visible particles are present; an air bubble is normal. Do not use if the seal is broken [74].

D) Testosterone Undecanoate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Preparation

a) Carefully remove gray plastic cap from vial; leave the aluminum metal ring and crimp seal

around the gray rubber stopper [63].

b) Using an 18-gauge needle at a 45-degree angle with the bevel oriented upward, inject 3 mL of air through the gray rubber stopper to create positive pressure in the vial, and then withdraw 3 mL (750 mg) of solution [64].

c) Expel any air bubbles from the syringe and change the syringe needle to a new IM needle [63].

d) .

2) Administration

a) For IM use only [63]

b) Slowly (over 60 to 90 seconds) inject IM deep into the gluteal muscle; care must be taken to avoid intravascular administration as this may lead to pulmonary oil microembolism; also avoid the superior gluteal arteries and sciatic nerve [63].

c) Discard any unused portion [63].

d) Alternate injection sites between left and right buttock between consecutive injections [63].

c) Oral route

1) Administration

a) Give with food [53][57].

E) Testosterone

1) Buccal mucosa route

a) Patch, Extended Release

1) Store at 20 to 25 degrees C (68 to 77 degrees F). Protect from heat and moisture [108].

2) Intramuscular route

a) Solution

1) Store at room temperature. Warming and rotating the vial between hands will redissolve any crystals that may have formed when stored at lower temperatures [88].

3) Nasal route

a) Gel/Jelly

1) Store at a controlled room temperature between 20 and 25 degree C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [22].

4) Oral route

a) Capsule

1) Refrigerate between 2 and 8 degrees C before dispensing. Do not refrigerate after dispensing. The shelf life is 3 years before opening when stored between 2 and 8 degrees C and 90 days at room temperature after the container has been opened [208].

5) Topical application route

a) Gel/Jelly/Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [28][25]. Do not freeze [21].

2) Store upright at a controlled room temperature of 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [209][183].

6) Transdermal route

a) Patch, Extended Release

1) Store at 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [182].

F) Testosterone Cypionate

1) Injection route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F); protect from light [83].

G) Testosterone Enanthate

1) Intramuscular route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F). If crystals form, warm and rotate vial between palms of hands to dissolve [73].

2) Subcutaneous route

a) Solution

1) Store in original carton at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F). Protect from light; do not refrigerate or freeze [74].

H) Testosterone Undecanoate

1) Intramuscular route

a) Solution

1) Store in original carton at a controlled room temperature of 25 degrees C (77 degrees F) , with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Discard any unused portion [59].

2) Oral route

a) Capsule

1) Store at a temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Store in a dry place and protect from moisture [57].

b) Capsule, Liquid Filled

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [53].

Comparative Efficacy

Acetylcarnitine

Aging, Male

a) Carnitines and testosterone both improved sexual dysfunction, depressed mood, and fatigue associated with male aging. However, testosterone treatment caused prostate enlargement, which carnitine treatment did not. In a randomized, placebo- controlled trial, men over age 60 with symptoms of decreased libido and erectile quality, depressed mood and intellectual concentration ability, irritability, fatigue, and serum testosterone lower than 6 picograms/milliliter were randomized to receive testosterone undecanoate 160 milligrams/day (mg/d) (n=40), propionyl-L-carnitine 2 grams/day (g/d) plus acetyl-L-carnitine 2 g/d (n=45), or placebo (n=45) for 6 months. At 6 months, peak systolic velocity, resistive index of the right cavernosal artery, and nocturnal penile tumescence were increased in both the testosterone group and the carnitines group and unchanged in the placebo group. Erectile function, sexual desire, and sexual satisfaction increased at 3 or 6 months or both in both active treatment groups. Carnitine scores were significantly better than testosterone scores with respect to erectile function at 3 months (p less than 0.05) and 6 month (p less than 0.01), orgasm at 6 months (p less than 0.01), and sexual well-being at 6 months (p less than 0.01). Other physiological scores were not different for the 2 groups. Both active treatments lowered the Hamilton Depression and Melancholia Scale scores, but carnitines more so (p less than 0.01, carnitines vs testosterone). Carnitines and testosterone equally decreased fatigue scale scores. Prostate volume increased with testosterone treatment from 15 cubic centimeters at baseline to 25 cubic centimeters at 6 months. Prostate volume was unchanged by carnitine or placebo treatment. In the testosterone group, prostate volume had decreased (to 18 cubic centimeters) by 6 months after termination of therapy but

remained elevated above baseline. All other parameters reverted to baseline levels by 6 months after termination of therapy [214].

Chlorotrianisene

Engorgement of breasts

a) SUMMARY: Chlorotrianisene is less effective than the combination of testosterone enanthate plus estradiol valerate in the treatment of postpartum breast engorgement.
b) In a double-blind study of lactation suppression in clinic patients, testosterone enanthate with estradiol valerate (Deladumone OB) 2 milliliters IM immediately prior to delivery was compared to chlorotrianisene 72 mg orally every 12 hours for 4 doses. At day 4, Deladumone OB(R) patients experienced significantly less breast tenderness and lactation than did patients receiving chlorotrianisene. Both drugs were significantly more effective than placebo [212].
c) In a study of 484 puerperal patients who did not wish to breast feed, testosterone enanthate with estradiol valerate was more effective than chlorotrianisene for inhibition of lactation and relief of breast engorgement and discomfort [213].

Chorionic Gonadotropin

Male hypogonadotropic hypogonadism

a) Weekly 5000 unit chorionic gonadotropin injections (n=16) were compared with monthly 250 milligram long-acting testosterone injections (n=22) in male hypogonadotropic hypogonadism patients [216]. Both treatments produced comparable virilizing effects measured as progression through Tanner stages. Chorionic gonadotropin, however, produced increases in testicular volume to near-normal, which did not occur with testosterone. This additional benefit of chorionic gonadotropin may enhance later induction of fertility when such treatment is undertaken.

Cyproterone

Contraception, Male

a) In a small study all men who received testosterone and cyproterone became azoospermic compared to 3 of 5 men receiving testosterone only. Fifteen men were randomized to receive cyproterone 50 mg orally twice daily plus testosterone enanthate 100 mg intramuscularly (IM) weekly; cyproterone 25 mg orally twice daily plus testosterone 100 mg IM weekly; or testosterone 100 mg IM weekly alone for 16 weeks. Patients in the cyproterone 100 mg, cyproterone 50 mg, and testosterone only groups achieved azoospermia at mean times of 6.8, 8.4, and 14 weeks, respectively. After treatment baseline sperm counts were achieved in all men. Lipoprotein profiles nor liver function tests were detected in any patient. No significant differences in sexual behavior were reported among the three groups [215].

Estrogen

Disorder of bone development

a) In a case report concerning a 31-year old hypogonadal male with aromatase deficiency, 50 micrograms of estradiol, given transdermally twice weekly for 9 months, was able to affect epiphyseal closure and improvement in bone pain. Prior treatment with testosterone enanthate, 250 milligrams intramuscularly every ten days for six months had not achieved these results. The baseline bone age of 14.8 years did not change with testosterone enanthate, but increased to more than 16 years after 9 months of estradiol therapy. Further research is required to confirm these results [211].

Fluoxymesterone

Anemia

a) A randomized clinical trial was conducted to compare the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis [210]. The patients received either testosterone enanthate 4 milligrams/kilogram intramuscularly weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 mg/kg orally daily, oxymetholone 1 mg/kg orally daily, or nandrolone decanoate 3 mg/kg intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; three courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had an increase of at least 5 percentage points in hematocrit following the administration of either injectable androgen.

Nandrolone

Anemia

a) A randomized clinical trial compared the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis. The patients received either testosterone enanthate 4 milligrams/kilogram of body weight intramuscularly weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 mg/kg of body weight orally daily, oxymetholone 1 mg/kg of body weight orally daily, or nandrolone decanoate 3 mg/kg of body weight intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; three courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had a 5% increase in hematocrit following the administration of either injectable androgen [217].

Oxymetholone

Anemia secondary to renal failure

a) A randomized clinical trial compared the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis. The patients received either testosterone enanthate 4 milligrams/kilogram intramuscularly weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 milligram/kilogram orally daily, oxymetholone 1 milligram/kilogram orally daily, or nandrolone decanoate 3 milligrams/kilogram intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; three courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had an increase of at least 5 percentage points in hematocrit following the administration of either injectable androgen [218].

Propionyl-L-Carnitine

Aging, Male

a) Carnitines and testosterone both improved sexual dysfunction, depressed mood, and fatigue associated with male aging. However, testosterone treatment caused prostate enlargement, which carnitine treatment did not. In a randomized, placebo- controlled trial, men over age 60 with symptoms of decreased libido and erectile quality, depressed mood and intellectual concentration ability, irritability, fatigue, and serum testosterone lower than 6 picograms/milliliter were randomized to receive testosterone undecanoate

160 milligrams/day (mg/d) (n=40), propionyl-L-carnitine 2 grams/day (g/d) plus acetyl-L-carnitine 2 g/d (n=45), or placebo (n=45) for 6 months. At 6 months, peak systolic velocity, resistive index of the right cavernosal artery, and nocturnal penile tumescence were increased in both the testosterone group and the carnitines group and unchanged in the placebo group. Erectile function, sexual desire, and sexual satisfaction increased at 3 or 6 months or both in both active treatment groups. Carnitine scores were significantly better than testosterone scores with respect to erectile function at 3 months (p less than 0.05) and 6 month (p less than 0.01), orgasm at 6 months (p less than 0.01), and sexual well-being at 6 months (p less than 0.01). Other physiological scores were not different for the 2 groups. Both active treatments lowered the Hamilton Depression and Melancholia Scale scores, but carnitines more so (p less than 0.01, carnitines vs testosterone). Carnitines and testosterone equally decreased fatigue scale scores. Prostate volume increased with testosterone treatment from 15 cubic centimeters at baseline to 25 cubic centimeters at 6 months. Prostate volume was unchanged by carnitine or placebo treatment. In the testosterone group, prostate volume had decreased (to 18 cubic centimeters) by 6 months after termination of therapy but remained elevated above baseline. All other parameters reverted to baseline levels by 6 months after termination of therapy [214].

Stanozolol

1) Efficacy

a) Oral stanozolol 6 mg/day produced more undesirable lipoprotein effects than intramuscular testosterone 200 mg once weekly in male weight lifters in a 6-week, crossover study [219]. Stanozolol reduced HDL-cholesterol and the HDL-2 subfraction by 33% and 71%, respectively; however, the HDL-cholesterol concentration was decreased by only 9% with testosterone, with the decrease being in the HDL-3 subfraction. Apolipoprotein A-1 levels were reduced by 8% and 40% with testosterone and stanozolol, respectively. LDL-cholesterol concentrations decreased 16% with testosterone, but increased by 29% with stanozolol. An increase in the postheparin hepatic triglyceride lipase activity of 123% was observed with stanozolol, however, increases with testosterone (25%) were not significant. Intramuscular testosterone is preferable to oral stanazolol for clinical indications requiring prolonged androgen or anabolic steroids.

Place In Therapy

A) Testosterone

1) Transdermal, Topical, Buccal, Intranasal

a) Testosterone preparations are indicated for primary hypogonadism (congenital or acquired) due to testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. Typically, low serum testosterone concentrations and high gonadotropin (FSH, LH) concentrations are present. Additionally, it is indicated for hypogonadotropic hypogonadism (congenital or acquired) due to idiopathic gonadotropin or luteinizing hormone releasing hormone (LHRH) deficiency or pituitary-hypothalmic injury from tumors, trauma or radiation. Typically, low serum testosterone concentrations and low to normal gonadotropin (FSH, LH) concentrations are present [22][23][85][84].

b) Testosterone preparations are also indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone including congenital or acquired primary hypogonadism and congenital or acquired hypogonadotropic hypogonadism [22][23][28][84].

B) Testosterone Cypionate

Testosterone cypionate is indicated for replacement therapy in adults and pediatric patients age 12 and older for conditions associated with a deficiency or absence of endogenous testosterone, such as:

Primary hypogonadism (congenital or acquired): testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy [83]
Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing

hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation [83]

1) Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater the younger the child. Assessment of bone age in the wrist and hand is recommended every 6 months [83].

C) Testosterone Enanthate

1) Delayed Puberty

a) Testosterone enanthate injection is indicated to stimulate puberty in select male patients with delayed puberty, for a limited duration of treatment such as 4 to 6 months. Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater in the younger child. Assessment of bone age in the wrist and hand every 6 months is recommended [73].

2) Male Hypogonadotropic hypogonadism

a) Testosterone enanthate injection is indicated in adult men for replacement therapy in congenital or acquired hypogonadotropic hypogonadism, such as gonadotropin or luteinizing hormone–releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation [74][75]. Testosterone enanthate IM injection is also indicated in adolescent males. Concurrent treatment with appropriate adrenal cortical and thyroid hormone replacement therapy are of primary importance, however. Replacement therapy needed prior to puberty will be needed during adolescence for secondary sexual characteristic development. Replacement therapy needed following puberty will require prolonged duration of therapy to maintain sexual characteristics [73].

3) Male Primary Hypogonadism

a) Testosterone enanthate injection is indicated in adult men for replacement therapy in primary congenital or acquired hypogonadism, such as testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy [74][75], Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals[74]. Testosterone enanthate IM injection is also indicated in adolescent males. Replacement therapy needed prior to puberty will be needed during adolescence for secondary sexual characteristic development. Replacement therapy needed following puberty will require prolonged duration of therapy to maintain sexual characteristics [73].

4) Metastatic Mammary Cancer in Women

a) IM testosterone enanthate is indicated for palliation of inoperable metastatic (skeletal) mammary cancer in women who are 1 to 5 years postmenopausal, when a goal of therapy includes ablation of the ovaries. Testosterone enanthate injection has also been used in premenopausal women with breast cancer who have benefited from oophorectomy and have a hormone-responsive tumor [73].

D) Testosterone Undecanoate

1) Testosterone undecanoate IM and oral capsules are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone. These include primary hypogonadism (congenital or acquired): testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals (men with these conditions have low serum testosterone concentrations and gonadotropins above the normal range) and hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation (men with these conditions have low serum testosterone concentrations and gonadotropins in the normal or low range) [53][57][59]. Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53]. Testosterone undecanoate IM should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis [59]. Safety and efficacy of testosterone undecanoate have not been established in males younger than 18 years old [57][59].

2) A mean 24-hour serum testosterone level within normal range (300 to 1080 nanograms/dL) was achieved in 80% of patients receiving testosterone undecanoate capsules (Tlando(R)) 225 mg twice daily with food for 24 days (N=95); no dosage adjustments were permitted. Majority of those not achieving a eugonadal range had a BMI of 30 kg/m(2) or greater [61].

3) Mean plasma total testosterone over 24 hours was within the normal eugonadal range in 87% of patients in a 4-month study of adult hypogonadal males who received testosterone undecanoate capsules [57].

4) In an 84-week study of hypogonadal adult male patients with low serum testosterone, 94% of patients maintained an average testosterone concentration within the normal range following the third injection of testosterone undecanoate IM [59].

MEDICATION SAFETY

Contraindications

A) Testosterone

1) Breast cancer, male [25][22][23][84][28][21][85][86][87][88]

2) Females who are pregnant, may become pregnant, or who are breastfeeding; known teratogen; exposure of female fetus or nursing infant to testosterone residue may result in varying degrees of virilization [25][22][23][84][28][21][85][86][87][88]

3) Hypersensitivity to testosterone or any component of the product [86][87][88]

4) Prostate cancer, known or suspected [25][22][23][84][28][21][85][86][87][88]

5) Use in women [84][86]

B) Testosterone Cypionate

1) Breast cancer, male [82]

2) Cardiac, hepatic, or renal disease, serious [82]

3) Women who are pregnant or may become pregnant [82]

4) Hypersensitivity to testosterone cypionate [82]

5) Prostate cancer, known or suspected [82]

C) Testosterone Enanthate

1) Breast cancer in males [74][75][73]

2) Females who are pregnant or may become pregnant; known teratogen [74][75][73]

3) Hypersensitivity to testosterone enanthate or any component of the product, including sesame oil [74][75][73]

4) Known or suspected prostate cancer [74][75][73]

5) Men with hypogonadal conditions, such as age-related hypogonadism, that are not associated with structural or genetic etiologies [74].

D) Testosterone Undecanoate

1) Breast carcinoma [57][59]

2) Hypersensitivity to testosterone undecanoate or any component of the product (eg, refined castor oil, benzyl benzoate) [57][59]

3) Pregnancy, nursing, or women of childbearing potential; may cause fetal harm and serious adverse reactions in nursing infants, such as virilization [57][92]

4) Known or suspected prostate carcinoma [57][59]

5) Hypogonadal conditions, such as age-related hypogonadism, that are not associated with structural or genetic etiologies [57]

Precautions

A) Testosterone

1) Beers Criteria: Avoid use unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious safety risks (eg, heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, infertility); if suspected, measure serum testosterone [89].

3) Cardiovascular: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [17][2][1][14][16][5][15][3][18].

4) Cardiovascular: Edema, with or without congestive heart failure, may occur in patients with preexisting cardiac, renal or hepatic disease [25][22][23][84][28][21][85][86][88][87]; discontinuation and diuretic therapy may be required [25][22][23].

5) Dermatologic: Use of magnetic resonance imaging has caused skin burns at application site due to the presence of aluminum in the patch [84].

6) Endocrine and metabolic: Increased risk of hypercalcemia and associated hypercalciuria in cancer patients; monitoring recommended [25][22][23][84][28][21][85][87][88]

7) Endocrine and metabolic: Dyslipidemia may occur; monitoring recommended [25][22][23]; dosage adjustment or discontinuation may be warranted [84][28][21][87][85].

8) Endocrine and metabolic: Decreased levels of thyroxine-binding globulins, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4, may occur [90].

9) Flammability: Alcohol-based formulations are flammable until dry [25][28][21][85][86][87].

10) Gastrointestinal: Gum-related adverse reactions, including severe gum irritation, have been reported and may warrant dental consultation; monitoring recommended [23].

11) Hematologic: Venous thromboembolic events, including DVT and pulmonary embolism, have been reported; monitoring recommended; discontinue use if suspected [17][2][1][14][16][5][15][3][18].

12) Hematologic: Polycythemia may occur; monitoring recommended [25][22] and dose adjustment may be warranted [25][23][84][28][21][85][86][88][87].

13) Hepatic: Serious hepatic adverse effects, including cholestatic jaundice, liver cancer, and peliosis hepatitis have been reported with prolonged use of high doses of orally active androgens [25][22][23][84][28][21][85][86][88][87]; discontinue use until cause is determined [25][22][23].

14) Musculoskeletal: Osteolysis may be stimulated by periods of immobilization and can result in hypercalcemia [88].

15) Neurologic: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [17][2][1][14][16][5][15][3][18].

16) Reproductive: Secondary exposure in children and women may result in virilization, inappropriate changes in genital size, and other serious adverse effects [25][28][21][85][86][87][91]; discontinue use until cause of virilization is determined [25].

17) Reproductive: Increased risk of worsening benign prostatic hyperplasia [25][22][23][84][28][21][85][86]; monitoring recommended [25][22][23][84][28][21][85]

18) Reproductive: Increased risk of prostate cancer with androgen use; monitoring recommended [25][22][23][84][28][21][85][86][87]

19) Reproductive: Gynecomastia, possibly persistent, may occur [25][22][23][84][28][21][85][86][88][87].

20) Reproductive: Suppression of spermatogenesis may occur with large doses [25][22][23].

21) Reproductive: Avoid use in men who are trying to conceive [26]

22) Respiratory: Nasal adverse reactions (ie, nasopharyngitis, rhinorrhea, epistaxis) have been reported and may require further evaluation or discontinuation [22].

23) Respiratory: Use is not recommended in patients with mucosal inflammatory disorders, sinus disease, or a history of nasal disorders, nasal or sinus surgery, nasal fracture (within last 6 months), or nasal fracture resulting in deviation of the anterior nasal septum [22].

24) Respiratory: Increased risk of sleep apnea in patients with obesity or chronic lung diseases [25][22][23][84][28][21][85][86][87]

B) Testosterone Cypionate

1) Beers Criteria: Avoid use unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious safety risks (eg, heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, infertility); if suspected, measure serum testosterone [89].

3) Cardiovascular: Possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

4) Cardiovascular: Possible increased risk of major adverse cardiovascular events (eg, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) have been reported with testosterone therapy in men [82]

5) Cardiovascular: Preexisting cardiac disease; edema may occur, with or without congestive heart failure [82]

6) Endocrine and metabolic: Gynecomastia may occur [82]

7) Endocrine and metabolic: Hypercalcemia may occur in immobilized patients; discontinue if occurs [82]

8) Hematologic: Thromboembolic events (eg, DVT and pulmonary embolism) have been reported with testosterone therapy; discontinue use if suspected [82]

9) Hepatic: Increased risk of hepatic adenomas, hepatocellular carcinoma, or peliosis hepatitis with prolonged use at high doses [82]

10) Hepatic: Preexisting hepatic disease; edema may occur, with or without congestive heart failure [82]

11) Neurologic: Possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

12) Renal: Preexisting renal disease; edema may occur, with or without congestive heart failure [82]

13) Reproductive: Delayed puberty in healthy male children; use may accelerate bone maturation and result in compromised adult stature; monitoring recommended [82]

14) Reproductive: Priapism or excessive sexual stimulation may occur; interrupt use and reduce the dosage if restarting therapy [82]

15) Reproductive: Oligospermia may occur with prolonged or excessive use; interrupt use and reduce the dosage if restarting therapy [82]

16) Reproductive: Avoid use in men who are trying to conceive [26]

17) Reproductive: Benign prostatic hypertrophy; increased risk of acute urethral obstruction; interrupt use and reduce the dosage if restarting therapy [82]

18) Special populations: Athletic performance enhancement; use not recommended [82]

19) Special populations: Contains benzyl alcohol, which may cause "gasping syndrome" and death in pediatric patients, with an increased risk in premature and low-birth weight infants [82]

20) Special populations: Elderly patients may be at increased risk of developing prostatic hypertrophy or prostatic carcinoma [82]

C) Testosterone Enanthate

1) Beers Criteria: Avoid unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious cardiovascular and psychiatric adverse reactions; if suspected, measure serum testosterone [74].

3) Cardiovascular: Possible increased risk of heart attack, stroke, or death has been reported [75] [93]; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

4) Cardiovascular: Edema, with or without congestive heart failure, may occur, especially in patients with preexisting cardiac, hepatic, or renal disease; discontinuation may be necessary [74] and/or

lower restarting dose used [75][73]

5) Endocrine and metabolic: Hypercalcemia may occur in patients with breast cancer or who are immobilized; discontinue use if occurs [75][73]

6) Endocrine and metabolic: Hypercalcemia, and associated hypercalciuria, may occur in cancer patients at risk; monitoring recommended [74]

7) Endocrine and metabolic: Altered serum cholesterol concentrations may occur, and caution should be used, especially in patients with history of myocardial infarction or coronary artery disease; monitoring recommended [75][73]

8) Endocrine and metabolic: Changes in serum lipid profile may occur; monitoring recommended and discontinuation of therapy may required [74]

9) Endocrine and metabolic: Thyroxine-binding globulin concentrations may be decreased [74]

10) Hematologic: Venous thromboembolic events, including DVT, have been reported with testosterone therapy; discontinue use if suspected [74][75]

11) Hematologic: Increases in hematocrit reflective of increases in red blood cell mass may occur; monitoring recommended and discontinuation may be required [74]

12) Hepatic: Prolonged use of high doses has been associated with serious hepatic adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice); discontinue therapy if hepatic dysfunction occurs [74]

13) Hepatic: Life threatening or fatal peliosis hepatitis or hepatic neoplasms (eg, hepatocellular carcinoma) may occur with prolonged use at high doses[74][75][73]

14) Hepatic: Cholestatic hepatitis accompanied by jaundice may occur; discontinue use [75][73]

15) Hepatic: Liver function test abnormalities may occur; discontinue use [75][73]

16) Musculoskeletal: Use cautiously in healthy males with delayed puberty, as effects on bone maturation may occur; monitoring recommended and dosage adjustment may be necessary [75] [73]

17) Musculoskeletal: Use caution in pediatric patients, as bone maturation may be accelerated, resulting in compromised adult stature; monitoring recommended [75][73]

18) Neurologic: Possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

19) Psychiatric: Depression and suicidal ideation and behavior, including completed suicide, have been reported; monitoring recommended [74]

20) Reproductive: Elderly patients; increased risk for prostatic hypertrophy or prostatic carcinoma [75][73]

21) Reproductive: Gynecomastia may occur and can possibly persist in those being treated for hypogonadism [74][75][73]

22) Reproductive: Use cautiously in female patients, as virilization may occur; monitoring recommended and discontinue use if suspected [75][73]

23) Reproductive: Worsening of benign prostatic hyperplasia may occur in patients with condition; monitoring recommended [74]

24) Reproductive: Increased risk of prostate cancer; evaluate for prostate cancer prior to and during therapy [74]

25) Reproductive: Spermatogenesis may be suppressed and result in adverse effects on semen parameters including sperm count [74]

26) Reproductive: Avoid use in men who are trying to conceive [26]

27) Respiratory: Venous thromboembolic events, including pulmonary embolism, have been reported; discontinue use if suspected [74][75]

28) Respiratory: Sleep apnea may occur, especially in patients with risk factors such as obesity or chronic lung disease [74]

D) Testosterone Undecanoate

1) Beers Criteria: Avoid use unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious safety risks (eg, heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, infertility); if suspected, measure serum testosterone [57][89].

3) Cardiovascular: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [57][63].

4) Cardiovascular: Edema with or without congestive heart failure may occur in patients with cardiac, hepatic, or renal disease; discontinuation may be necessary [57][92].

5) Endocrine and metabolic: Lipid abnormalities may occur; discontinuation may be necessary [57][92]; monitoring recommended [57].

6) Endocrine and metabolic: Cancer patients at risk for hypercalcemia or hypercalciuria; monitoring recommended [57][92]

7) Hematologic: Hematocrit and red blood cell mass increases may occur and increase risk for thromboembolism; monitoring recommended and interrupt or discontinue if necessary [57][92].

8) Hematologic: Venous thromboembolic events, including DVT and pulmonary embolism, have been reported; monitoring recommended; discontinue use if suspected [57][63].

9) Hepatic: Serious hepatic adverse effects (eg, peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, jaundice) have been reported with prolonged use of high doses of other androgens (eg, oral methyltestosterone); discontinue use if suspected [57][92].

10) Neurologic: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [57][63].

11) Psychiatric: Depression and suicidal ideation have been reported [57]

12) Reproductive: Prostate cancer may occur; monitoring recommended [57][92].

13) Reproductive: Worsening of signs and symptoms of benign prostatic hyperplasia (BPH) may occur in patients with BPH; monitoring recommended [57][92].

14) Reproductive: Virilizing effects may occur in women (unapproved use) [57][92].

15) Reproductive: Spermatogenesis suppression, resulting in adverse effects on sperm count, may occur with large doses of androgens [57][92].

16) Reproductive: Avoid use in men who are trying to conceive [26]

17) Reproductive: Gynecomastia may occur in patients treated for hypogonadism [57][92].

18) Respiratory: Sleep apnea may occur; increased risk with obesity or chronic lung disease [57][92].

Adverse Effects

Cardiovascular Effects

Testosterone

Death, Cardiovascular

a) General Information

1) May increase risk of major adverse cardiovascular events, such as cardiovascular death [17][2][1][14][16][5][15][3][18].

Disease of cardiovascular system, acute

a) General Information

1) Risk of acute cardiovascular events may be increased following initiation of IM injection versus the transdermal gel [105].

b) Adult Clinical Trials

1) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with a 26% increased risk of composite acute cardiovascular (CV) events (myocardial infarction, unstable angina, stroke) compared with transdermal

gels when assessed over a 1-year followup period. There was no significant difference in the risk of acute CV events between the transdermal gel or patch [105].

Edema

a) General Information

1) Androgens may promote sodium and water retention [23][25][22]

2) Edema, with or without congestive heart failure, may be serious complication in patients with cardiac, renal, or hepatic disease [23][25][22][99][86][100][88][87][94]

b) Prevention and Management

1) Discontinuation and diuretic therapy may be required if edema occurs [23][25][22][86][100][88][87][94]

c) Adult Postmarketing

1) Edema has been reported [87]

Hypertension

a) Incidence: Up to 3% [28][87][99][100]

b) Prevention and Management

1) Clinicians should monitor development of hypertension in elderly patients are at increased risk for cardiovascular disease [106].

c) Adult Clinical Trials

1) Replacement therapy (transdermal route): Less than 1% [100]

2) Replacement therapy (topical route): 2.1% vs 0% with placebo [28]

3) Replacement therapy (topical route): 0% to 3% [87][28]

4) Replacement therapy (topical route): At least 2 of 155 patients [99]

Increased blood oxygen pressure

a) Incidence: 3% or less [25][22][99][86]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Less than 3% [22]

2) Replacement therapy (topical route): Less than 1% [99]

3) Replacement therapy (topical route): 1% vs 0% with placebo [25][86]

Myocardial infarction

a) General Information

1) Myocardial infarction has been reported with use of anabolic steroids [101][102].

2) May increase risk of major adverse cardiovascular events, such as myocardial infarction [17][2][1][14][16][5][15][3][18].

3) An increased risk of serious cardiovascular effects has been reported in men treated with testosterone therapy [103][104].

4) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [97].

b) Adult Clinical Trials

1) Low serum testosterone levels: increased risk of myocardial infarction, stroke, and all-cause mortality, 29% [103]

2) Low serum testosterone levels: 2-fold increased risk of acute nonfatal myocardial infarction within 90 days among men 65 years or older [104].

3) Low serum testosterone levels: 2- to 3-fold increased risk of heart attack within the 90 days in men younger than 65 years with preexisting heart disease [104]

4) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with a 30% increased risk of myocardial infarction (MI) compared with transdermal gels when assessed over a 1-year followup period. Risk of MI was slightly increased with use of patch versus gel, but there was no significant difference in overall risk of acute cardiovascular events (ie, MI, unstable angina, stroke) between the 2 transdermal forms [105].

c) Postmarketing

1) Has been reported [17][2][1][14][16][5][15][3][18]

Unstable angina

a) General Information

1) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

b) Adult Clinical Trials

1) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with a 21% increased risk of unstable angina compared with transdermal gels when assessed over a 1-year followup period. There was no significant difference in the risk of unstable angina between the transdermal gel or patch [105].

Vasodilatation

a) Incidence: Less than 1% [87]

b) Adult Clinical Trials

1) Replacement therapy (topical route): Less than 1% [87]

Testosterone Cypionate

Myocardial infarction

a) General Information

1) Has occurred with some androgens [82]

2) Increased risk of major adverse cardiovascular events reported in some, but not all, studies of testosterone replacement therapy in men [82]

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [97].

Testosterone Enanthate

Death, Cardiovascular

a) General Information

1) May increase risk of major adverse cardiovascular events, such as cardiovascular death [75].

Hypertension

a) Incidence: 2.3% to 12.7% [74]

b) General Information

1) In clinical trials, systolic blood pressure increased by an average of 4 mmHg during the first 12 weeks of treatment, and by an average of 4 mmHg from baseline following 1 year of treatment [74].

2) Ten percent of patients required initiation or adjustment of antihypertensive medications [74].

3) Increases in blood pressure may increase risk for major adverse cardiovascular events, especially in patients with established cardiovascular disease. In some patients the blood pressure elevation may be too small to detect but may still lead to increased cardiovascular risk [74].

c) Prevention and Management

1) Prior to initiation, consider baseline cardiovascular risk and ensure blood pressure is adequately controlled [74].

2) Initiation or adjustment of antihypertensive medication may be necessary [74].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): 12.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Myocardial infarction

a) General Information

1) May increase risk of major adverse cardiovascular events, such as myocardial infarction [75].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in transwomen or transmen compared with reference men [97].

b) Postmarketing

1) Has been reported [75]

Peripheral edema

a) Incidence: 2.7% [74]

b) General Information

1) Edema, with or without congestive heart failure, may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease [74].

2) Androgens may promote sodium and water retention [74].

c) Prevention and Management

1) Diuretic therapy may be necessary [74].

2) Drug discontinuation may be required [74].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Testosterone Undecanoate

Angina pectoris

a) Postmarketing

1) Has been reported [58]

Death, Cardiovascular

a) General Information

1) May increase risk of major adverse cardiovascular events, such as cardiovascular death [53][58].

b) Postmarketing

1) Has been reported [58]

Edema

a) Incidence: Greater than 2% [57]

b) General Information

1) May promote sodium and water retention [53][57][58]

2) May be a serious complication in patients with preexisting renal, cardiac, or hepatic disease [53][57][58]

c) Prevention and Management

1) Discontinuation and diuretic therapy may be required [53][57][58]

d) Adult Clinical Trials

1) Testosterone replacement (oral route): Peripheral edema, greater than 2% with testosterone undecanoate (Study N=569) [57]

Hypertension

a) Incidence: Greater than 2% to 5.1% [53][57][58]

b) General Information

1) In clinical trials after 4 months of treatment, systolic blood pressure increased by an average of 4.9 mmHg and 2.8 mmHg [57], and 4.3 mmHg and 4.8 mmHg [53], as measured by ambulatory blood pressure monitoring and blood pressure cuff, respectively; and average blood pressure had not plateaued by trial termination [57].

2) Led to initiation of antihypertensive medication or intensification of preexisting antihypertensives medications in 7% of patients in clinical trials over 4 months [57].

3) Increases risk for major adverse cardiovascular events (MACE), with greatest risk in patients with established cardiovascular disease or risk factors for cardiovascular disease [53][57].

4) In some patients, increase in blood pressure may be too small to detect, but may still increase the risk for MACE [53][57].

5) Increases in blood pressure were larger in patients with a history of hypertension [57].

c) Management

1) Treat new-onset or exacerbations of preexisting hypertension [53][57].

d) Adult Clinical Trials

1) Testosterone replacement (Tlando(R), oral route): 5.1% with testosterone undecanoate (Study N=138); lead to treatment discontinuation in 1.4% [53]

2) Testosterone replacement (Jatenzo(R), oral route): 3.6% with testosterone undecanoate (Study N=166) [57]

3) Testosterone replacement (Jatenzo(R), oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

4) Hypogonadism (IM route): At least 3% [58]

Myocardial infarction

a) General Information

1) May increase risk of major adverse cardiovascular events, such as myocardial infarction [53][58].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [97].

b) Postmarketing

1) Has been reported [53][57][58]

Dermatologic Effects

Testosterone

Acne

a) Incidence: Up to 8% [25][28][87][100]
b) Adult Clinical Trials

1) Replacement therapy (transdermal route) Less than 1% [100]

2) Replacement therapy (topical route): Less than 1% [25]

3) Replacement therapy (topical route): 1% to 8% (incidence increases with increasing dose) [87]

4) Replacement therapy (topical route): 2% or less [28]

5) Replacement therapy (topical route): 3.1% [87]

6) Replacement therapy (topical route): At least 2 out of 155 patients [99]

c) Adult Case Reports

1) Acne fulminans on face and shoulders developed in a 21-year-old man following self-administration of testosterone or other anabolic steroids for 4 weeks [112].

Alopecia

a) Incidence: Up to 1% [87]
b) General Information

1) Hair loss has been reported with anabolic steroid use [102].

c) Adult Clinical Trials

1) Replacement therapy (topical route): Up to 1% [87].

Application site erythema

a) Incidence: 5% to 7% [99][100]
b) Prevention and Management

1) Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the Androderm(R) system has been shown to reduce the incidence and severity of skin irritation, and does not significantly alter transdermal absorption of testosterone from the system (Wilson et al, 1998).

2) Ointment formulations should not be used for pretreatment, however, as they may significantly reduce testosterone absorption (Wilson et al, 1998).

c) Adult Clinical Trials

1) Replacement therapy (topical route): 5% to 7% [99]

2) Replacement therapy (transdermal route): 7% [100]

Application site irritation

a) Incidence: Up to 8% [28][99]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 0.9% [28]

2) Replacement therapy (topical route): 7% to 8% [99]

Application site reaction

a) Incidence: 2% to 16.1% [110][25]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 16.1% with testosterone gel (N=149) [110]

2) Replacement therapy (topical route): 2% to 4% vs 3% with placebo [25]

Burning pain

a) Incidence: 3% [100]
b) Adult Clinical Trials

1) Replacement therapy (transdermal route): 3% [100]

Contact dermatitis

a) Incidence: 2.1% to 4% [28][100]
b) General Information

1) Nonscrotal systems produced contact allergy and more topical irritation than scrotal systems in one study [111].

c) Adult Clinical Trials

1) Replacement therapy (topical route): 2.1% vs 0% with placebo [28].

2) Replacement therapy (transdermal route): 4% [100].

Erythema, Generalized

a) Adult Clinical Trials

1) Replacement therapy (topical route): At least 2 out of 155 patients [99]

Flushing

a) Adult Clinical Trials

1) Replacement therapy (topical route): Hot flushes, 1% with testosterone 50 mg (n=103) and 0% with testosterone 100 mg (n=149) vs 0% with placebo (n=99) [90]

Injection site pain, Intramuscular injection

a) General Information

1) Inflammation and pain at the site of IM injection has been reported [88][94].

Pruritus

a) Incidence: 37% [100]

b) Prevention and Management

1) Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the Androderm(R) system has been shown to reduce the incidence and severity of skin irritation, and does not significantly alter transdermal absorption of testosterone from the system (Wilson et al, 1998).

2) Ointment formulations should not be used for pretreatment, however, as they may significantly reduce testosterone absorption (Wilson et al, 1998).

c) Adult Clinical Trials

1) Replacement therapy (transdermal route): 37% [100]

2) Replacement therapy (topical route): Pruritus, 1.9% [87]

Psoriasis

a) Adult Case Reports

1) Exacerbation of psoriasis was precipitated by an estradiol 50 mg/testosterone 100 mg implant in a 47-year-old woman [113].

Rash

a) Incidence: 2% [100]

b) Prevention and Management

1) Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the Androderm(R) system has been shown to reduce the incidence and severity of skin irritation, and does not significantly alter transdermal absorption of testosterone from the system (Wilson et al, 1998).

2) Ointment formulations should not be used for pretreatment, however, as they may significantly reduce testosterone absorption (Wilson et al, 1998).

c) Adult Clinical Trials

1) Replacement therapy (transdermal route): 2% [100]

Scab of skin, Nasal

a) Incidence: 3.8% to 5.8% [22]

b) General Information

1) One of the most common adverse reactions with intranasal form [22]

2) Symptoms usually mild to moderate [22]

c) Prevention and Management

1) Consider further evaluation or possible withdrawal if condition occurs [22]

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 5.8% [22]

Skin eschar

a) Adult Case Reports

1) A 78-year-old man who received testosterone 5 mg transdermal patches for hypogonadism experienced occasional irritation and subsequent eschar formation at the application site [114].

Testosterone Cypionate

Acne

a) Acne may occur in patients receiving testosterone cypionate [83].

Alopecia

a) Male pattern baldness may occur in patients receiving testosterone cypionate [83].

Hirsutism

a) Hirsutism may occur in patients receiving testosterone cypionate [83].

Injection site inflammation

a) Inflammation at the injection site may occur in patients receiving testosterone cypionate [83].

Injection site pain

a) Pain at the injection site may occur in patients receiving testosterone cypionate [83].

Seborrheic dermatitis

a) Seborrhea may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Acne

a) Incidence: 2.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Alopecia

a) General Information

1) Male pattern baldness has been reported following administration of testosterone enanthate [73].

Erythema at injection site

a) Incidence: 2.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Hirsutism

a) General Information

1) Hirsutism has been reported following administration of testosterone enanthate [73].

Injection site bruising

a) Incidence: 3.8% to 6.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 6.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3.8% with testosterone enanthate (n=133) [74]

Injection site hemorrhage

a) Incidence: 3.3% to 6% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 3.3% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 6% with testosterone enanthate (n=133) [74]

Injection site inflammation

a) General Information

1) Inflammation at the injection site has been reported following administration of testosterone enanthate [73].

Injection site pain

a) General Information

1) Pain at the injection site has been reported following administration of testosterone enanthate [73].

Testosterone Undecanoate

Acne

a) Incidence: 5.2% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 5.2% with testosterone undecanoate (Study N=153) [59]

Erythema at injection site

a) Incidence: 1.3% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Hyperhidrosis

a) Incidence: 1.3% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Injection site pain

a) Incidence: 4.6% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 4.6% with testosterone undecanoate (Study N=153) [59]

Endocrine/Metabolic Effects

Testosterone

Decreased body growth

a) General Information

1) May accelerate bone maturation and cause premature closure of epiphyses in pediatric patients [25][22][88]

2) Use in pediatric patients may reduce adult stature, with greatest impact among youngest children [88]

b) Pediatric Clinical Trials

1) Replacement therapy: Height stunting in adolescents has been reported with anabolic steroid use [102]

Gynecomastia

a) Incidence: 1% to 3% [25][86][87]
b) General Information

1) May occur with testosterone therapy for hypogonadism [23][25][22][100][94][88]

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

c) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

d) Adult Clinical Trials

1) Replacement therapy (topical route): 1% vs 0% with placebo [25][86]

2) Replacement therapy (topical route): 1% to 3% [87]

Hypercalcemia

a) General Information

1) Increased risk among those with cancer [23][25][22] and immobilized patients [88][94].

b) Prevention and Management

1) Regularly monitor at-risk patients [23][25][22]

2) Discontinue if condition occurs [88][94]

Hyperthyroidism

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): 1 patient [22]

Hypokalemia

a) Adult Clinical Trials

1) Replacement therapy (topical route): Abnormal laboratory tests including hypokalemia, less than 1% [87]

Increased glucose level

a) General Information

1) Insulin sensitivity or glycemic control may change in patients treated with androgens [25][87].

2) In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements [25][87].

b) Adult Clinical Trials

1) Replacement therapy (topical route): Increased blood glucose in at least 2 of 155 patients [85]

2) Replacement therapy (topical route): Abnormal laboratory tests, including elevated glucose levels in less than 1% [87]

Lipids abnormal

a) Incidence: Up to 2% [28]

b) General Information

1) The serum lipid profile may change[23], including lipid abnormalities, such as LDL-C elevations and severe HDL-C reductions [102].

c) Prevention and Management

1) Monitor lipid profiles periodically, especially after treatment initiation [23][25] [22] and with dosage increases [25].

2) Discontinuation may be required with changes in serum lipid profile [22].

d) Adult Clinical Trials

1) Replacement therapy (topical route): Hyperlipidemia, up to 2% [28]

2) Replacement therapy (topical route): Changes in serum lipid levels (ie, hyperlipidemia, elevated triglycerides, and decreased HDL), less than 1% [87]

Thyroxine transport defect

a) General Information

1) Androgens may decrease thyroxine-binding globulin concentrations [25][22] [23]; however, there has been no clinical evidence of thyroid dysfunction with androgen use [23].

Testosterone Cypionate

Gynecomastia

a) General Information

1) Gynecomastia may occur in patients receiving testosterone cypionate [83].

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

b) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

Testosterone Enanthate

Hypercalcemia

a) General Information

1) Hypercalcemia has been reported following administration of testosterone enanthate. If hypercalcemia occurs, therapy should be discontinued [73].

b) Prevention

1) Use caution in cancer patients at risk for hypercalcemia [74]

Hypernatremia

a) General Information

1) Sodium and water retention has been reported following administration of testosterone enanthate. In patients with preexisting cardiac, renal, or hepatic disease, there is an increased risk of edema with or without congestive heart failure [73].

Increased cholesterol esters

a) General Information

1) Increased serum cholesterol has been reported following administration of testosterone enanthate [73].

b) Management

1) Adjustment of lipid lowering therapy or discontinuation of testosterone therapy may be necessary [74]

Increased testosterone level

a) Incidence: 2.7% [74]

b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Testosterone Undecanoate

Decreased HDL level

a) Incidence: 3% [57]

b) Management

1) Adjustment of lipid lowering drugs may be necessary [57].

2) Discontinuation may be necessary [57].

c) Adult Clinical Trials

1) Testosterone replacement (oral route): 3% with testosterone undecanoate (Study N=166) [57]

Diabetes mellitus

a) Postmarketing

1) Diabetes mellitus was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Disorder of lipid metabolism

a) General Information

1) Changes in serum lipid profile may occur [53][57].

b) Management

1) Adjustment of lipid lowering drugs may be necessary [53][57].

2) Discontinuation may be necessary [53][57].

Gynecomastia

a) General Information

1) May develop and persist in patients being treated for hypogonadism [53][57][59]

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

b) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

c) Postmarketing

1) Gynecomastia was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Hyperprolactinemia

a) Incidence: 6.3% [53]
b) General Information

1) The mean increase from baseline in serum prolactin was 7 nanograms/mL in a 24-day study (Study N=93) [53]

c) Management

1) If serum prolactin remains elevated, discontinue [53]

d) Adult Clinical Trials

1) Testosterone replacement (oral route): 6.3% with testosterone undecanoate (Study N=93) [53]

Increased estradiol level

a) Incidence: 2.6% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 2.6% with testosterone undecanoate (Study N=153) [59]

Weight increased

a) Incidence: 1.3% to 2.1% [53][59]
b) General Information

1) Led to treatment discontinuation in 1 patient in a clinical trial (Study N=138) [53]

c) Adult Clinical Trials

1) Testosterone replacement (oral route): 2.1% with testosterone undecanoate (Study N=95) [53]

2) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Gastrointestinal Effects

Testosterone

Decrease in appetite

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): 1 patient [22]

Diarrhea

a) Incidence: 3% to 4% [85]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 3% to 4% [85]

Gastrointestinal hemorrhage

a) Incidence: 2% [100]
b) Adult Clinical Trials

1) Replacement therapy (transdermal route): 2% [100]

Lip swelling

a) Postmarketing

1) Has been reported during postmarketing use [23].

Nausea

a) General Information

1) May occur with injectable, topical, and intranasal forms [22][87][88][94]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): 1 patient [22]

c) Adult Postmarketing

1) Nausea has been reported [87]

Oral irritation

a) Incidence: 9.2% [108]
b) General Information
1) Irritation generally resolved in 1 to 8 days [108]
2) Tenderness generally resolved in 1 to 14 days [108]
c) Adult Clinical Trials
1) Replacement therapy (buccal route): Gum or mouth irritation, 9.2% [108]

Sore gums

a) Incidence: 3.1% [108]
b) General Information
1) Irritation generally resolved in 1 to 8 days, and tenderness generally resolved in 1 to 14 days for the buccal system [108]
c) Adult Clinical Trials
1) Replacement therapy (buccal route): Gum pain and tenderness: 3.1% [108]

Stomatitis

a) Postmarketing
1) Has been reported during postmarketing use [23]

Swollen gums

a) Incidence: 2% [108]
b) General Information
1) Irritation generally resolved in 1 to 8 days, and tenderness generally resolved in 1 to 14 days for the buccal system [108]
c) Adult Clinical Trials
1) Replacement therapy (buccal route): 2% [108]
d) Postmarketing
1) Gingival swelling has been reported during postmarketing use [23].

Taste sense altered

a) Incidence: 1% to 4.1% [25][22]
b) General Information
1) Cause of treatment discontinuation with intranasal form [22]
c) Adult Clinical Trials
1) Replacement therapy (topical route): Taste disorder, 1% vs 0% with placebo [25]
2) Replacement therapy (intranasal route): Dysgeusia, less than 3%, with treatment discontinuation in 1 patient [22]
3) Replacement therapy (buccal route): Bitter taste or taste perversion, 2% to 4.1% [108]
d) Postmarketing
1) Dysgeusia has been reported during postmarketing use [23].

Ulcer of mouth

a) Postmarketing
1) Has been reported during postmarketing use [23]

Vomiting

a) Incidence: 3% to 4% [85]
b) Adult Clinical Trials
1) Replacement therapy (topical route): 3% to 4% [85]

Xerostomia

a) Postmarketing
1) Dry mouth has been reported during postmarketing use [23].

Testosterone Cypionate

Nausea

a) Nausea may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Abdominal pain

a) Incidence: 2% [74]
b) Adult Clinical Trials
1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

Nausea

a) Incidence: 2.3% [74]
b) General Information
1) Nausea has been reported following administration of testosterone enanthate [73].
c) Adult Clinical Trials
1) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Testosterone Undecanoate

Diarrhea

a) Incidence: Greater than 2% [57]
b) Adult Clinical Trials
1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Gastric ulcer with hemorrhage

a) General Information
1) Led to discontinuation in 1.1% of patients in a clinical trial (Study N=95) [53]

Indigestion

a) Incidence: Greater than 2% [57]
b) Adult Clinical Trials
1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Nausea

a) Incidence: Greater than 2% to 2.4% [57]
b) Adult Clinical Trials
1) Testosterone replacement (oral route): 2.4% with testosterone undecanoate (Study N=166) [57]
2) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Hematologic Effects

Testosterone

Deep venous thrombosis

a) General Information
1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85]
b) Prevention and Management
1) Evaluate for DVT if lower-limb warmth, pain, erythema, or edema develop [17][2][1][14][16][5][15][3][18]
2) Evaluate for pulmonary embolism in patients with acute shortness of breath [17][2][1][14][16][5][15][3][18]
3) Discontinue if condition suspected and initiate workup and management [17][2][1][14][16][5][15][3][18]
c) Adult Clinical Trials
1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of

treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Adult Postmarketing

1) Venous thromboembolism, including DVT and PE, has been reported [17][2][1][14][16][5][15][3][18]

Erythrocytosis

a) General Information

1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85]

2) Polycythemia has been reported with injectable testosterone [94][88].

b) Prevention and Management

1) Assess hematocrit level at baseline and repeat 3 to 6 months after treatment initiation [25][51][85] and annually thereafter [25][22][51]

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Dose reduction or interruption may be required if condition occurs [25][22][51][85]; therapy may resume when hematocrit decreases to an acceptable level [25]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): Hematocrit increase, four subjects developed hematocrit levels above 55% from baseline levels of 48% to 51%. No hematocrit levels exceeded 58% [22]

2) Replacement therapy (topical route): Hematocrit or hemoglobin increase, 2.1% vs 0% with placebo [28]

3) Replacement therapy (topical route): Hematocrit increase, 4% to 7% [85]

4) Replacement therapy (topical route): Hematocrit or hemoglobin increase, 1% to 2% vs 0% with placebo [25][86]

d) Adult Case Reports

1) Two cases of IM testosterone-induced polycythemia were reported to have been reversed by switching to transdermal testosterone [95].

2) A report of secondary polycythemia characterized by increases in RBC, hemoglobin, hematocrit, and red cell volume with decreases in serum B12 levels and erythropoietin was documented following the use of transdermal testosterone patches (10 mg androstanolone daily) in a 73-year-old man [96].

Hematocrit - PCV - high

a) Incidence: 4% to 7% [85]

b) General Information

1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85][23].

c) Prevention and Management

1) Assess hematocrit level at baseline and repeat 3 to 6 months after treatment initiation [25][51][85] and annually thereafter [25][22][51][23].

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Dose reduction or interruption may be required if condition occurs [25][22][51][85]; therapy may resume when hematocrit decreases to an acceptable level [25][23].

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): hematocrit increase, 4 subjects developed hematocrit levels above 55% from baseline levels of 48% to 51%; no hematocrit levels exceeded 58% [22]

2) Replacement therapy (topical route): hematocrit or hemoglobin increase, 2.1% vs 0% with placebo [28]

3) Replacement therapy (topical route): hematocrit increase, 4% to 7% [85]

4) Replacement therapy (topical route): hematocrit or hemoglobin increase, 1% to 2% vs 0% with placebo [25][86]

e) Postmarketing

1) Red blood cell increase has been reported in postmarketing use [23].

Hemorrhage

a) General Information

1) Suppression of clotting factors II, V, VII and X, and bleeding in patients receiving concomitant anticoagulant therapy have been reported [94][88].

Increased hemoglobin

a) Adult Clinical Trials

1) Replacement therapy (topical route): hematocrit or hemoglobin increase, 2.1% vs 0% with placebo [28]

2) Replacement therapy (topical route): hematocrit or hemoglobin increase, 1% to 2% vs 0% with placebo [25][86]

b) Adult Case Reports

1) Replacement therapy (topical route): Hemoglobin increases were reported in at least 2 men with 120 days of treatment [85].

Venous thromboembolism

a) General Information

1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85]

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Prevention and Management

1) Evaluate for DVT if lower-limb warmth, pain, erythema, or edema develop [25] [22]

2) Evaluate for pulmonary embolism (PE) if acute dyspnea develops [25][22]

3) Discontinue if thromboembolic event suspected and initiate workup and management [25][22]

c) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215) -control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Adult Postmarketing

1) Venous thromboembolism, including DVT and PE, has been reported with testosterone products [25][22]

Testosterone Cypionate

Deep venous thrombosis

a) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215) -control (n=909,530) population-based study; a trend of decreased

risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

Erythrocytosis

a) General Information

1) Polycythemia may occur in patients receiving testosterone cypionate [83].

2) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

b) Management

1) Intervention is required if hematocrit is 54% or greater during treatment, such as dose reduction or temporary discontinuation [26].

Hemorrhage

a) General Information

1) Suppression of clotting factors II, V, VII and X, and bleeding in patients receiving concomitant anticoagulant therapy may occur with testosterone cypionate [83].

Venous thromboembolism

a) General Information

1) Transgender

a) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

Testosterone Enanthate

Deep venous thrombosis

a) Prevention and Management

1) Evaluate patients with pain, edema, warmth, or erythema in the lower extremity for DVT and those with acute shortness of breath for pulmonary embolism [74].

2) Discontinue use if suspected and initiate appropriate work up and management [74].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing use in patients using testosterone products [74].

Erythrocytosis

a) Incidence: 1.8% to 2% [74]

b) General Information

1) Polycythemia has been reported following administration of testosterone enanthate [73].

2) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

3) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Prevention and Management

1) Ensure hematocrit is not elevated prior to initiating therapy [74].

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Interruption or discontinuation of therapy may be necessary [74].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 1.8% with testosterone enanthate in pooled studies (n=283) [74]

Hematocrit - PCV - high

a) Incidence: 8.3% to 14% [74]

b) General Information

1) In clinical studies; treated resulted in mean hemotocrit increases of 3.8 +/- 3.4% at 6 months and 5.4+/- 3.4% at 1 year [74]

2) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

3) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Management

1) Intervention is required if hematocrit is 54% or greater during treatment, such as dose reduction or temporary discontinuation [26].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): Hematocrit increased, 14% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): Hematocrit increased, 8.3% with testosterone enanthate (n=133) [74]

3) Hypogonadism (subQ route): Hematocrit increased to 55% or greater, 4.2% with testosterone enanthate in pooled studies (n=283) [74]

Hemorrhage

a) General Information

1) Suppression of clotting factors II, V, VII and X, and bleeding in patients receiving concomitant anticoagulant therapy has been reported with testosterone enanthate [73].

Increased hemoglobin

a) General Information

1) In clinical studies, mean hemoglobin increases of 1 +/- 1.1 g/dL at 6 months and 1.1 +/- 1.4 g/dL at 1 year were reported [74]

2) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following

IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

3) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

Increased white blood cell count

a) General Information

1) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

Thromboembolic disorder

a) General Information

1) Transgender

a) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Prevention and Management

1) Evaluate patients with pain, edema, warmth, or erythema in the lower extremity for DVT and those with acute shortness of breath for pulmonary embolism [74].

2) Discontinue use if suspected and initiate appropriate work up and management [74].

c) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing use in patients using testosterone products [74].

Testosterone Undecanoate

Deep venous thrombosis

a) Prevention and Management

1) Evaluate patients who experience symptoms of pain, edema, warmth, and erythema in the lower extremity for DVT [53][57][58].

2) Discontinue use and initiate appropriate workup and management if suspected [53][57][58].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215) -control (n=909,530) population-based study; a trend of decreased

risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing experience [53][57][58].

Erythrocytosis

a) Incidence: Greater than 2% [57]
b) General Information

1) Hematocrit elevations, which reflect increased red blood cell mass, may increase the risk of thromboembolic events [92]

2) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Prevention and Management

1) Monitor hematocrit levels at baseline and during therapy [92].

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Dose interruption or discontinuation may be necessary [53][92]

d) Adult Clinical Trials

1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

e) Postmarketing

1) Polycythemia was reported during postmarketing surveillance [92]

Hematocrit - PCV - high

a) Incidence: 1.3% to 4.8% [53][57][92]
b) General Information

1) Hematocrit elevations, which reflect increased red blood cell mass, may increase the risk of thromboembolic events [53][92][92]

2) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Prevention and Management

1) Intervention is required if hematocrit is 54% or greater during treatment [26].

2) Increases in hematocrit, reflective of increases in red blood cell mass, may necessitate lowering of the dose or permanent discontinuation of therapy [53][57][92].

d) Adult Clinical Trials

1) Testosterone replacement (Tlando(R), oral route): 4.3% with testosterone undecanoate (Study N=138) [53]

2) Testosterone replacement (Jatenzo(R), oral route): 4.8% with testosterone undecanoate (Study N=166) [57]

3) Testosterone replacement (Jatenzo(R), oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

4) Hypogonadism (IM route): 1.3% [92]

Increased hemoglobin

a) Incidence: 2% [92]
b) General Information

1) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Adult Clinical Trials

1) Hypogonadism (IM route): 2% [92]

Venous thromboembolism

a) General Information

1) Transgender

a) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with

reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Prevention and Management

1) Evaluate patients who experience symptoms of pain, edema, warmth, and erythema in the lower extremity for DVT and those who present with shortness of breath for pulmonary embolism [53][57].

2) Discontinue use and initiate appropriate workup and management if suspected [53][57].

c) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Postmarketing

1) There have been postmarketing reports of venous thromboembolic events, including DVT and pulmonary embolism, in patients using testosterone replacement [53][57].

Hepatic Effects

Testosterone

Cholestatic jaundice syndrome

a) General Information

1) Cholestatic hepatitis may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23][25][22][86][87][100][94][88]

b) Prevention and Management

1) Discontinue if condition occurs [23][25][22]

c) Pediatric Case Reports

1) Fanconi anemia: Multiple hepatic tumors with cholestasis and peliosis hepatitis were reported in a 13-year-old boy following several years of androgen and corticosteroid therapy, including testosterone propionate 20 mg/day [109].

Jaundice

a) General Information

1) Jaundice may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23].

b) Prevention and Management

1) Discontinue use immediately if jaundice occurs [23].

Liver carcinoma

a) General Information

1) Hepatocellular carcinoma has been reported rarely in patients receiving long-term oral therapy with androgens in high doses; androgen withdrawal did not lead to regression of the tumors in all cases[86][87][100][88][94].

Liver function tests abnormal

a) General Information

1) Alterations in liver function tests have occurred with testosterone therapy [94] [88].

b) Postmarketing

1) Abnormal liver function tests (eg, transaminases, elevated GGTP, and bilirubin) have been reported during postmarketing surveillance of testosterone gel [87].

Neoplasm of liver

a) General Information

1) Hepatic neoplasms may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23][25][22][86][87][100][94][88].

b) Prevention and Management

1) Discontinue if condition occurs [23][25][22]

Peliosis hepatis

a) General Information

1) Life-threatening peliosis hepatitis may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23][25][22][86][87][100][94][88].

b) Prevention and Management

1) Discontinue use if condition occurs [25][22][23]

Testosterone Cypionate

Cholestatic jaundice syndrome

a) Cholestatic jaundice may occur in patients receiving testosterone cypionate [83].

Liver function tests abnormal

a) Altered liver function tests may occur in patients receiving testosterone cypionate [83].

Neoplasm of liver

a) Hepatocellular neoplasm may rarely occur in patients receiving testosterone cypionate [83].

Peliosis hepatis

a) Peliosis hepatis may rarely occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Cholestatic hepatitis

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74].

Hepatotoxicity

a) Adult Case Reports

1) A 26-year-old body builder developed toxic hepatitis with hepatocellular necrosis after self-administration of stanozolol 40 mg/day, IM testosterone enanthate 500 mg twice weekly, and oral methylandrostenediol 30 mg/day for 5 weeks. On admission to the hospital, the patient's AST and ALT levels were 5870 and 10,580 international units/L, respectively. The patient's bilirubin and alkaline phosphatase were also elevated. Liver biopsy showed toxic hepatic lesions. After supportive care and within 12 weeks of discontinuation of androgenic/anabolic steroids, clinical signs and laboratory findings improved substantially [122].

Jaundice

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

2) Cholestatic jaundice has been reported following administration of testosterone enanthate [73].

3) Jaundice is reversible with drug therapy discontinuation [73].

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74][73].

c) Adult Case Reports

1) A case of anabolic steroid-induced cholestasis was reported in a 29-year-old male bodybuilder. Following self-administered testosterone enanthate injections once weekly for 4 weeks, the patient developed pruritus and deep jaundice. These symptoms, along with weight loss, persisted for 2 months. After this time period, the patient received corticosteroids and complete resolution of jaundice occurred within 2 weeks [123].

Liver function tests abnormal

a) General Information

1) Altered liver function tests have been reported in patients receiving testosterone enanthate [73].

b) Management

1) If altered liver function tests occur, therapy should be discontinued and etiology determined [73].

Neoplasm of liver

a) General Information

1) Hepatocellular neoplasms have rarely been reported following administration of testosterone enanthate [73].

2) Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas [74][108].

3) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74].

Peliosis hepatis

a) General Information

1) Peliosis hepatitis has rarely been reported following administration of testosterone enanthate [73].

2) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

3) May be life-threatening or fatal [74]

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74].

Testosterone Undecanoate

Cholestatic hepatitis

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including jaundice; testosterone undecanoate has not been reported to cause this adverse event [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Hepatitis, Peliosis

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including peliosis hepatitis; testosterone undecanoate has not been reported to cause this adverse event [53][57].

2) May be life-threatening or fatal [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Jaundice

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including jaundice; testosterone undecanoate has not been reported to cause this adverse event [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Malignant neoplasm of liver

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including hepatic neoplasms; testosterone undecanoate has not been reported to cause this adverse event [53][57].

2) Long-term therapy with IM testosterone enanthate has produced multiple hepatic adenomas [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Immunologic Effects

Testosterone

Hypersensitivity reaction

a) General Information

1) Allergic reaction (eg, hives, lip and tongue swelling) cause of treatment discontinuation with intranasal form [22]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Allergic reaction was cause of treatment discontinuation in 1 patient [22]

Testosterone Cypionate

Hypersensitivity reaction

a) Hypersensitivity reactions, including anaphylactoid reactions, may occur in patients receiving testosterone cypionate [83].

Non-allergic anaphylaxis

a) Hypersensitivity reactions, including anaphylactoid reactions, may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Non-allergic anaphylaxis

a) General Information

1) Anaphylactoid reactions have rarely been reported following administration of testosterone enanthate [73].

Testosterone Undecanoate

Anaphylaxis

a) General Information

1) Anaphylaxis may occur after the first dose or with any injection during the course of therapy [59].

b) Adult Clinical Trials

1) Anaphylaxis occurred in 2 hypogonadal men who received IM testosterone undecanoate during 18 clinical trials (n=3556) [59].

c) Postmarketing

1) Episodes of anaphylaxis, including life-threatening reactions, were reported during postmarketing surveillance [59].

Hypersensitivity reaction

a) Postmarketing

1) Hypersensitivity was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Systemic lupus erythematosus

a) Postmarketing

1) Systemic lupus erythematosus was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Musculoskeletal Effects

Testosterone

Advanced bone age

a) General Information

1) May accelerate bone maturation and cause premature closure of epiphyses in pediatric patients [25][22][88]

2) Use in pediatric patients may reduce adult stature, with greatest impact among youngest children [88]

b) Pediatric Clinical Trials

1) Replacement therapy: Height stunting in adolescents has been reported with anabolic steroid use [102]

Myalgia

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): Cause of treatment discontinuation in combination with arthralgia, fever, chills, and petechiae in 1 patient [22]

Pain in limb

a) Incidence: 4.3% [22]
b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Pain in extremity, 4.3% [22]

Testosterone Enanthate

Arthralgia

a) Incidence: 2% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

Backache

a) Incidence: 3.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 3.3% with testosterone enanthate (n=150) [74]

Increased creatine kinase level

a) Incidence: 3.3% to 3.8% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 3.3 with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3.8% with testosterone enanthate (n=133) [74]

Testosterone Undecanoate

Musculoskeletal pain

a) Incidence: 2.1% [53]
b) Adult Clinical Trials

1) Testosterone replacement (oral route): 2.1% with testosterone undecanoate (Study N=95) [53]

Neurologic Effects

Testosterone

Amnesia

a) Incidence: Less than 1% [87]
b) Adult Clinical Trials

1) Replacement therapy (topical route): Less than 1% [87]

Cerebrovascular accident

a) General Information

1) May increase risk of major adverse cardiovascular events, such as stroke [17][2][1][14][16][5][15][3][18].

2) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Adult Clinical Trials

1) Low serum testosterone levels: increased risk of myocardial infarction, stroke, and all-cause mortality, 29% during a median of 531 days after coronary angiography [103]

2) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with 21% increased risk of stroke compared with transdermal gels when assessed over a 1-year followup period. There was no significant difference in the risk of stroke between the transdermal gel or patch [105].

c) Adult Case Reports and Postmarketing

1) Has been reported [17][2][1][14][16][5][15][3][18]

2) A cerebrovascular accident involving the basal ganglia and internal capsule was reported in a 21-year-old man without other predisposing factors for thromboembolism [107]

Headache

a) Incidence: 1% to 6% [25][22][85][86][87][100][108]
b) General Information

1) One of the most common adverse reactions and cause of treatment withdrawal with intranasal form [22]

2) Has been reported with administration via injection, intranasal, or topical routes

[22][85][86][87][100][108]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 4.3%, with treatment withdrawal in 1 patient [22]

2) Replacement therapy (topical route): 5% to 6% [85]

3) Replacement therapy (topical route): 1% vs 0% with placebo [25][86]

4) Replacement therapy (topical route): 0% to 4% [87]

5) Replacement therapy (transdermal route): 4% [100]

6) Replacement therapy (buccal route): 3.1% [108]

Insomnia

a) Incidence: Up to 2% [25][28]

b) Adult Clinical Trials

1) Replacement therapy (topical route): 0% to 1% vs 0% with placebo [25]

2) Replacement therapy (topical route): 2% or less [28].

Paresthesia

a) Incidence: Less than 1% [87][100]

b) General Information

1) Generalized paresthesias have been reported with oral testosterone and testosterone injections [94].

c) Adult Clinical Trials

1) Replacement therapy (topical route): Less than 1% [87]

2) Replacement therapy (transdermal route): Less than 1% [100]

Testosterone Cypionate

Anxiety

a) General Information

1) Has occurred with some androgens [83]

Cerebrovascular accident

a) General Information

1) Has occurred with some androgens [82]

2) Increased risk of major adverse cardiovascular events reported in some, but not all, studies of testosterone replacement therapy in men [82]

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

Headache

a) General Information

1) Has occurred with some androgens [83]

Paresthesia

a) General Information

1) Has occurred with some androgens [83]

Testosterone Enanthate

Cerebrovascular accident

a) General Information

1) May increase risk of major adverse cardiovascular events, such as stroke [75].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Postmarketing

1) Has been reported [75]

Headache

a) Incidence: 5.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 5.3% with testosterone enanthate (n=150) [74]

Insomnia

a) Incidence: 2.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Paresthesia

a) Adult Clinical Trials

1) Hypogonadism (IM route): has been reported [73].

Testosterone Undecanoate

Cerebrovascular accident

a) General Information

1) May increase risk of major adverse cardiovascular events, such as stroke [53] [58].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Postmarketing

1) Has been reported [53][57][58]

Dizziness

a) General Information

1) Led to discontinuation in 1 patient in a clinical trial (Study N=138) [53]

Headache

a) Incidence: Greater than 2% to 4.8% [53][57]
b) Adult Clinical Trials

1) Testosterone replacement (Tlando(R), oral route): 2.1% with testosterone undecanoate (Study N=95) [57]

2) Testosterone replacement (Jatenzo(R), oral route): 4.8% with testosterone undecanoate (Study N=166); led to treatment discontinuation in 1.2% of patients[57]

3) Testosterone replacement (Jatenzo(R), oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Insomnia

a) Incidence: 2% [58]
b) General Information
1) Led to treatment discontinuation in 1 patient in a clinical trial (Study N=138) [53]
c) Adult Clinical Trials
1) Hypogonadism (IM route): 2% [58]

Transient ischemic attack
a) Postmarketing
1) Has been reported [58]

Psychiatric Effects

Testosterone

Anxiety
a) Incidence: Less than 1% [87]
b) General Information
1) Anxiety has been reported with injectable and buccal testosterone [108][88][94].
c) Adult Clinical Trials
1) Replacement therapy (topical route): At least 2 out of 155 patients [85]
2) Replacement therapy (topical route): Less than 1% [87]

Depression
a) Incidence: 3% [100]
b) General Information
1) Depression has been reported with injectable testosterone [88][94].
c) Adult Clinical Trials
1) Replacement therapy (transdermal route): 3% [100]
2) Replacement therapy (buccal route): 1 of 117 patients treated for at least 6 months [108]

Dream disorder
a) Incidence: 1.3% [110]
b) Adult Clinical Trials
1) Replacement therapy (topical route): Abnormal dreams, 1.3% with testosterone gel (N=149) [110]

Hostile behavior
a) Incidence: Less than 1% [87]
b) Adult Clinical Trials
1) Replacement therapy (topical route): Hostility, less than 1% [87]

Mood swings
a) Incidence: Up to 1% [25]
b) Adult Clinical Trials
1) Replacement therapy (topical route): 0% to 1% vs 0% with placebo [25]
2) Replacement therapy (topical route): Emotional lability, 2.6% vs 0% with placebo [28]

Testosterone Cypionate

Depression
a) Depression may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Anxiety
a) Management

1) Advise patients to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes [74].

b) Adult Clinical Trials

1) Hypogonadism (IM route): has been reported [73].

Depression

a) General Information

1) Depression and suicidal ideation and behavior have been reported [74].

2) Depression leading to discontinuation occurred in 2 patients in pooled results from clinical studies (n=283) [74].

b) Management

1) Advise patients to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes [74].

c) Adult Clinical Trials

1) Hypogonadism (IM route): has been reported [73].

Suicidal thoughts

a) General Information

1) Depression and suicidal ideation and behavior have been reported [74].

2) Suicide attempts (1 complete and 1 incomplete) were reported in pooled results from clinical studies (n=283) [74].

b) Management

1) Advise patients to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes [74].

Testosterone Undecanoate

Aggressive behavior

a) Incidence: 1.3% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Depression

a) General Information

1) Has been reported [57]

b) Prevention and Management

1) Advise patients to seek medical attention for new onset or worsening of depression, suicidal ideation or behavior, anxiety, or other mood changes [57].

Irritability

a) Incidence: 2% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 2% with testosterone undecanoate (Study N=153) [59]

Mood swings

a) Incidence: 2% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 2% with testosterone undecanoate (Study N=153) [59]

Suicidal thoughts

a) General Information

1) Has been reported [57]

b) Prevention and Management

1) Advise patients to seek medical attention for new onset or worsening of depression, suicidal ideation or behavior, anxiety, or other mood changes [57].

Renal Effects

Testosterone

Increased frequency of urination

a) Incidence: Up to 2% [28]
b) Increased frequency of urination

1) Replacement therapy (topical route): 2% or less [28]

Testosterone Enanthate

Hematuria

a) Incidence: 2% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

Urinary tract infectious disease

a) Incidence: 2.7% to 3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3% with testosterone enanthate (n=133) [74]

Reproductive Effects

Testosterone

Atrophy of testis

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): Testicular atrophy in 1 patient [22]

b) Adult Postmarketing

1) Reported during postmarketing surveillance of testosterone gel [87]

Azoospermia disorder

a) General Information

1) Azoospermia may occur with exogenous androgen administration [22]

Benign prostatic hyperplasia

a) Incidence: Up to 2% [28]
b) General Information

1) Patients with benign hyperplasia are at an increased risk of exacerbation with androgen treatment [23][25][22][51][22].

2) Geriatric patients are at greater risk for benign prostatic hyperplasia [22] and prostatic hypertrophy [86].

c) Prevention and Management

1) Monitor for worsening signs and symptoms [23][25][22][51].

d) Adult Clinical Trials

1) Replacement therapy (topical route): Up to 2% [28]

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative

invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Drug-induced virilization

a) General Information

1) Virilization in children who were secondarily exposed to testosterone gel has been reported [25][85][87]. [87].

2) Reported signs and symptoms have included enlargement of the penis or clitoris, premature development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age [87].

3) Upon removal of the testosterone gel exposure, signs and symptoms regressed in a majority or cases. However, in a few cases, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age [87].

4) In some cases, direct contact with the application site of testosterone gel was reported, and in at least one case, exposure was suspected to be secondary to exposure to the testosterone gel user's shirt, towels, and/or sheets [87].

5) Amenorrhea, menstrual irregularities, the inhibition of gonadotropin secretion, and virilization are the most common side effects of androgen therapy in women [88].

Large prostate

a) Incidence: 11.7% [87]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 11.7% [87]

Oligozoospermia

a) General Information

1) Oligospermia may occur with high-dose androgen treatment [25][22] for prolonged periods [94][88].

2) Large doses of androgens may suppress spermatogenesis and adversely affect semen, including decreased sperm count [23].

b) Adult Postmarketing

1) Oligospermia has been reported [87].

Penile erection, Spontaneous

a) Incidence: 1% [90]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 1% with testosterone 50 mg (n=103) and 0% with testosterone 100 mg (n=149) vs 0% with placebo (n=99) [90]

Priapism

a) Pediatric Case Reports and Postmarketing

1) A case of priapism was reported in a 15-year-old boy following the administration of an IM injection of Triolandren(R), a combination of testosterone esters [116].

2) Priapism has been reported during postmarketing surveillance [87].

Prostate cancer

a) Incidence: Up to 1.2% [51][100]
b) General Information

1) Androgen treatment increases risk for prostate cancer [23][25][22][51].

2) Geriatric patients are at increased risk for prostatic carcinoma [86].

3) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs matched control patients without prostate cancer (n=1378) who received testosterone replacement

therapy between 2009 and 2012; the risk did not increased when analyzed by form (gel vs other forms) or timing/duration of therapy [117].

c) Prevention and Management

1) Contraindicated in patients with prostate cancer [23][25][22]

2) Evaluate patients at baseline [23], within 3 to 6 months of treatment initiation, and thereafter per screening guidelines [22].

d) Adult Clinical Trials

1) Replacement therapy (topical route): Prostatic carcinoma, 1.2% [51]

2) Replacement therapy (transdermal route): Prostatic carcinoma, less than 1% [100]

e) Adult Postmarketing

1) Replacement therapy: Two cases of prostatic adenocarcinoma and one case of chronic impotence occurred in 3 men during testosterone treatment [118]

2) Impotence (IM route): Adenocarcinoma developed in a 58-year-old man treated with testosterone 180 mg every 2 weeks [119]

Raised prostate specific antigen

a) Incidence: 1% to 11.1% [22][28][85]

b) General Information

1) One of the most common adverse reactions and cause of treatment discontinuation with intranasal form [22]

c) Prevention and Management

1) Evaluate for prostate cancer at baseline, within 3 to 6 months of treatment initiation, and thereafter per screening guidelines [22]

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): 5.1% to 5.8%, with mean serum PSA level increases of 0.1 to 0.2 ng/mL; and treatment discontinuation in 1 patient [22]

2) Replacement therapy (topical route): PSA level increase, 11.1% (mean 0.14 nanograms/mL) vs 0% (mean 0.12 ng/mL) with placebo [28]

3) Replacement therapy (topical route): PSA levels increased by a significant 21.9% (between 0.19 to 0.61 nanograms/dL) from baseline in treatment-inexperienced men with baseline testosterone levels of less than 250 ng/mL; nonsignificant elevations in PSA levels occurred in men with baseline testosterone levels of 250 ng/dL or more. PSA levels significantly decreased in both groups over 12 months of treatment [120].

4) Replacement therapy (topical route): 1% to 4% [85]

5) Replacement therapy (topical route): Serum PSA levels increased by 18%, with a significant 0.26 ng/mL increase during the initial 6 months of treatment and an overall mean change from baseline of 0.11 ng/mL over 3 years. Prostate cancer was detected in 2 patients [87].

Reduced libido

a) Incidence: Up to 2% [28]

b) Adult Clinical Trials

1) Replacement therapy (topical route): 2% or less [28]

2) Replacement therapy (transdermal route): Less than 1% [100]

Testosterone Cypionate

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative

invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Excessive erection

a) Excessive frequency and duration of penile erections may occur in patients receiving testosterone cypionate [83].

Increased libido

a) Increased libido may occur in patients receiving testosterone cypionate [83].

Oligozoospermia

a) Oligospermia may occur in patients receiving high doses of testosterone cypionate [83].

Prostate cancer

a) General Information

1) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs matched control patients without prostate cancer (n=1378) who received testosterone replacement therapy between 2009 and 2012; the risk did not increased when analyzed by form (gel vs other forms) or timing/duration of therapy [117].

Reduced libido

a) Decreased libido may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Amenorrhea

a) General Information

1) Amenorrhea has commonly been reported in female patients following administration of testosterone enanthate [73].

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Excessive erection

a) General Information

1) Excessive frequency and duration of penile erections has been reported following administration of testosterone enanthate [73].

Gynecomastia

a) General Information

1) Gynecomastia has been reported [74][73].

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

b) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

Increased libido

a) General Information

1) Increased libido has been reported following administration of testosterone enanthate [73].

Oligozoospermia

a) General Information

1) Oligospermia and spermatogenesis has been reported following administration of testosterone enanthate at high doses [74][73].

Priapism

a) Adult Case Reports

1) A case of testosterone-induced priapism was documented in a 23-year-old man with hypergonadotropic hypogonadism. The patient received 250 mg testosterone enanthate IM every 14 days. Upon the fourth injection, a dose of 500 mg was administered at the patient's request. Severe priapism developed 12 hours later, which lasted until the patient presented in the emergency room 36 hours later. Complete detumescence was achieved 17 hours after a corporeal glandular shunt was performed. Two months postoperatively, the patient continued with biweekly testosterone injections at a dose of 250 mg without further incidence of priapism. These data suggest that priapism was related to a high dose of testosterone and that testosterone-induced priapism may be dose-dependent [125].

2) Severe priapism in a 20-year-old man following IM injections of testosterone enanthate 250 mg every 2 weeks has been reported. Three days after the third injection, the patient developed a painful erection that was not accompanied by sexual stimulation. Subsequent conservative therapy failed to reverse the priapism and the patient had to undergo 2 surgical procedures to achieve detumescence [126].

Prostate cancer

a) General Information

1) Patients treated with androgens may be at increased risk for prostate cancer [74].

b) Prevention

1) Evaluate for prostate cancer prior to beginning thearpy [74].

c) Adult Clinical Trials

1) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs matched control patients without prostate cancer (n=1378) who received testosterone replacement therapy between 2009 and 2012; the risk did not increased when analyzed by form (gel vs other forms) or timing/duration of therapy [117].

d) Adult Case Report

1) A case of prostate cancer was reported in a patient with Klinefelter syndrome who had undergone long-term testosterone replacement therapy since childhood. Intramuscular testosterone enanthate every 1 to 2 weeks was initiated at age 16 and continued for 35 years. The patient's initial prostate-specific antigen (PSA) level at age 49 was 3.6 ng/dL. The following year, his PSA level rose to 5.4 ng/dL and 6 months later, the PSA level reached 12.2 ng/dL. The rise in PSA was accompanied by a slight increase in irritative voiding symptoms and adenocarcinoma was confirmed. Radical prostatectomy was performed and the patient recovered well from surgery. Androgen replacement therapy was not reintroduced until the patient remained recurrence-free for a minimum of 1 year following surgery [127].

Prostatitis

a) Incidence: 2.7% to 3% [74]

b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3% with testosterone enanthate (n=133) [74]

Raised prostate specific antigen

a) Incidence: 3% to 12% [74]

b) General Information

1) Defined as a increase from baseline of at least 1.4 nanogram (ng)/mL, or greater than 4 ng/mL [74]

2) Led to discontinuation in 4.6% of patients in clinical studies [74]

c) Adult Clinical Trials

1) Hypogonadism (subQ route): 12% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3% with testosterone enanthate (n=133) [74]

Reduced libido

a) General Information

1) Decreased libido has been reported following administration of testosterone enanthate [73].

Virilization

a) General Information

1) Virilization, including inhibition of gonadotropin secretion, deepening of the voice, and enlargement of the clitoris has commonly been reported in female patients following administration of testosterone enanthate. If administered during pregnancy, virilization of the external genitalia may occur in female fetuses [73].

Testosterone Undecanoate

Benign prostatic hyperplasia

a) General Information

1) Patients treated with androgens are at an increased risk for worsening of signs and symptoms of benign prostatic hyperplasia (BPH) [53][57].

b) Prevention

1) Monitor for worsening signs or symptoms of BPH [53][57]

c) Postmarketing

1) BPH was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Disorder of ejaculation

a) Incidence: 1.3% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Disorder of prostate, Induration

a) Incidence: 1.3% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Hypogonadism

a) Incidence: 2.6% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 2.6% with testosterone undecanoate (Study N=153) [59]

Large prostate

a) Adult Clinical Trials

1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Prostate cancer

a) Incidence: 1.3% [59]
b) General Information

1) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs controls (n=1378) who received testosterone replacement therapy; the risk did not increased when analyzed by form (gel vs other forms) or timing or duration of therapy [117].

c) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

d) Incidence: 1.3% [59]
e) General Information

1) Patients treated with androgens are at an increased risk for prostate cancer [53][57].

f) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Raised prostate specific antigen

a) Incidence: 4.6% [59]
b) General Information

1) Mean increase in prostate specific antigen (PSA) in a clinical trial was 0.2 nanograms (ng)/mL from baseline with testosterone undecanoate (n=161); increases in serum PSA from baseline of at least 1.4 ng/mL or PSA greater than 4 ng/mL occurred in 1.9% of patients [57]

c) Adult Clinical Trials

1) Hypogonadism (IM route): 4.6% with testosterone undecanoate (Study N=153) [59]

Respiratory Effects

Testosterone

Bleeding from nose

a) Incidence: 3.8% to 6.5% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

2) Symptoms usually mild to moderate [22]

c) Prevention and Management

1) Consider further evaluation or possible withdrawal if condition occurs [22]

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 6.5% [22]

Bronchitis

a) Incidence: 3.8% to 4.3% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 4.3% [22]

Cough

a) Incidence: Less than 3% [22]
b) Adult Clinical Trials
1) Replacement therapy (intranasal route): Less than 3% [22]

Discomfort, Nasal

a) Incidence: 3.8% to 5.9% [22]
b) General Information
1) One of the most common adverse reactions and cause of treatment discontinuation with intranasal form [22]
2) Symptoms usually mild to moderate [22]
c) Prevention and Management
1) Consider further evaluation or possible withdrawal if condition occurs [22]
d) Adult Clinical Trials
1) Replacement therapy (intranasal route): Nasal discomfort, 3.8% to 5.9%, with treatment withdrawal in 1 subject [22]

Excoriation of skin, Nasal

a) Adult Clinical Trials
1) Replacement therapy (intranasal route): 1 patient [22]

Nasal congestion

a) Incidence: Up to 3.9% [22]
b) Adult Clinical Trials
1) Replacement therapy (intranasal route): More than 2% to 3.9% [22]

Nasal discharge

a) Incidence: 3.8% to 7.8% [22]
b) General Information
1) Rhinorrhea was of the most common adverse reactions with intranasal form [22]
2) Symptoms usually mild to moderate [22]
c) Prevention and Management
1) Consider further evaluation or possible withdrawal if condition occurs [22]
d) Adult Clinical Trials
1) Replacement therapy (intranasal route): Rhinorrhea, 3.8% to 7.8% [22]

Nasal mucosa dry

a) Incidence: Up to 4.2% [22]
b) Adult Clinical Trials
1) Replacement therapy (intranasal route): More than 2% to 4.2% [22]

Nasopharyngitis

a) Incidence: 3.8% to 8.7% [22]
b) General Information
1) One of the most common adverse reactions with intranasal form [22]
2) Symptoms usually mild to moderate [22]
c) Prevention and Management
1) Consider further evaluation or possible withdrawal if condition occurs [22]
d) Adult Clinical Trials
1) Replacement therapy (intranasal route): 3.8% to 8.7% [22]

Pulmonary embolism

a) Prevention and Management
1) Evaluate for pulmonary embolism (PE) if acute dyspnea develops [25][22]
2) Discontinue if condition suspected and initiate workup and treatment [25][22]
b) Adult Clinical Trials
1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case

(n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Adult Postmarketing

1) Venous thromboembolism, including DVT and PE, has been reported in postmarketing surveillance [25][22]

Sense of smell altered

a) Incidence: 5.8% [22]
b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Parosmia, 5.8% [22]

Sinusitis

a) Incidence: 3.8% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% [22]

Sleep apnea

a) General Information

1) Testosterone may contribute to sleep apnea onset, particularly in at-risk (eg, obesity or chronic lung disease) hypogonadal men [23][25][22][85][86][87].

Upper respiratory infection

a) Incidence: 3.8% to 4.3% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 4.3% [22]

Testosterone Cypionate

Pulmonary embolism

a) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

Testosterone Enanthate

Cough

a) Incidence: 2.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Pulmonary embolism

a) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

b) Prevention and Management

1) Evaluate patients with pain, edema, warmth, or erythema in the lower extremity for DVT and those with acute shortness of breath for pulmonary embolism [74].

2) Discontinue use if suspected and initiate appropriate work up and management [74].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing use in patients using testosterone products [74].

Sleep apnea

a) Incidence: 2% [74]

b) General Information

1) Treatment with testosterone products may potentiate sleep apnea [74].

2) Increased likelihood in at risk patients (eg, obesity, chronic lung disease) [74]

c) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

d) Adult Case Reports

1) After receiving intramuscular testosterone enanthate weekly for a period of 10 months as an experimental contraceptive agent, and human chorionic gonadotropin (5000 international units) intramuscularly for 3 months, a 36-year-old moderately obese man began to experience difficulty in sleeping, daytime somnolence, and mood depression. His medical history and physical examination were unremarkable; routine hematologic and blood-chemistry studies were normal. In addition, he had received cimetidine (300 mg 3 times daily) for reflux esophagitis, and amoxapine (150 mg daily) for depression. Upper airway examination had revealed no source of obstruction; however, pulmonary function tests revealed a reduced functional residual capacity consistent with obesity as well as a mild obstructive defect. Sleep studies, testosterone levels, discontinuance of testosterone, and repeat rechallenge confirmed an association with exacerbations of clinical symptoms and testosterone administration. In comparison with normal apnea index values (less than 5 episodes of apnea lasting for more than 10 seconds per hour of sleep), his values increased to 26 and 40 following testosterone administration. Discontinuation of the drug resulted in normalization of most laboratory values (apneic index, total sleep time, free testosterone, hypoxic and hypercapnic ventilatory response, oxygen consumption) within 5 weeks. Complete reversal was achieved after 6 months [124].

Testosterone Undecanoate

Pulmonary embolism

a) Prevention and Management

1) Evaluate patients who present with shortness of breath for pulmonary embolism [53][57][92].

2) Discontinue use and initiate appropriate workup and management if suspected [53][57][58].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing experience [53][57][92].

Pulmonary embolism, Oil microembolism

a) General Information

1) Symptoms such as coughing, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness, and syncope occurred during or immediately after the injection [59].

2) Although the majority of reactions lasted a few minutes and responded to supportive care, some lasted several hours and required emergency intervention and/or hospitalization [59].

3) POME reactions may occur after the first dose or with any injection during the course of therapy [59].

b) Adult Clinical Trials

1) Pulmonary oil microembolism (POME) occurred in 8 hypogonadal men (9 total events) who received IM testosterone undecanoate during 18 clinical trials (n=3556) [59].

c) Postmarketing

1) Serious POME reactions were also reported with testosterone undecanoate 1000 mg IM during postmarketing surveillance [59].

Sleep apnea

a) General Information

1) Treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors (eg, obesity, chronic lung disease) [53][57][59].

b) Postmarketing

1) Sleep apnea syndrome was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Upper respiratory infection

a) Incidence: 3.6% [53]

b) Adult Clinical Trials

1) Testosterone replacement (oral route): 3.6% with testosterone undecanoate (Study N=138) [53]

Other

Testosterone

Death

a) General Information

1) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

b) Adult Clinical Trials

1) Low serum testosterone levels (unspecified route): increased risk of myocardial infarction, stroke, and all-cause mortality, 29% [103]

2) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with 34% more deaths compared with transdermal gels when assessed over a 1-year followup period. There was no significant difference in the risk of death between the transdermal gel or patch [105].

Pain of breast

a) Incidence: 1% to 3% [87]

b) Adult Clinical Trials

1) Replacement therapy (topical route): 1% to 3% [87]

Persistent pain following procedure

a) Incidence: 4.3% [22]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Procedural pain, 4.3% [22]

Testosterone Cypionate

Drug abuse

a) The dependence on a combination of anabolic and androgenic steroids including testosterone cypionate was reported in a 24-year-old, noncompetitive male weight lifter. The patient met the DSM-III-R criteria for psychoactive substance dependence, and appeared depressed with some anxiety. Mild psychomotor retardation was present, and prior to medical examination the patient reported suicidal tendencies [128].

Testosterone Enanthate

Fatigue

a) Incidence: 2% to 2.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Neoplasm of liver

a) General Information

1) Hepatocellular neoplasms have rarely been reported following administration of testosterone enanthate [73].

2) Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas [108].

Testosterone Undecanoate

Fatigue

a) Incidence: 2% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 2% with testosterone undecanoate (Study N=153) [59]

Black Box Warning

1) Testosterone

a) Topical (Gel/Jelly)

Secondary Exposure to Testosterone

Virilization has been reported in children who were secondarily exposed to testosterone gel.
Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel.
Healthcare providers should advise patients to strictly adhere to recommended instructions for use [15][5][18][3][2].

b) Topical (Solution)

Secondary Exposure to Testosterone

Virilization has been reported in children who were secondarily exposed to topical testosterone products.
Children should avoid contact with unwashed or unclothed application sites in men using testosterone topical solution.
Healthcare providers should advise patients to strictly adhere to recommended instructions for use [1].

2) Testosterone Enanthate

a) Subcutaneous (Solution)

1) Warning: Blood Pressure Increases

Testosterone enanthate can cause blood pressure (BP) increases that can increase the risk for major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, with greater risk for MACE in patients with cardiovascular risk factors or established cardiovascular disease.

Before initiating testosterone enanthate, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled.

Starting approximately 6 weeks after initiating therapy, periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension in patients on testosterone enanthate.

Re-evaluate whether the benefits of testosterone enanthate outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease while on treatment.

Due to this risk, use testosterone enanthate only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies [74].

3) Testosterone Undecanoate

a) Intramuscular (Solution)

Serious Pulmonary Oil Microembolism (POME) Reactions and Anaphylaxis

Serious POME reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose.
Following each injection of testosterone undecanoate, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis.
Because of the risks of serious POME reactions and anaphylaxis, testosterone undecanoate is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Aveed(R) REMS Program [58].

b) Oral (Capsule)

Warning: Blood Pressure Increases

Testosterone undecanoate can cause blood pressure (BP) increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, with greater risk for MACE in patients with cardiovascular risk factors or established cardiovascular disease.
Before initiating testosterone undecanoate, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled.
Starting approximately 3 weeks after initiating therapy or changing the dose, periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension in patients on testosterone undecanoate.
Re-evaluate whether the benefits of testosterone undecanoate outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease while on treatment.
Due to this risk, use testosterone undecanoate only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies [57].

REMS

No results available

Drug Interactions (single)

Drug-Drug Combinations

Alclometasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Amcinonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Anisindione

1) Interaction Effect: increased risk of bleeding
2) Summary: A number of case reports have demonstrated that coadministration of oral anticoagulants and 17-alkylated androgens (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) has resulted in a prolonged prothrombin time and hemorrhages[134][135][136][137][138]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may result in bleeding in patients receiving concomitant anticoagulant therapy [139].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of anabolic steroids and anisindione should be avoided when possible. If the drugs must be used together, frequent monitoring of the anticoagulant response must be maintained.
7) Probable Mechanism: unknown
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol. The anabolic steroids enhance dicumarol's anticoagulant activity perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [129][130][131][132][133].

Beclomethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Betamethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Budesonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Bupropion

1) Interaction Effect: lowering of the seizure threshold
2) Summary: Concomitant administration of buPROPion and agents that lower seizure threshold, such as systemic steroids, should be undertaken with caution. In addition to using small initial doses and gradual dose increases, follow the dosing regimen recommendation according to each product labeling as xaximum daily dose varies by product formulation and indication[157][158][159][160][161].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of buPROPion and systemic steroids should be used with caution. Maximum daily dose varies by product formulation and indication: 1) When coadministration of buPROPion immediate-release (Wellbutrin(R)) is required, do not exceed the total daily dose of 450 mg. Minimize the risk of seizure by giving the daily dose three times daily, and limit each single dose to 150 mg or less[157]. 2) When coadministered with buPROPion extended-release tablets (Wellbutrin XL(R)), do not exceed the total daily dose of 450 mg [158]. 3) Coadministration of sustained-release buPROPion (Wellbutrin SR(R)) should not exceed the total daily maximum of 400 mg, and should be given twice daily. Each single dose should not be higher than 200 mg to minimize high peak concentration of buPROPion [159]. 4) When administration of buPROPion extended-release or sustained-release buPROPion (Zyban(R)) is indicated for smoking cessation, the total daily dose should not exceed more than 300 mg. Give the daily dose twice daily, and limit each single dose to 150 mg or less [160][161]. Furthermore, consider using small initial doses and gradual dose increases.
7) Probable Mechanism: unknown

Ciclesonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Clobetasol

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Clobetasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Clocortolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Corticotropin

1) Interaction Effect: increased risk of edema
2) Summary: Coadministration of testosterone with corticotropin (ACTH) may enhance the formation of edema, especially in the susceptible patient with a history of cardiac or hepatic dysfunction[156].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Testosterone and corticotropin should be co-administered with caution, especially in patients with cardiac or hepatic disease.
7) Probable Mechanism: unknown

Cortisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Cyclosporine

1) Interaction Effect: an increased risk of cycloSPORINE toxicity (renal dysfunction, cholestasis, paresthesias)
2) Summary: Concomitant administration of cycloSPORINE and anabolic steroids may result in increased cycloSPORINE blood levels and toxicity[153][154][155].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If clinically possible, avoid this combination. If these two drugs are given concomitantly, monitor circulating cycloSPORINE levels and adjust cycloSPORINE dosage as necessary; also, monitor patients for increased cycloSPORINE toxicity (renal dysfunction, neurotoxicity).
7) Probable Mechanism: decreased cycloSPORINE metabolism
8) Literature Reports

a) Concomitant administration of cycloSPORINE and anabolic steroids may result in increased cycloSPORINE blood levels and toxicity. This effect has been observed in 2 case studies with methyltestosterone and in 1 case study with danazol [150][151][152].

Dehydroepiandrosterone

1) Interaction Effect: increased risk of adverse androgenic and hepatic effects
2) Summary: Patients electing to take both dehydroepiandrosterone (DHEA) and testosterone are at increased risk for androgenic side effects. Data are conflicting on the extent that DHEA increases the testosterone-epitestosterone (T/E) ratio[174][175]. The effect appears to be dose-dependent, and at doses commonly used by body-builders (e.g. 1000 milligrams), androgenic effects are likely. Concomitant use is not advised.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and testosterone. DHEA may increase testosterone levels, increasing the incidence of adverse androgenic adverse effects such as oligospermia (in men), gynecomastia, prostatic hypertrophy (especially in elderly males), and virilization in women (deepening voice, hirsutism, acne, clitoromegaly, and menstrual irregularities). Libido may increase or decrease. Adverse hepatic effects may also occur (peliosis hepatitis, hepatic neoplasms).
7) Probable Mechanism: additive androgenic effect, since dehydroepiandrosterone appears to act as a pro-drug for testosterone
8) Literature Reports

a) Dehydroepiandrosterone (DHEA) increased the testosterone-epitestosterone (T/E) ratio in an uncontrolled study of 4 human volunteers. Two over the counter DHEA preparations were used in this study. Nature's Pride "DHEA 50 mg+" (product A) contained DHEA 50 milligrams (mg), suma 25 mg, Korean ginseng 25 mg, muira pauma 25 mg, shitake mushroom concentration 15 mg, and green tea extract 5 mg. The second product, YourLife DHEA (product B), contained DHEA 25 mg as the only active ingredient listed on the label. Neither product contained testosterone as detected by gas chromatography-mass spectrometry (GC-MS) analyses. All subjects (except subject 4) took the product once daily for 4 days at breakfast. Subject 1 (age 47) took both preparations at 3 dosage levels at different times over a 6 month period: product A 50 mg/day, product A 100 mg/day, and product B 150 mg/day for 4 days. Subjects 2 (age 61) and 3 (age 28) took product B 50 mg/day and 100 mg/day, respectively. Subject 4 (age 27) took product A 100 mg/day for 2 days. A 24-hour urine was collected on day 3 and spot urine samples were taken in the morning and evening of day 4. Subject 1 at DHEA doses of 50 mg/day, 100 mg/day, and 150 mg/day had T/E ratios of 8.1, 11.4, and 14.4, respectively, compared to a pre-dose ratio of 2.4. Pre-dose T/E ratios for subjects 2 and 3 were 1.3 and 1.7, respectively, and T/E ratios were 1.6 and 3.9, respectively after DHEA. Subject 4 had a pre-dose T/E ratio of 0.8 and a T/E ratio of 1.1 following DHEA. Ratios exceeding 6:1 are used by several organizations including the United States Military and the International Olympic Committee (IOC) as an indication

that additional tests are warranted to rule out use of exogenous physiological steroids. Manipulation of the steroid endocrine system to improve athletic performance has led some DHEA supplement providers on the internet to recommend up to 1000 mg/day [171].

b) Differences in baseline mean T/E ratios and dehydroepiandrosterone (DHEA) treatment mean ratios were not significant in 7 healthy subjects. Mean baseline T/E ratio was 0.67 (range: 0.1 to 1.2). DHEA 50 mg was taken each morning for 30 days with urinary samples collected before and two to three hours after ingestion with no voiding before collection. Individual variation was prevalent. The greatest individual variation from baseline to treatment mean T/E ratio was 1.20 to 2.11. The greatest difference from baseline mean to peak treatment mean T/E ratio was 1.2 to 3.7. A single dose of DHEA 250 mg resulted in a 40% increase in the T/E ratio relative to the pre-dose value (peak T/E ratio equal to 1.2). DHEA at this dose had a minimal effect on urine T/E ratios and would not be expected to result in a positive screen for testosterone abuse as the T/E ratio must exceed 6:1 [172].

c) Two female volunteers demonstrated three to four fold increases in plasma testosterone levels following dehydroepiandrosterone (DHEA) 100 mg administration. In subject 1, the pre-DHEA testosterone level was 0.07 mcg/100 mL compared to a maximum level of 0.28 mcg/100 mL ninety minutes after DHEA administration. In subject 2, the pre-DHEA testosterone level was 0.08 mcg/100 mL compared to a maximum level of 0.28 mcg/100 mL sixty minutes after DHEA administration. This demonstrates that in vivo conversion of DHEA to testosterone occurs in women as well as men [173].

Desonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Desoximetasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Dexamethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase

fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: Concomitant use of dicumarol and testosterone may result in an increased risk of bleeding. A number of case reports have demonstrated prolonged prothrombin time and hemorrhages with coadministration of oral anticoagulants and 17-alkylated androgens[141][142][146][144][147]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may lead to bleeding in patients receiving concomitant anticoagulant therapy [88]. If coadministration of dicoumarol and testosterone is deemed necessary, make INR determinations and increase prothrombin time monitoring, particularly when androgen treatment is initiated or discontinued [140] [88].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If the concomitant use of oral anticoagulants and testosterone is required, make INR determinations and increase monitoring of prothrombin time, particularly at androgen treatment initiation and discontinuation[140][88].
7) Probable Mechanism: modification of coagulation factor, hepatic synthesis, and competitive inhibition of plasma protein binding by testosterone
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol. The anabolic steroids enhance anticoagulant activity of dicumarol perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [141][142][143][144][145].

Diflorasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Diflucortolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Difluprednate

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may

increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Dong Quai

1) Interaction Effect: increased androgenic and/or adverse effects of testosterone
2) Summary: Dong quai (Angelica dahurica) extract significantly inhibited the metabolism of testosterone in vitro[177]. The effect of dong quai on the metabolism of nifedipine in humans is unknown, as the dose used in the animal study (1 gram/kilogram) is higher than that usually used in humans. Theoretically, if dong quai similarly affects the pharmacokinetics of testosterone in humans, increased levels of testosterone may occur which may result in greater androgenic effect. It is suspected that dong quai may affect other drugs metabolized by CYP2C11, CYP3A, and CYP1A enzymes. Caution is advised.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Monitor for increased androgenic effects of testosterone (such as acne, hirsutism, behavior changes) in patients taking testosterone and dong quai concomitantly.
7) Probable Mechanism: inhibition of hepatic cytochrome P450 enzyme metabolism of testosterone
8) Literature Reports

a) Angelica dahurica (dong quai) extract 1 gram/kilogram orally significantly inhibited 2-alpha-hydroxylase, 16-alpha-hydroxylase, and 6-beta-hydroxylase activity in rat liver microsomes. 2-alpha-hydroxylase activity was inhibited from one to 24 hours after dong quai administration (p less than 0.01), with 17.2 percent to 68.7 percent of its activity remaining. 16-alpha-hydroxylase activity was inhibited from 1 to 6 hours after dong quai administration (p less than 0.01), with 28.5 percent to 39.8 percent of its activity remaining. 6-beta-hydroxylase activity was inhibited 6 hours after dong quai administration (p less than 0.05), with 70 percent of its activity remaining. Cytochrome P450 (CYP) 2C11 mediates 2-alpha- and 16-alpha-hydroxylase activity, while CYP3A and CYP1A mediate 6-beta-hydroxylase activity [176].

Flucloronide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fludrocortisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Flumethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Flunisolide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocinolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocinonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocortin

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocortolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluorometholone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluticasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Glimepiride

1) Interaction Effect: increased blood glucose lowering effect and increased risk of hypoglycemia
2) Summary: Exercise caution when coadministering glimepiride and androgens as this may increase the risk of hypoglycemia. If concomitant use is required, monitor more

closely for hypoglycemia. Upon discontinuation of androgens, monitor the patient for worsening of glycemic control[149].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of glimepiride and androgens may increase the risk of hypoglycemia. If concomitant use is required, monitor more closely for hypoglycemia. Upon discontinuation of androgens, monitor the patient for worsening of glycemic control[149].
7) Probable Mechanism: unknown

Halcinonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Hydrocortisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Insulin

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Aspart, Recombinant

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in

changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Bovine

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Degludec

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Detemir

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Glargine, Recombinant

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Glulisine

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Lispro, Recombinant

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Licorice

1) Interaction Effect: decreased testosterone effectiveness
2) Summary: Licorice significantly reduced endogenous testosterone levels in healthy men and in women with polycystic ovary disease[166][167]. This may occur in clinically significant levels and may adversely affect testosterone supplementation. Licorice may inhibit conversion of androstenedione to testosterone through inhibition of 17-beta-hydroxysteroid dehydrogenase and 17,20-lyase [166][168][169]. Indirect evidence suggests that licorice may also stimulate aromatase activity and thereby increase the estradiol to testosterone ratio [170][169][167].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of licorice and testosterone. Patients reporting decreased libido or other sexual dysfunction for which testosterone supplementation is being considered should be questioned regarding licorice use and advised to discontinue licorice.
7) Probable Mechanism: inhibition of 17-beta-hydroxysteroid dehydrogenase and 17,20-lyase which catalyze the conversion of androstenedione to testosterone; increased estradiol synthesis though aromatase stimulation
8) Literature Reports

a) Licorice decreased testosterone levels in 7 healthy men (age 22 to 24 years). Subjects received licorice 7 grams daily, administered as a commercial tablet preparation (Saila, Bologna, Italy), each containing 0.5 grams of glycyrrhizic acid as confirmed by gas chromatography-mass spectrometry. Baseline testosterone levels were 740 nanograms/deciliter (ng/dL), decreasing to 414 ng/dL by day 4 (p less than 0.001), and remained significantly decreased on day 7 at 484 ng/dL (p less than 0.001). Four days after licorice discontinuation, testosterone increased to 704 ng/dL. This demonstrates that licorice inhibits 17-beta-hydroxysteroid dehydrogenase conversion of androstenedione to testosterone. A comparable increase in 17-hydroxyprogesterone occurred by day 7 with no increase in androstenedione, indicating inhibition of 17,20-lyase, which catalyzes conversion of 17-hydroxyprogesterone to androstenedione. The authors conclude that since this amount of licorice is eaten by many people, that men with decreased libido or other sexual dysfunction should be questioned regarding licorice use [164].

b) An herbal combination of peony root and licorice root reduced serum testosterone levels in 34 infertile Japanese women with polycystic ovary disease. Women received 7.5 grams of the combination for 24 weeks. At 4 weeks, serum testosterone and free testosterone levels were significantly decreased by 56.3% and 59.3%, respectively. The mean testosterone level at 4 weeks was 85.3 ng/dL compared with the baseline level of 137.1 ng/dL (p less than 0.001). At 12 and 24 weeks, mean testosterone levels remained significantly lower than pretreatment levels (p less than 0.001 and p less than 0.01, respectively). Serum testosterone levels were significantly lower after 12 weeks in patients who became pregnant after treatment versus those who did not (p less than 0.05). The estrogen to testosterone ratio increased significantly after 4 weeks (p less than 0.05). After 24 weeks, the luteinizing hormone to follicle stimulating hormone ratio was significantly reduced for the first time (p less than 0.001) [165].

Loteprednol

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Methylprednisolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Mometasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Oxyphenbutazone

1) Interaction Effect: elevated serum levels of oxyphenbutazone
2) Summary: Coadministration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone[148].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Clinicians should be aware that concomitant use of testosterone and oxyphenbutazone may result in elevated serum levels of oxyphenbutazone.
7) Probable Mechanism: unknown

Paclitaxel

1) Interaction Effect: increased paclitaxel exposure resulting in increased risk of paclitaxel toxicity
2) Summary: Testosterone, a known inhibitor of the isoenzyme CYP2C8, inhibits the metabolism of paclitaxel to its primary metabolite 6-alpha-hydroxypaclitaxel, in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo in the presence of a CYP2C8 inhibitor. Caution should be exercised with the concomitant use of paclitaxel and CYP2C8 inhibitors such as testosterone[162].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects due to paclitaxel toxicity including bone marrow suppression, myalgia/arthralgia, nausea/vomiting, and mucositis. Dose adjustment for either medication may be required.
7) Probable Mechanism: inhibition of CYP2C8-mediated paclitaxel metabolism by testosterone

Paclitaxel Protein-Bound

1) Interaction Effect: increased paclitaxel exposure resulting in increased risk of paclitaxel toxicity
2) Summary: Testosterone, a known inhibitor of the isoenzyme CYP2C8, inhibits the metabolism of paclitaxel to its primary metabolite 6-alpha-hydroxypaclitaxel, in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo in the presence of a CYP2C8 inhibitor. Caution should be exercised with the concomitant use of paclitaxel protein-bound and CYP2C8 inhibitors such as testosterone[163].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects due to paclitaxel toxicity including bone marrow suppression, myalgia/arthralgia, nausea/vomiting, and mucositis. Dose adjustment for either medication may be required.
7) Probable Mechanism: inhibition of CYP2C8-mediated paclitaxel metabolism by testosterone

Phenprocoumon

1) Interaction Effect: an increased risk of bleeding
2) Summary: Concomitant use of phenprocoumon and testosterone may result in an increased risk of bleeding. A number of case reports have demonstrated prolonged prothrombin time and hemorrhages with coadministration of oral anticoagulants and 17-alkylated androgens[141][142][146][144][147]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may lead to bleeding in patients receiving concomitant anticoagulant therapy [88]. If coadministration of phenprocoumon and warfarin is deemed necessary, make INR determinations and increase prothrombin time monitoring, particularly when androgen treatment is initiated or discontinued [140] [88].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If the concomitant use of oral anticoagulants and testosterone is required, make INR determinations and increase monitoring of prothrombin time, particularly at androgen treatment initiation and discontinuation[140][88].
7) Probable Mechanism: modification of coagulation factor, hepatic synthesis, and competitive inhibition of plasma protein binding
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol, another anticoagulant. Anabolic steroids enhance the anticoagulant activity of dicumarol perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [141][142][143][144] [145].

Prednicarbate

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Prednisolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Prednisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Rimexolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Triamcinolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those

with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: Concomitant use of testosterone and warfarin may result in an increased risk of bleeding. A number of case reports have demonstrated prolonged prothrombin time and hemorrhages with coadministration of oral anticoagulants and 17-alkylated androgens[141][142][146][144][147]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may lead to bleeding in patients on concomitant anticoagulant therapy [88]. If coadministration of testosterone and warfarin is deemed necessary, make INR determinations and increase prothrombin time monitoring, particularly when treatment with testosterone is initiated or discontinued [140][88].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If the concomitant use of oral anticoagulants and testosterone is required, make INR determinations and increase monitoring of prothrombin time, particularly at androgen treatment initiation and discontinuation[140][88].
7) Probable Mechanism: modification of coagulation factor, hepatic synthesis, and competitive inhibition of plasma protein binding by testosterone
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol, another anticoagulant. Anabolic steroids enhance the anticoagulant activity of dicumarol perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [141][142][143][144][145].

b) Significant enhancement of the anticoagulant effects of warfarin was described in a 69-year-old woman following application of a vaginal ointment of testosterone propionate [141]. The mechanism of interaction is unclear.

IV Compatibility (single)

No results available

Pregnancy & Lactation

A) Teratogenicity/Effects in Pregnancy

1) Micromedex Pregnancy Rating: Contraindicated

a) Avoid use of this drug during pregnancy and prescribe an alternative. Evidence has demonstrated fetal abnormalities or risks when used during pregnancy. Advise women of childbearing potential of fetal risk.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Yes

3) Clinical Management

a) Testosterone is not indicated for use in women and should not be used in women [85][108][181][182]. Testosterone is contraindicated during pregnancy [57][74]. Advise patient of possible consequences to the fetus if pregnancy occurs during use[28], including masculinization of the

external genitalia of the female fetus. Pregnant women or those who may become pregnant should be aware of potential transfer of testosterone by men being treated with this drug [183][88].

4) Literature Reports

a) Based on animal findings and its mechanism of action, testosterone is teratogenic and can cause fetal harm when given to a pregnant woman [57][74][28][85].

b) Exposure of a female fetus to testosterone may result in varying degrees of virilization [57][74][22][85]. At least 16 cases have been reported of female offspring with virilization of genitalia after their mothers were treated with either testosterone or methyltestosterone during pregnancy [178][179]. In addition, clitoromegaly with or without labioscrotal fusion were reported in these cases. In one follow-up case, female endocrine function was normal with secondary sexual development occurring at puberty, and the internal female sex organs were also normal [180].

c) Suppressed spermatogenesis via feedback inhibition of the hypothalamic-pituitary-testicular axis may occur with treatment using large doses of exogenous androgens, including testosterone. Decreased fertility has been noted in some men receiving testosterone replacement therapy, and may be irreversible [57][74].

d) In animal developmental studies, structural impairments in male (ie, increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen) and female (ie, increased ano-genital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment) offspring were observed when pregnant animals received IM testosterone during organogenesis at doses that were comparable to doses used for testosterone replacement therapy. In addition, increased pituitary weight was observed in both male and female offspring, as well as hormonal and behavioral changes. At testosterone doses that were about twice the doses used for testosterone replacement therapy, hypertension was observed in pregnant female rats and in their offspring [57][74].

B) Breastfeeding

1) World Health Organization Rating: Avoid breastfeeding.

2) Micromedex Lactation Rating: Infant risk has been demonstrated.

a) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue breastfeeding.

3) Clinical Management

a) Testosterone is not indicated for use in women [57][74]. Testosterone is contraindicated in nursing women [108][182][88][181].

4) Literature Reports

a) It is not known how much testosterone transfers into human milk [85][28]. However, testosterone has been concentrated in the breast tissue of women with breast cancer [185].

5) Drug Levels in Breastmilk

a) Active Metabolites

1) dihydrotestosterone [200][205]

Monitoring

A) Testosterone

1) Therapeutic

a) Laboratory Parameters

1) Buccal

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [17]

b) Monitor morning serum testosterone 4 to 12 weeks after initiating therapy to assess therapeutic response [23].

c) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

2) Nasal Gel

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [16]

b) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; intranasal formulations should be measured between two to four weeks after initiation [26].

c) Monitor serum testosterone levels periodically during therapy to assess therapeutic response [22].

d) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

3) Topical Gel

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [5][15][3][2][18].

b) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; topical gels should be measured between two to four weeks after initiation [26].

c) Monitor serum testosterone levels periodically during therapy to ensure proper dosing [25] and assess therapeutic response [51][4].

d) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

4) Topical Solution

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [1].

b) Monitor serum testosterone levels within 2 to 8 hours and at least 14 days after initiating therapy (or dose adjustment) to assess therapeutic response [85].

c) Once therapeutic levels have been achieved, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

5) Transdermal

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [14].

b) Two weeks after therapy initiation, following system application the previous evening, evaluate the early morning serum testosterone level to assess therapeutic response [84].

c) Two weeks after switching from the 2.5, 5, and 7.5 mg/day systems to the 2, 4, and 6 mg/day systems, following system application the previous evening, assess the early morning serum testosterone level [84].

d) Once therapeutic levels have been achieved, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

2) Toxic

a) Laboratory Parameters

1) Assess serum prostate specific antigen (PSA) periodically during therapy (buccal, nasal gel, topical gel) [25][22][23][51][4]. For topical solution and transdermal system, evaluate PSA levels prior to initiating therapy, every 3 to 6 months during therapy, and in accordance with prostate cancer screening practices thereafter [84][85].

2) Monitor hematocrit levels [25] prior to initiation of therapy, at 3 to 6 months after initiation, and annually thereafter [22][23][51][4][84][85]. It is recommended that periodic monitoring of hematocrit levels should be standard practice in testosterone replacement therapy, especially in older men, due to reports linking topical testosterone with the development of polycythemia [96].

3) For topical solution, topical gel, and transdermal testosterone system, monitor hemoglobin levels prior to initiation of therapy, at 3 to 6 months after initiation, and annually thereafter [51] [4][84][85].

4) Periodically monitor liver function tests [51][4][84][85].

5) Periodically monitor lipid concentrations [25][22][23][51][4][84][85], particularly after initiation of therapy [22].

6) Regularly monitor serum calcium levels in cancer patients who have an increased risk of hypercalcemia and associated hypercalciuria [25][22][23][51][4][84][85].

b) Physical Findings

1) Evaluate for prostate cancer prior to and during therapy [25][23][51][4]. In patients receiving nasal gel or transdermal testosterone treatment, evaluate for prostate cancer prior to initiating treatment, 3 to 6 months following therapy initiation, and then in accordance with prostate cancer screening practices [22][84].

2) Monitor patient for signs and symptoms of worsening benign prostatic hyperplasia [25][22][23], especially in geriatric patients [22][51][4][84][85].

B) Testosterone Cypionate

1) Therapeutic

a) Laboratory Parameters

1) Improvement in serum testosterone levels may be indicative of efficacy.

2) Measure serum testosterone in the morning on at least 2 separate days before therapy initiation to confirm hypogonadism [82].

3) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; testosterone cypionate should be measured no earlier than three to four cycles [26].

4) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

2) Toxic

a) Laboratory Parameters

1) Monitor hematocrit and hemoglobin levels at baseline [26] and periodically for polycythemia during long-term therapy [82][83].

b) Physical Findings

1) Monitor bone maturation and assess the bone age of the wrist and hand every 6 months in pediatric males with delayed puberty [82][83].

C) Testosterone Enanthate

1) Therapeutic

a) Laboratory Parameters

1) Improvement in serum testosterone levels may be indicative of efficacy in hypogonadal males.

2) Measure serum testosterone and confirm hypogonadism diagnosis prior to treatment initiation [74][75].

3) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; testosterone enanthate should be measured no earlier than three to four cycles [26].

4) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

b) Physical Findings

1) Ablation of the ovaries may indicate efficacy in women with advancing inoperable metastatic mammary cancer [75].

2) Toxic

a) Laboratory Parameters

1) Xyosted(TM)

a) Monitor hematocrit before initiating therapy and every 3 months during therapy [74].

b) Monitor PSA before initiating therapy and periodically during treatment [74].

c) Monitor lipid concentrations periodically, particularly after starting testosterone therapy [74].

d) Monitor calcium concentrations regularly in cancer patients at risk of hypercalcemia [74].

2) Delatestryl(R)

a) Monitor serum hematocrit and hemoglobin levels at baseline [26] and periodically for polycythemia during high-dose androgen therapy [75].

b) Periodically monitor lipid concentrations, particularly in patients with a history of myocardial infarction or coronary artery disease [75].

c) Monitor serum and urine calcium levels frequently in women with disseminated breast cancer [75].

b) Physical Findings

1) Xyosted(TM)

a) Assess blood pressure before initiating therapy, approximately 6 weeks after initiation, and periodically thereafter [74].

b) Monitor patients with benign prostatic hyperplasia (BPH) for worsening signs and symptoms [74]

2) Delatestryl(R)

a) Close clinical monitoring is necessary in women treated for metastatic breast carcinoma because androgen therapy occasionally appears to accelerate the disease [75].

b) Observe female patients for signs of virilization including deepening of the voice, hirsutism, acne, clitoromegaly, or menstrual irregularities [75].

c) In prepubertal males treated for delayed puberty, obtain an x-ray of the wrist and hand every 6 months to monitor bone age, the rate of bone maturation, and the effect of the drug on epiphyseal closure [75].

D) Testosterone Undecanoate

1) Therapeutic

a) Laboratory Parameters

1) Measure serum testosterone in the morning on at least 2 separate days before therapy initiation to confirm hypogonadism [57]. Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved. IM testosterone undecanoate should be tested halfway between the first two 10-week injections [26]. For oral capsules, measure serum testosterone concentrations 6 hours after the morning dose. Wait 7 days after treatment initiation or dose adjustment before checking the serum testosterone concentration [57]. Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

b) Physical Findings

1) Improvement in serum testosterone levels may be indicative of efficacy.

2) Re-evaluate whether benefits outweigh potential risks in patients who develop cardiovascular risk factors or cardiovascular disease during treatment [57].

2) Toxic

a) Laboratory Parameters

1) Monitor hemoglobin at baseline [26] and periodically during treatment [58].

2) Monitor prostatic specific antigen (PSA) periodically during treatment [57].

3) Monitor serum lipid profile periodically during treatment [57][58], particularly after starting testosterone therapy [57].

4) (Jatenzo(R)) Evaluate hematocrit prior to treatment and every 3 months during use [57]

5) (Aveed(R)) Evaluate hematocrit prior to treatment, 3 to 6 months after initiation of treatment, and annually thereafter [58].

6) Regularly monitor serum calcium concentrations in cancer patients at risk for hypercalcemia [57][58].

7) If testosterone abuse is suspected, check testosterone concentrations to ensure they are within normal limits [57].

b) Physical Findings

1) Observe patients for signs of anaphylaxis or serious pulmonary oil microembolism reactions (ie, urge to cough, dyspnea, tightening of the throat, chest pain, dizziness, or syncope) for 30 minutes after each injection [58].

2) Monitor patients with benign prostatic hyperplasia for exacerbation or worsening signs or symptoms [57][58].

3) Evaluate for prostate cancer prior to and during treatment [57][58].

4) Consider baseline cardiovascular risk prior to therapy [57].

5) Assure blood pressure is adequately controlled prior to therapy and periodically monitor for new-onset hypertension or exacerbations of pre-existing hypertension starting approximately 3 weeks after initiation of therapy [57].

6) Evaluate patients for signs or symptoms consistent with DVT or pulmonary embolism [57].

Do Not Confuse

No results available

MECHANISM OF ACTION

Mechanism of Action

A) Testosterone

1) Mechanism of Action

a) Testosterone is an endogenous androgen. Androgens are responsible for normal growth and development of male sex organs. Testosterone is involved in the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution (eg, beard, pubic, chest and axillary hair); laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution [22][28][85].

B) Testosterone Cypionate

1) Mechanism of Action

a) Testosterone is an endogenous androgen. Androgens are responsible for normal growth and development of male sex organs and maintenance of secondary sex characteristics. Testosterone is involved in the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution (eg, beard, pubic, chest and axillary hair); laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution [83].

C) Testosterone Enanthate

1) Mechanism of Action

a) Testosterone is an endogenous androgen. Androgens are responsible for normal growth and development of male sex organs and maintenance of secondary sex characteristics. Testosterone is involved in the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution (eg, beard, pubic, chest and axillary hair); laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution [74] [73].

D) Testosterone Undecanoate

1) Mechanism of Action

a) Metabolites of testosterone undecanoate, testosterone and dihydrotestosterone (DHT), modulate the normal growth and development of male sex organs (eg, prostate, seminal vesicles, penis and scrotum) and maintain male secondary sex characteristics such as facial, pubic, chest, and axillary hair, laryngeal enlargement, vocal chord thickening, and body musculature and fat distribution alterations [53][59].

PHARMACOKINETICS

Pharmacokinetics

Onset and Duration

A) Onset

1) Testosterone

a) Peak Response

1) Hypogonadism, transdermal: 3 to 24 months [186].

a) Full effect of transdermal testosterone 3 to 9 milligrams/day on bone mineral density was achieved at 24 months while full effects on lean muscle mass, erythropoiesis, prostate volume, energy, and sexual function occurred within 3 to 6 months [186].

2) Testosterone Undecanoate

a) Peak Response

1) Hypogonadism, IM: 7 days [59]

a) Serum testosterone concentrations reach maximum levels after a median of 7 days (range, 4 to 42 days) following a testosterone undecanoate 750 IM injection and then levels slowly decline [59].

2) Hypogonadism, oral: Cannot be characterized [53]

a) There is insufficient data to characterize an exposure-response relationship or time course of pharmacodynamic response of orally administered testosterone undecanoate [53].

B) Duration

1) Testosterone

a) Multiple Dose

1) Hypogonadism: 2 to 10 days (topical) [28][187][85]; 24 hours (transdermal) [84]

a) Following the last application of AndroGel(R) 1.62%, serum testosterone levels return to pretreatment levels within 48 to 72 hours [28].

b) By the fifth day after last application of AndroGel(R), serum testosterone levels return to pretreatment levels [187].

c) Testosterone serum concentrations returned to pretreatment levels 7 to 10 days following discontinuation of testosterone topical solution (administered until steady state was achieved) [85].

d) Testosterone serum concentrations returned to pretreatment levels 24 hours following the removal of the testosterone patch [84].

2) Testosterone Undecanoate

a) Single Dose

1) Hypogonadism, IM: 10 weeks [59]

a) Testosterone undecanoate 750 mg IM produces a steady state serum total testosterone level in the normal range (300 to 1000 nanograms/dL) for 10 weeks [59].

2) Hypogonadism, oral: Cannot be characterized [53]

a) There is insufficient data to characterize an exposure-response relationship or time course of pharmacodynamic response or orally administered testosterone undecanoate [53].

Drug Concentration Levels

A) Testosterone

1) Therapeutic Drug Concentration

a) Hypogonadism, Intranasal, Topical, and Transdermal: 300 to 1050 nanograms/dL (approximately normal physiologic circulating testosterone ranges) [85]

1) Following intranasal administration of testosterone gel 33 mg/day, the circulating testosterone concentrations achieved in men with hypogonadism are similar to those observed in healthy men (ie, 300 to 1050 nanogram/dL) [22].

2) Following axillary administration, testosterone topical solution delivers approximately normal physiologic circulating testosterone ranges (300 to 1050 nanograms/dL) as seen in healthy men [85].

3) Following application of testosterone 1.62% topical gel, approximately normal physiologic circulating testosterone ranges (300 to 1000 nanograms/dL) are achieved [28].

4) Transdermal testosterone delivers a continuous daily dose of testosterone resulting in normal physiologic concentrations of testosterone (300 to 1030 nanograms/dL) in healthy adult men [84].

2) Peak Concentration

a) Sublingual (solution), single-dose: 3.79 nanograms (ng)/mL (0.25 mg); 5.31 ng/mL (0.5 mg); 6.73 ng/mL (0.75 mg) [189]

1) In 16 premenopausal women, single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg yielded total testosterone mean Cmax values of 3.79 nanogram (ng)/mL (% coefficient variation (CV), 39.9), 5.31 ng/mL (%CV, 37.8), and 6.73 ng/mL (%CV, 39.6), respectively. Mean free testosterone Cmax levels following single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg were 0.021 ng/mL (%CV, 39.7), 0.032 ng/mL (%CV, 37.6), and 0.043 ng/mL (%CV, 45.7), respectively. The difference in Cmax was statistically different between all 3 doses for both total and free testosterone measurements (p less than 0.0001) [189].

b) Topical (solution), multiple-dose, hypogonadal men (30 mg to 120 mg): within normal range [85]

1) In a multicenter, open-label, efficacy study, hypogonadal men (n=155; median age, 53 years; range, 19 to 78 years) received testosterone topical solution 60 mg daily to the axilla for 15 days, then maintenance or titration upward or downward on day 45 and day 90 to 30-, 60-, 90-, or 120 mg based on serum testosterone concentration measured on day 15 and day 60, respectively. The table below describes the mean testosterone Cmax (normal serum testosterone range, 300 to 1050 nanograms/dL) in patients who completed the 120 day treatment (n=135) [85]:

Day	Testosterone topical solution dose				
	30 mg	60 mg	90 mg	120 mg	Overall (n=135)
	Cmax nanograms/dL				
Day 15		744 +/- 502 (n=135)			744 +/- 502
Day 60	491 (n=1)	898 +/- 664 (n=105)	646 +/- 382 (n=29)		840 +/- 620
Day 120	779 +/- 416 (n=3)	839 +/- 436 (n=97)	664 +/- 336 (n=25)	658 +/- 353 (n=10)	792 +/- 417
KEY: mg = milligrams; dL = deciliter.					

2) Following axillary administration of testosterone topical solution 30-, 60-, or 90-mg daily, steady-state concentrations were achieved in approximately 14 days. The mean steady-state dihydrotestosterone (DHT, active metabolite)-to-testosterone ratio remained within normal limits during treatment, ranging from 0.17 to 0.26 across all doses on days 15, 60, and 120 [85].

c) Topical (gel), multiple-dose, effect of sunscreen or moisturizing lotion (40.5 mg): 13% to 17% increase [28]

1) Application of sunscreen or moisturizing lotion increased exposure to testosterone in a randomized, 3-way crossover study of hypogonadal men (n=18). Subjects applied testosterone 1.62% gel 40.5 mg topically to the upper arms/shoulders followed in 1 hour by

sunscreen (SPF 50), moisturizing lotion, or nothing, for 7 days. The testosterone Cmax increased 13% and 17% when sunscreen and moisturizing lotion, respectively, were applied, compared with the control phase [28].

d) Transdermal, single-dose: 925 nanograms (ng)/dL (two 2.5 mg/day patches); 905 ng/dL (single 5 mg/day patch)[84]

1) In a study of 20 hypogonadal patients, average Cmax concentrations over 24 hours were 925 +/- 340 nanograms (ng)/dL, following the application of two 2.5 mg/day patches and 905 +/- 254 ng/dL following the application of a single 5 mg/day patch [84].

e) Transfer to Non-treated Women

1) Topical (solution), single-dose, transferred testosterone to nontreated subjects, 60 mg: 17% to 297% increase [85]

a) A clinical study of potential transfer of testosterone from treated men to nontreated women revealed a 17% increase in testosterone Cmax in the nontreated females. Using a 2% testosterone formulation, men (n=10) received testosterone 60 mg topically to each axilla and then covered the area with a T-shirt. Two hours after application, women rubbed their forearms on the axilla of the men for 15 minutes. The women were monitored for 72 hours after the transfer procedure. The transfer procedure led to a 17% increase in testosterone Cmax in the women compared with baseline. Another study in men who received a 1% testosterone formulation topically revealed a 297% increase in testosterone Cmax following direct skin-to-skin transfer compared with indirect (T-shirt) transfer [85].

2) Topical (gel), single-dose, transferred testosterone to nontreated subjects, 81 mg: 11% to 267% increase [28]

a) A clinical study of potential transfer of testosterone from treated men to nontreated women increased testosterone Cmax 11% in the nontreated females. Using a 1.62% testosterone gel formulation, men (n=12) received testosterone 81 mg topically to the shoulders and upper arms, then covered the area with a T-shirt. Two hours after application, women rubbed their hands, arms, and shoulders to the application site of the men for 15 minutes. The women were monitored for 24 hours after the transfer procedure. The transfer procedure led to an 11% increase in testosterone Cmax in the women compared with baseline. Another study in 8 men who received a 1.62% testosterone formulation topically revealed a 267% increase in testosterone Cmax following direct skin-to-skin transfer compared with indirect (T-shirt) transfer [28].

3) Time to Peak Concentration

a) Buccal system: 0.4 to 12 hours [192][193][194].

1) The mean peak serum testosterone level of 26.7 nanomoles/liter (nmol/liter) was reached 4.8 hours after administration of 30 milligram buccal testosterone given twice daily in 12 testosterone-deficient men with a mean age of 44.4 years. Steady state was achieved within the first 24 hours of treatment and was maintained in the normal range with a mean of 19.3 nmol/liter [192].

2) The mean maximum serum total testosterone concentrations (Cmax) are reached within 10 to 12 hours. The Cmax ranges from 910 to 970 nanograms/deciliter [193].

3) Serum concentrations of testosterone reach steady state levels after the second dose of testosterone buccal system. The mean average serum total testosterone concentrations at steady state in clinical studies ranged from 520 to 550 nanograms/deciliter [193].

4) In 6 healthy, postmenopausal women, maximum testosterone concentrations were achieved 0.6 hour after the first transbuccal dose of testosterone 2 milligrams and 0.4 hour after 2 weeks of treatment (steady state). Maximum hormone concentrations were 35.4 and 34.9 nanomole/liter, respectively [194].

b) Intranasal, gel: 40 minutes [22]

1) The Tmax is approximately 40 minutes following intranasal testosterone gel administration [22].

c) Oral, capsules: 6 hours [188].

1) To avoid the problem of endogenous levels and fluctuations of testosterone and dihydrotestosterone, 45 women were enrolled in a randomized, open-label pharmacokinetic study of oral testosterone undecanoate. Two doses each of 20, 40 and 80 milligrams (mg) were given every 12 hours to 45 healthy women without childbearing potential. Maximum

serum concentrations of testosterone after the first dose (Cmax1) of oral testosterone undecanoate 20, 40, and 80 mg were 1.82, 3.86, and 7.68 nanograms/mL, respectively. The time to each was 6, 6, and 5.5 hours, respectively. The maximum serum concentrations of testosterone after the second dose (Cmax2) at 20, 40, and 80 mg were 1.56, 2.65, and 5.20 nanograms/mL, respectively. Time to each was 5.98, 5.97, and 5.97 hours, respectively.

d) Subcutaneous, pellet: 63 days [195].

e) Sublingual (solution): 14.3 to 15.6 minutes [189]

1) In 16 premenopausal women, mean Tmax values after SL testosterone doses of 0.25 mg, 0.5 mg, and 0.75 mg were 15.6 minutes (+/- 5.4 minutes), 15.1 minutes (+/- 5.5 minutes), and 14.3 minutes (+/- 5.3 minutes), respectively. Free testosterone mean Tmax values following single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg were 15.6 minutes (+/- 5.1 minutes), 14.4 minutes (+/- 5.5 minutes), and 12.8 minutes (+/- 6.3 minutes), respectively. The differences between doses were not statistically different for total or free testosterone [189].

f) Transdermal: 2 to 6 hours, Testoderm(R) [196][191]; 4 to 12 hours, Androderm(R) [84]

1) With Testoderm(R) application, the serum testosterone concentration rises to a maximum at 2 to 4 hours [196].

2) With daily Androderm(R) application a continuous daily dose of testosterone is absorbed over 24 hours with a median Tmax of 8 hours (4 to 12 hours); corresponding Cmax is 905 to 925 nanograms (ng)/dL [84].

3) Absorption of transdermal testosterone was improved when a heat-generating 5 milligram (mg) patch was utilized. Over a 12-hour study period, the heat-generating patch reached a mean maximum serum testosterone concentration of 939 nanograms/dL at 4 hours compared to a standard 5 mg patch which achieved a maximum concentration of 635 nanograms/dL at 6 hours [191].

g) Topical gel: 4 hours [187].

1) An increase in serum testosterone was seen in all patients within 30 minutes after administration of 10 grams of testosterone 1% gel. Normal range testosterone levels (298 to 1043 nanograms/dL) were seen in 8 of 9 patients within 4 hours after initial application. Steady-state concentrations are reached on day 2 or 3. The average steady-state serum concentrations on day 30 in patients using 5 and 10 grams daily were 566 +/- 262 nanograms/dL and 792 +/- 294 nanograms/dL, respectively [187].

4) Steady State

a) Intranasal gel, multiple-dose, 33 mg/day: 421 nanogram/dL [22]

1) The average daily testosterone level was 421 +/- 116 nanogram/dL following administration of intranasal testosterone gel 33 mg/day (11 mg 3 times daily) for 90 days in hypogonadal men (N=69) [22].

b) Intranasal gel, multiple-dose, patients with allergic rhinitis, 11 mg: 21% to 24% decrease [22]

1) Patients with allergic rhinitis who received intranasal testosterone 11 mg 3 times daily for 3 doses had total serum testosterone levels that were 21% to 24% lower during a symptomatic phase than during an asymptomatic phase (N=18) [22].

c) Transdermal, single dose: 424 nanograms (ng)/dL (single 2.5 mg/day patch); 584 ng/dL (two 2.5 mg/day patches); 766 ng/dL (three 2.5 mg/day patches)[84]

1) In a study of 12 hypogonadal men with an average baseline serum testosterone concentration of 76 nanograms (ng)/dL, average morning testosterone concentrations were 424 nanograms (ng)/dL, 584 ng/dL, and 766 ng/dL at steady state following the nightly application of 1, 2, or 3 (2.5 mg/day) transdermal testosterone patches, respectively. Equivalent serum testosterone concentrations were observed following the application of two 2.5 mg/day patches compared with the application of one 5 mg/day patch in a study of 20 hypogonadal patients. Average steady state concentrations were 613 +/- 169 ng/dL following the application of two 2.5 mg/day patches and 621 +/- 176 ng/dL following the application of a single 5 mg/day patch [84].

5) Area Under the Curve

a) Oral (capsules): 10 to 76 nanograms x hours/milliliters [188].

1) Two doses each of testosterone undecanoate 20, 40, and 80 milligrams were give 12 hours apart to 45 healthy women without childbearing potential. The areas under the curve (AUC) from 0 to 12 hours for the 20, 40, and 80 mg dose were 10.3, 18.8, and 35.6 nanograms x hour/mL, respectively. The AUCs from 0 to the sampling time of the last measurable concentration after administration of the second dose were 25.8, 40.1, and 76.0 nanograms x hour/mL, respectively [188].

b) Sublingual (solution), single-dose: 194 nanograms (ng) x min/mL (0.25 mg); 266 ng x min/mL (0.5 mg); 337 ng x min/mL (0.75 mg) [189]

1) In 16 premenopausal women, single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg yielded baseline corrected total testosterone mean AUCs of 194 nanogram (ng) x min/mL (% coefficient variation (CV), 37.2), 266 ng x min/mL (%CV, 37.6), and 337 ng x min/mL (%CV, 34.7), respectively. Free testosterone AUCs following single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg were 0.95 ng x min/mL (%CV, 51.8), 1.51 ng x min/mL (%CV, 40.2), and 1.87 ng x min/mL (%CV, 47.8), respectively There was a statistically significant difference in AUC between the 3 doses for both total and free testosterone measurements (p less than 0.0001), and the increase in AUC was dose-dependent [189].

c) Topical (gel), single-dose (50 mg): 4499 to 5865 nanograms x hours/deciliter [190].

1) The area under the curve of plasma testosterone concentration versus time achieved by a single dose of topical testosterone 50 milligram gel ranged from 4499.1 to 5864.5 nanograms x hour/deciliter [190].

d) Transdermal: 6273 to 8402 nanograms x hour/dL [191].

1) The AUC of testosterone was 6273 to 8402 nanograms x hour/dL following transdermal administration. There is no accumulation of testosterone during continuous treatment [191].

2) Increased Systemic Exposure With a Heat-Generating Patch

a) The area under the curve of plasma testosterone concentration versus time achieved by a heat-generating patch was 8402 nanograms x hour/dL versus a standard 5 mg patch which achieved a value of 6273 nanograms x hour/dL [191].

3) Systemic Exposure After Showering

a) In a two-way crossover study of 16 hypogonadal males, showering 3 hours after the application of a single 4 mg/day transdermal testosterone patch did not increase the systemic exposure of testosterone compared with not showering [84].

e) Topical (solution), single-dose, transfer to nontreated subjects (60 mg): 13% to 131% increased exposure [85]

1) A clinical study of potential transfer of testosterone from treated men to nontreated women showed a 13% increase in testosterone AUC (0 to 24 hours) in the nontreated females. Using a 2% testosterone formulation, men (n=10) received testosterone 60 mg topically to each axilla and then covered the area with a T-shirt. Two hours after the application, women rubbed their forearms on the axilla of the men for 15 minutes. The women were monitored for 72 hours after the transfer procedure. The transfer procedure led to a 13% increase in testosterone AUC (0 to 24 hours) in the women compared with baseline. Another study in men who received a 1% testosterone formulation topically revealed a 131% increase in testosterone AUC (0 to 72 hours) following direct skin-to-skin transfer compared with indirect (T-shirt) transfer [85].

f) Topical (solution), single-dose, effect of showering/washing (30 mg): up to 35% decreased exposure [85]

1) The effect of showering/washing on testosterone exposure was examined in a parallel design clinical study of healthy, premenopausal women (n=12). Subjects received testosterone 30 mg topically to one axilla and either washed with soap and water 2 or 6 hours later (n=6) or did not wash (n=6). Blood samples collected over 72 hours from all subjects revealed up to a 35% decrease in testosterone AUC (0 to 72 hours) in subjects who washed compared with subjects who did not wash. Patients should not swim or wash the application site for 2 hours following administration [85].

g) Topical (solution), single-dose, effect of deodorant/antiperspirant (30 mg): up to 33% decreased exposure [85]

1) In a parallel-group, clinical study on the effects of deodorant/antiperspirant use with testosterone topical solution, the testosterone AUC decreased up to 33% when a single-dose

of testosterone 30 mg topical solution was applied to the axilla of healthy premenopausal women 2 minutes after application of deodorant/antiperspirant spray (n=6) or stick (n=6) or deodorant spray (n=6) compared with the control group (n=6) [85].

B) Testosterone Enanthate

1) Therapeutic Drug Concentration

a) SubQ: 300 to 1100 nanograms/dL (approximately normal physiologic circulating testosterone ranges) [74]

1) SubQ administration of testosterone enanthate results in approximately normal physiologic concentrations of testosterone (300 to 1100 nanograms/dL) in healthy men [74].

2) The mean average concentration (0 to 168 hours) of total testosterone was 553 +/- 127 nanograms/dL following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks [74].

2) Peak Concentration

a) SubQ, multiple-dose: 790 nanograms/dL [74]

1) The mean Cmax of total testosterone was 790 +/- 215 nanograms/dL following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks [74].

2) Following weekly administration, the mean Cmax of testosterone enanthate was 169 +/- 68 nanograms/dL at week 12 [74].

3) Time to Peak Concentration

a) IM: 24 hours [206][207]

1) The mean peak testosterone serum concentration following the administration of intramuscular testosterone enanthate 200 mg in 7 hypogonadal subjects was 1233 +/- 484 nanograms/dL 24 hours after injection; this was an increase of 1138 nanograms/dL from a basal serum level of 95 +/- 10 nanograms/dL [206].

2) The mean peak testosterone serum concentration following the administration of intramuscular testosterone enanthate 200 mg in 7 eugonadal subjects was 1965 +/- 391 nanograms/dL 6 hours after injection; this was an increase of 1486 nanograms/dL from a basal serum level of 497 +/- 63 nanograms/dL. The mean peak testosterone serum concentration following the administration of intramuscular testosterone enanthate 100 mg in 7 eugonadal subjects was 1181 +/- 204.7 nanograms/dL 24 hours after injection; this was an increase of 669 nanograms/dL from a basal serum level of 521 +/- 51.2 nanograms/dL [206].

b) SubQ: 11.9 hours [74]

1) The Cmax of total testosterone occurred at a median Tmax of 11.9 hours post-dose (range, 5.8 to 168.7 hours) following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks. Steady state concentrations were achieved by week 6 [74].

4) Area Under the Curve

a) SubQ, multiple-dose: 92,955 nanograms x hr/dL [74]

1) The mean AUC(0 to 168 hours) of total testosterone was 92,955 +/- 21,385 nanograms x hr/dL following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks [74].

C) Testosterone Undecanoate

1) Therapeutic Drug Concentration

a) Oral Route

1) Hypogonadism, oral: 476 nanograms (ng)/dL [53]

a) The average serum testosterone concentrations over 24 hours following oral administration of 225 mg was 476 ng/dL [53].

2) Hypogonadism, oral: 403 nanograms (ng)/dL [57]

a) The average daily NaF-EDTA plasma testosterone concentration was 403 +/- 128 ng/dL at the end of treatment, where the normal eugonadal range in NaF-EDTA plasma was 252 to 907 ng/dL in this study. Hypogonadal males received testosterone capsules 158 to 395 mg orally twice daily for at least 105 days [57].

b) Intramuscular Route

1) Hypogonadism, IM: 300 to 1000 nanograms/dL (750 mg) [59]

a) Testosterone undecanoate 750 mg IM produces circulating testosterone levels consistent with normal concentrations in health men (300 to 1000 nanograms/dL) [59].

2) Peak Concentration

a) Oral route, multiple doses, 225 mg twice daily: 979 to 989 nanograms (ng)/dL[53]

1) Mean Cmax serum testosterone concentrations following morning and evening doses were 979 ng/dL and 989 ng/dL, respectively, with an observed median Tmax of 5 hours [53].

b) Oral route, multiple doses, 158 to 396 mg twice daily: 1008 nanograms (ng)/dL [57]

1) The mean Cmax was 1008 +/- 581 ng/dL in a study of hypogonadal males (N=151) receiving testosterone capsules 158 to 396 mg orally twice daily for at least 105 days [57].

c) IM, single dose: 90.9 nanograms/dL [59]

1) The mean testosterone undecanoate Cmax was 90.9 +/- 68.8 nanograms/dL, achieved 4 days after a testosterone undecanoate IM injection [59].

3) Time to Peak Concentration

a) Oral Route

1) Testosterone

a) Oral route: 5 hours [53]

1) Mean Cmax serum testosterone concentrations following morning and evening doses were 979 ng/dL and 989 ng/dL, respectively, with an observed median Tmax of around 5 hours [53].

b) Intramuscular Route

1) Testosterone Undecanoate

a) IM: 4 days [59]

1) The mean testosterone undecanoate Cmax was 90.9 +/- 68.8 nanograms/dL, achieved 4 days after a testosterone undecanoate IM injection [59].

2) Testosterone

a) IM: 7 days [59]

1) Serum testosterone concentrations reach maximum levels after a median of 7 days (range, 4 to 42 days) following a testosterone undecanoate 750 IM injection and then levels slowly decline [59].

ADME

Absorption

A) Testosterone

1) Bioavailability

a) Oral: absorbed from the GI tract, oral mucosa, and skin; however, the oral route of administration is not used due to almost complete first-pass hepatic metabolism [197].

1) A significant and reproducible rise in serum testosterone was detected following the ingestion of testosterone crystals in 26 male subjects [198].

b) Subcutaneous: slow [195].

1) Following subcutaneous implantations using testosterone pellets, absorption has been reported to be complete by day 189. The daily release rate is 1.18 mg per 200 mg pellet [195].

c) Sublingual (solution): decreases with increasing doses [189]

1) In a study with 16 premenopausal women, the bioavailability decreased with increasing doses of SL testosterone. Since there was no IV standard, investigators used the lowest dose (0.25 mg) as a reference value of 100%. The bioavailability of 0.5 mg and 0.75 mg doses were calculated as 69% and 58%, respectively [189].

d) Transdermal: good [84]

1) Transdermal testosterone, administered as two 2.5 mg/day patches, resulted in an average testosterone absorption of 4 to 5 mg over 24 hours in 34 hypogonadal men when applied to the abdomen, back, thighs, or upper arms. When applied to the chest or shins the average absorption rate was 3 to 4 mg over 24 hours. Similar concentration profiles were observed for the abdomen, back, thigh, and upper arm application sites while more interindividual variability was observed when transdermal testosterone was applied to the either the chest or shins. The table below describes the mean testosterone concentration for various application sites over 24 hours following a single-dose application of two 2.5 mg/day patches [84].

Sample Time (hour)	Abdomen (nanograms/dL)	Back (nanograms/dL)	Thigh (nanograms/dL)	Upper Arm (nanograms/dL)
0	90 +/- 82	80 +/- 74	85 +/-76	81 +/- 69
3	286 +/- 201	429 +/- 252	271 +/- 201	308 +/- 226
6	476 +/- 236	608 +/- 250	489 +/- 254	468 +/- 245
9	570 +/- 234	613 +/- 214	592 +/- 251	534 +/- 204
12	575 +/- 244	588 +/- 233	594 +/- 247	527 +/- 199
24	352 +/- 164	403 +/- 174	367 +/- 161	332 +/- 124

e) Topical (gel): approximately 10% [199][187]

1) Approximately 10% of the applied testosterone gel dose is absorbed during a 24-hour period [199][187].

B) Testosterone Cypionate

1) Bioavailability

a) absorbed slowly [83]

1) Testosterone esters in oil administered IM are absorbed slowly from the lipid phase, which permits dosing every 2 to 4 weeks [83].

C) Testosterone Enanthate

1) Bioavailability

a) Absorbed slowly [73]

1) Testosterone esters in oil administered IM are absorbed slowly from the lipid phase, which permits dosing every 2 to 4 weeks [73].

D) Testosterone Undecanoate

1) Effects of Food

a) Reduced exposure when administered without food [53]

1) Administration in fasting conditions reduced exposure (AUC) by approximately 38% when compared to administration with high-fat food [53].

b) Reduced exposure when administered with a lesser amount of food [57]

1) When testosterone oral capsules were administered with a 15 g fat breakfast, there was a 25% decrease in testosterone exposure compared with a 30 g breakfast [57].

Distribution

A) Distribution Sites

1) Testosterone

a) Protein Binding

1) Testosterone-estradiol binding globulin: 98% [200][201].

a) Testosterone is bound to specific testosterone-estradiol binding globulin. The remaining 2% of testosterone remains free in plasma, and the amount of free testosterone determines its half-life [193][200][201][187].

2) Sex hormone-binding globulin: 40% [22][84][28][85]

a) Approximately 40% of testosterone is bound to sex hormone-binding globulin. Approximately 2% is free or unbound, and the remainder is bound to albumin and other proteins [22][84][28][85].

2) Testosterone Cypionate

a) Protein Binding

1) 98% [83]

a) Testosterone is 98% bound to a specific testosterone-estradiol binding globulin [83].

b) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma [83].

3) Testosterone Enanthate

a) Protein Binding

1) Specific testosterone-estradiol binding globulin: 98% [73]

a) Testosterone is 98% bound to a specific testosterone-estradiol binding globulin [73].

b) Approximately 40% of testosterone is bound to sex hormone-binding globulin. Approximately 2% is free or unbound, and the remainder is bound to albumin and other proteins [74].

c) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma [73].

4) Testosterone Undecanoate

a) Protein Binding

1) Albumin, unknown amount; Sex hormone binding hormone, 40% [53][57][59]

a) Testosterone is mostly bound to sex binding hormone (40%) and albumin; 2% of testosterone is unbound and the rest is loosely bound to albumin and other proteins [53][57][59].

B) Distribution Kinetics

1) Volume of Distribution

a) 74.9 to 122.5 L/kg [202].

1) The Vd at steady state in 2 healthy subjects following a single intramuscular 25 mg injection of testosterone propionate was reported as 74.9 and 122.5 L/kg, respectively [202].

Metabolism

A) Metabolism Sites and Kinetics

1) Testosterone

a) Liver, extensive first-pass hepatic metabolism [28][200][201][85].

1) Testosterone administered orally is not recommended [197]. Testosterone is metabolized in the liver to various 17-ketosteroids via 2 different pathways. Glucuronic and sulfuric acid conjugates of testosterone are found in urine with approximately 6% of testosterone excreted unchanged in the feces [22][28][200][201].

2) Testosterone is primarily inactivated in the liver [22][28][85].

b) Liver, transbuccal delivery of testosterone circumvents first-pass metabolism [193].

2) Testosterone Cypionate

a) Liver: primary site [83]

1) Testosterone activity depends on reduction to dihydrotestosterone in responsive

tissues [83].

2) Inactivation of testosterone happens primarily in the liver [83].

3) Testosterone Enanthate

a) Liver: Primary site [74][73]

1) Testosterone enanthate is metabolized to testosterone by ester cleavage of the enanthate group. Testosterone is metabolized to various 17-ketosteroids via 2 different pathways [74].

2) Testosterone activity depends on reduction to dihydrotestosterone in responsive tissues [73].

3) Inactivation of testosterone happens primarily in the liver [74][73].

4) Testosterone Undecanoate

a) Serum esterases (testosterone undecanoate): Primary [53]

1) Testosterone undecanoate is metabolized to active testosterone via ester cleavage of the undecanoate group [53]

b) Liver: Primary (testosterone) [53]

1) Inactivation of testosterone (the active metabolite of testosterone undecanoate) occurs primarily in the liver [53].

B) Metabolites

1) Testosterone

a) Estradiol and dihydrotestosterone (DHT): active [22][84][28][85]

1) Estradiol and dihydrotestosterone (DHT) are the major active metabolites of testosterone [22][84][28][85][200][201][187]. DHT concentration was linearly related to testosterone concentration during treatment with testosterone topical solution via axillary administration [85].

2) The average DHT:T and E2:T ratios, respectively, were 1:10 and 1:200 during steady-state pharmacokinetic studies in hypogonadal men [84].

b) Testosterone glucuronic conjugate, activity unknown [200][201].

c) Testosterone sulfuric acid conjugate, activity unknown [200][201].

1) In addition to testosterone glucuronic and sulfuric acid conjugates, 17-ketosteroid metabolites of testosterone are produced by 2 different metabolic pathways in the liver [22][85][200][201][187].

d) Testosterone-19-d3, active [202]

1) Active metabolite of testosterone propionate [202]

2) Testosterone Enanthate

a) Dihydrotestosterone (major): Active [74]

1) Dihydrotestosterone (DHT) is a major active metabolite of testosterone [74].

2) Following weekly administration of testosterone enanthate, the mean DHT/testosterone ratio was within normal range (0.07) pre-dose of week 12 [74].

b) Estradiol (major): Active [74]

1) Estradiol is a major active metabolite of testosterone [74].

c) Testosterone glucuronic conjugate: [74][73] Unknown activity

d) Testosterone sulfuric acid conjugate: [74][73] Unknown activity

e) 17-ketosteroid metabolites of testosterone: Inactive [74][73]

1) In addition to testosterone glucuronic and sulfuric acid conjugates, 17-ketosteroid metabolites of testosterone are produced by 2 different metabolic pathways in the liver [74][73]

3) Testosterone Undecanoate

a) Testosterone: Active (major) [53][57][59]

1) Testosterone undecanoate is metabolized to testosterone by ester cleavage. Testosterone is metabolized to various 17-keto steroids through 2 different pathways to estradiol and dihydrotestosterone [53][57][59].

Excretion

A) Kidney

1) Testosterone

a) Renal Clearance (rate)

1) approximately 2 L/min [202].

a) Clearance in 2 healthy male subjects following a single 25 mg intramuscular injection of testosterone propionate was reported as 2317.4 and 1958.0 mL/min, respectively [202].

b) Renal Excretion (%)

1) 90% [22][84][88][200].

a) Following an intramuscular dose of testosterone, approximately 90% is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and testosterone metabolites [22][84][28][200][88][85].

2) Testosterone Cypionate

a) Renal Excretion (%)

1) 90% [83]

a) Approximately 90% of a testosterone dose is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and it's metabolites [83].

3) Testosterone Enanthate

a) Renal Excretion (%)

1) 90%, changed [74][73]

a) Following IM administration, approximately 90% of a testosterone dose is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and it's metabolites [74][73].

4) Testosterone Undecanoate

a) 90%, as conjugated metabolites [53][59]

1) Approximately 90% of an IM testosterone dose is excreted in the urine as glucuronic and sulfuric acid conjugates or other metabolites [53][59].

B) Feces

1) Testosterone

a) 6% [22][84][28][200][88][85]

1) Approximately 6% of a IM testosterone dose is excreted in feces, mainly in the unconjugated form [22][84][28][200][88][85].

2) Testosterone Cypionate

a) 6% [83]

1) Approximately 6% of a testosterone dose is excreted in the feces; the majority as the unconjugated form [83].

3) Testosterone Enanthate

a) 6%, mostly unchanged [74][73]

1) Following IM administration, approximately 6% of a testosterone dose is excreted in the feces; the majority as the unconjugated form [74][73].

4) Testosterone Undecanoate

a) 6% [53][59]

1) Approximately 6% of an IM testosterone dose is excreted in the feces as unconjugated testosterone [53][59].

Elimination Half-life

A) Parent Compound

1) Testosterone

a) 5.7 hours, buccal [192]; 2 to 3 hours, oral [188]; 70.8 days, subQ implanted pellet[195]; 49.7 to 58.5 minutes, sublingual (solution) [189];10 to 100 minutes [22] [84][199][204][201][85]

1) The mean half life of total testosterone following SL doses of 0.25 mg, 0.5 mg, and 0.75 mg in healthy premenopausal women (n=16) was 49.8 +/- 16 minutes, 49.7 +/- 22.4 minutes, and 58.5 +/- 24.6 minutes, respectively. The calculated half-life of total testosterone was significantly different only between the 0.5 mg and 0.75 mg doses (p=0.0125). The mean half life of free testosterone following SL doses of 0.25 mg, 0.5 mg, and 0.75 mg in healthy premenopausal women (n=16) was 42.3 +/- 14.6 minutes, 55.7 +/- 27.5 minutes, and 51.1 +/- 26.4 minutes, respectively. There was no statistical difference in half-life of free testosterone between the 3 doses [189].

2) The half-life of testosterone is highly variable, ranging from 10 to 100 minutes [22] [84][28][199][204][201][85]

3) The elimination half-life of buccal testosterone 30 milligrams given twice daily for 7 days to 12 testosterone-deficient men was 5.7 hours [192].

4) Two doses each of testosterone undecanoate 20, 40, and 80 milligrams were give 12 hours apart to 45 healthy women without childbearing potential. The baseline-corrected elimination half-lives for each dose were 2.35, 2.43, and 2.58 hours, respectively [188].

5) The terminal elimination half-life for subcutaneously implanted testosterone pellets is reported to be 70.8 days. Men with larger body mass apparently have a lower half-life [195].

2) Testosterone Cypionate

a) 10 to 100 minutes [83]

1) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma. The half-life of testosterone is variable, and can range from 10 to 100 minutes [83].

2) The amount of free testosterone (non-protein-bound) determines its half-life. The half-life of testosterone depends upon the route of administration and which testosterone ester is used; the half-life for intramuscularly administered testosterone cypionate is approximately 8 days [200].

3) Testosterone Enanthate

a) 10 to 100 minutes [73]

1) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma. The half-life of testosterone is variable, and can range from 10 to 100 minutes [73].

B) Metabolites

1) Testosterone Undecanoate

a) Testosterone

1) 10 to 100 minutes [53][59]

a) There is considerable variation in the half-life of testosterone, with reports ranging from 10 to 100 minutes [53][59].

PATIENT EDUCATION

Medication Counseling

No results available

Patient Handouts

A) Testosterone (Absorbed through the skin)
Testosterone

Treats low testosterone levels.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:
Patch

Your doctor will tell you how many patches to use, where to apply them, and how often to apply them. Do not use more patches or apply them more often than your doctor tells you to.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
Wash your hands with soap and water before and after applying a patch.
Leave the patch in its sealed wrapper until you are ready to put it on. Tear the wrapper open carefully. NEVER CUT the wrapper or the patch with scissors. Do not use any patch that has been cut by accident.
The patient instructions will show the body areas where you can wear the patch. When putting on each new patch, choose a different place within these areas. Do not put the new patch on the same place you wore the last one. Be sure to remove the old patch before applying a new one.
Apply the patch to clean, dry skin with very little hair, on your back, abdomen, upper arms, or thighs. Apply the patch at about the same time every night.
Do not put the patch over burns, cuts, or irritated skin. Do not put the patch on oily or sweaty skin or on a spot that might put extra pressure on it (such as over a joint).
Bathing or swimming should not affect the patch. However, wait at least 3 hours after you apply the patch before you wash the skin area or shower or swim. Heavy exercise and sweating may cause the patch to fall off.
If the patch becomes loose, smooth it down and press it back onto your skin. If the patch comes off before 12 o'clock noon, put on a new patch, and then replace the new patch at your regular time. If the patch comes off after noon, just wait and put on a new patch at your next regular time.
Do not tape the patch to your skin.
Missed dose: If you forget to wear or change a patch, put one on as soon as you can. If it is almost time to put on your next patch, wait until then to apply a new patch and skip the one you missed. Do not apply extra patches to make up for a missed dose.
Store the patches at room temperature in a closed container, away from heat, moisture, and direct light.
Fold the used patch in half with the sticky sides together. Throw any used patch away so that children or pets cannot get to it. You will also need to throw away old patches after the expiration date has passed.
Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Blood thinner (including warfarin)
Corticosteroid (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, cancer, diabetes, an enlarged prostate, heart disease, lung disease, sleep apnea, or a history of heart attack or stroke.
This medicine may cause the following problems:

Increased numbers of red blood cells
Increased risk of prostate cancer
Blood clot in your leg or lung
Increase risk of heart attack or stroke
Lower sperm count (with large doses)

The skin patch contains aluminum, which may cause skin burns if you have an MRI (magnetic resonance imaging) scan. You must remove the patch before an MRI.
This medicine is not indicated for use in women and should never be used by a pregnant woman.
This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain that may spread to your arms, jaw, back, or neck, trouble breathing, coughing up blood, unusual sweating, faintness
Chest pain, trouble breathing, or coughing up blood
Numbness or weakness on one side of your body, sudden or severe headache, problems with vision, speech, or walking
Pain, redness, or swelling in your arm or leg
Severe skin blisters, redness, swelling, or burning where the patch is applied
Swelling in your hands, ankles, or feet
Unusual bleeding or bruising

If you notice these less serious side effects, talk with your doctor:

Mild skin soreness, redness, itching, or irritation where the patch was applied
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.
B) Testosterone (Between cheek and gum)
Testosterone

Treats low testosterone levels. Testosterone is a male hormone.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:
Patch

Your doctor will tell you how much medicine to use. Do not use more than directed.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
This medicine looks like a tablet, but it sticks to your gum like a patch. To use the patch:

Put the flat side of the patch on your fingertip. Place the patch against your gum and to the left or right of your front teeth. Gently push it up as high as it will go. Then press on the patch from the outside of your lip for at least 30 seconds. The patch should stick to your gum.
Do not chew or swallow the patch.
Each time you put in a new patch, put it on the opposite side from where you put the last one.
Keep the patch in your mouth all the time, unless you are changing patches. Check to make sure

the patch is still in place after you eat or drink, use mouthwash, or brush your teeth.
To remove a patch, use your finger to gently loosen it. Then slide it down over your teeth and take it out.
Use this medicine 2 times a day, once in the morning and once in the evening (about 12 hours apart), unless your doctor tells you differently.

Missed dose: If the patch falls off within the first 8 hours, take it out and put in a new one. Put in the next patch at the regular time. If the patch falls off after more than 8 hours, take it out and put in a new one. This will count as your next dose, and the patch can stay in place for 12 hours.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Blood thinner (including warfarin)
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, diabetes, an enlarged prostate, heart disease, high cholesterol, sleep apnea, a history of heart attack or stroke.
This medicine may cause the following problems:

Increased risk of prostate cancer
Blood clot in your leg or lung
Possible increased risk of heart attack or stroke
Lower sperm count

This medicine is not indicated for use in women and should never be used by a pregnant woman.
This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain that may spread, trouble breathing, coughing up blood, unusual sweating, faintness
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, or feet

If you notice these less serious side effects, talk with your doctor:

Gum pain, tenderness, or swelling
More erections than usual or erections that last a long time
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.

C) Testosterone (By injection)

Testosterone

Treats low or no testosterone levels. Also treats breast cancer in women and delayed puberty in male teenagers.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. You should not receive it if you had an allergic reaction to testosterone, benzyl benzoate, refined castor oil, or sesame oil. A man should not receive this medicine if he has breast cancer, prostate cancer, or age-related hypogonadism. A woman should not receive this medicine if she is pregnant or breastfeeding.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into a muscle in the buttocks. Xyosted™ is given as a shot under your skin in the stomach area.
A nurse or other health provider will give you this medicine.
Xyosted™:
You may be taught how to give your medicine at home. Make sure you understand all instructions before giving yourself an injection. Do not use more medicine or use it more often than your doctor tells you to.
You will be shown the body areas where this shot can be given. Use a different body area each time you give yourself a shot. Keep track of where you give each shot to make sure you rotate body areas.
Check the liquid in the prefilled syringe or autoinjector. It should be colorless to slightly yellow. Do not use the medicine if the liquid is cloudy, discolored, or has particles in it.
Use a new needle and syringe each time you inject your medicine.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.
Missed dose: Call your doctor or pharmacist for instructions.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:
Oxyphenbutazone
Blood thinner (including warfarin)
Insulin or oral diabetes medicine
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:
It is not safe to take this medicine during pregnancy. It could harm an unborn baby. Tell your doctor right away if you become pregnant.
Tell your doctor if you have kidney disease, liver disease, lung disease, diabetes, an enlarged prostate, blood vessel or heart disease, heart failure, high cholesterol, lung disease, obesity, sleep apnea, or a history of heart attack or stroke.
This medicine may cause the following problems:
High blood pressure
Serious lung reaction called pulmonary oil embolism (may be life-threatening)
Increased risk of prostate cancer
Increased number of red blood cells
Blood clot in your leg or lung
Slow growth in children
Increased risk of heart attack or stroke

Liver problems
Changes in mood or behavior

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
This medicine may lower your sperm count (with large doses). Talk with your doctor before using this medicine if you plan to have children. Some men who use this medicine have become infertile (unable to have children).
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain, cough, trouble breathing, dizziness, tightening of your throat, unusual sweating
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, or feet
Unusual mood or behavior, thoughts of killing oneself
Unusual bleeding, bruising, or weakness

If you notice these less serious side effects, talk with your doctor:

Acne, hoarse voice, facial hair growth (women)
Changes in menstrual periods
More erections than usual or erections that last a long time
Pain, redness, or swelling where the shot was given
Swollen breasts (men)

If you notice other side effects that you think are caused by this medicine, tell your doctor.
D) Testosterone (By mouth)
Testosterone Undecanoate

Treats low or no testosterone levels.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone. Male patients who have breast cancer, prostate cancer, or age-related hypogonadism should not use this medicine. This medicine is not for use in women, especially if pregnant or breastfeeding.

How to Use This Medicine:
Capsule

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.
It is best to take this medicine with food or milk.
This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.
Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Blood thinner (including warfarin)
Pain or cold medicine
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have liver disease, kidney disease, heart or blood vessel disease, blood disease, lung disease, diabetes, an enlarged prostate, heart failure, obesity, sleep apnea, high cholesterol, thyroid problems, or a history of heart attack or stroke.
This medicine may cause the following problems:

High blood pressure
Increased number of red blood cells
Increased risk of prostate cancer
Blood clot in your leg or lung
Increased risk of heart attack or stroke
Liver problems
Changes in mood or behavior, including thoughts of suicide

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
This medicine may lower your sperm count (with large doses). Talk with your doctor before using this medicine if you plan to have children. Some men who use this medicine have become infertile (unable to have children).
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Bone or muscle pain
Change in how much or how often you urinate, trouble urinating
Chest pain, cough, trouble breathing, tightening of your throat, unusual sweating, bluish-colored skin
Confusion, constipation, dry mouth, weight loss
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Dizziness, lightheadedness, or fainting
Numbness or weakness in your arm or leg, or on one side of your body, pain in your lower leg, sudden or severe headache, problems with vision, speech, or walking
Rapid weight gain, swelling in your hands, ankles, or feet
Unusual mood or behavior, thoughts of killing oneself
Unusual bleeding, bruising, or weakness

If you notice these less serious side effects, talk with your doctor:

Enlarged, swollen, or painful breasts in men
More erections than usual or erections that last a long time
Runny or stuffy nose, sore throat

If you notice other side effects that you think are caused by this medicine, tell your doctor.

E) Testosterone (Into the nose)

Testosterone

Treats low testosterone levels. Testosterone is a male hormone.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:

Gel/Jelly

Your doctor will tell you how much medicine to use. Do not use more than directed.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
This medicine is for use only in the nose. Do not get any of it in your eyes or on your skin. If it does get on these areas, rinse it off right away.
To use:

Prime the pump the first time you use this medicine. To do this, hold the pump upside down over a sink, and slowly press the pump 10 times. Rinse the sink with warm water. Wipe the tip with a clean, dry tissue. The medicine is now ready to use.
If you get the medicine on your hands, wash them with warm water and soap.
Gently blow your nose to clear the nostrils.
Insert the tip of the pump into your left nostril and gently tilt it so that it touches the side of your nose. This will make sure the medicine is applied properly.
Slowly press the pump until it stops. Remove the tip from your nose.
Repeat these steps to apply the medicine into your right nostril.
After you use the pump, wipe the tip with a clean, dry tissue and put the cap back on.
Press your nostrils together just below the bridge of your nose and lightly rub them together.
Do not blow your nose or sniff for 1 hour after you use this medicine.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Other medicine that you use in your nose (including oxymetazoline)
Blood thinner (including warfarin)
Steroid (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, diabetes, an enlarged prostate, heart disease, high cholesterol, lung disease, sleep apnea, or a history of heart attack or stroke. Also tell your doctor if you have any nose or sinus problems, including allergies or history of nose or sinus surgery or a broken nose.
This medicine may cause the following problems:

Increased risk of prostate cancer
Blood clot in your leg or lung
Possible increased risk of heart attack or stroke
Lower sperm count

This medicine is not indicated for use in women and should never be used by a pregnant woman.
This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

APPELLEES' APPENDIX
VOLUME 3 OF 10 (Tabs 175-25 – 175-26)

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TAB 175-25 (continued)

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain that may spread, trouble breathing, coughing up blood, unusual sweating, faintness
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, legs, or feet

If you notice these less serious side effects, talk with your doctor:

More erections than usual or erections that last a long time
Runny or stuffy nose, sneezing, nosebleeds, or discomfort, scabbing, or dryness of your nose
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.
F) Testosterone (On the skin)
Testosterone

Treats low testosterone levels. Testosterone is a male hormone.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:
Gel/Jelly, Kit, Liquid

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.
This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.
Apply this medicine at the same time every day in the morning, unless your doctor tells you differently.
Apply the medicine to clean, dry, intact skin. Do not apply to skin that has a cut, scrape, or other injury.
Follow the manufacturer's directions on how to prime the pump before you use it the first time. Do not use the medicine that comes out during priming. Rinse it down the drain.
Gel:

Apply the gel only to your shoulders, upper arms, or thighs. Do not apply this medicine to your scrotum or penis.
Allow the gel to dry before you cover the area with clothing. Wait for at least 2 to 5 hours after you apply this medicine before you shower or swim.

Children and women should avoid contact with the unwashed or unclothed area where the testosterone gel has been applied. If another person accidentally gets this medicine on his or her skin, wash the area with soap and water right away.
Solution:

This medicine comes in 2 forms: a pump actuated metered dose bottle and a twist actuated metered dose bottle.
Apply an antiperspirant or deodorant spray at least 2 minutes before you apply this medicine.
Use an applicator to apply the solution to clean and dry underarms. Do not apply this medicine to any other part of your body.
Wipe any medicine that drips or runs with an applicator. Do not rub the solution with your fingers or hand.
Rinse the applicator cup with water and pat it dry with a tissue. Put the cup and cap back onto the pump actuated metered dose bottle. Put the lid back on the twist actuated metered dose bottle.
Allow the solution to dry for at least 3 minutes before you cover the area with clothing. Do not shower or swim for at least 2 hours.

Wash your hands with soap and warm water after you use this medicine.
If any medicine gets in your eyes, rinse them right away with water and call your doctor. Do not drink this medicine.
The medicine is flammable until it dries on the skin. Do not smoke or go near an open flame until the gel or solution has dried and you have covered the area with clothing.
Missed dose: Apply a dose as soon as you can. If it is almost time for your next dose, wait until then and apply a regular dose. Do not apply extra medicine to make up for a missed dose.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.
Throw away the empty pump, tube, or packet in a place where children and pets cannot reach it.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin, oxyphenbutazone
Blood thinner (including warfarin)
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, heart disease, lung disease, blood clotting problems, diabetes, an enlarged prostate, high cholesterol, sleep apnea, or a history of heart attack or stroke.
This medicine may cause the following problems:

Increased risk of prostate cancer
Blood clot in your leg or lung
Possible increased risk of heart attack or stroke
Lower sperm count
Liver problems

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Tell any doctor or dentist who treats you that you are using this medicine. This medicine may affect certain medical test results.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Changes in how much or how often you urinate, trouble urinating
Chest pain that may spread, trouble breathing, coughing up blood, unusual sweating, faintness
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, or feet

If you notice these less serious side effects, talk with your doctor:

More erections than usual or erections that last a long time
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.

TOXICOLOGY

Clinical Effects

No results available

Range of Toxicity

No results available

Treatment

No results available

ABOUT

How Supplied

No results available

Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

Testosterone
Testosterone, Micronized
Testosterone Cyp
Testosterone Cypionate
Testosterone Decanoate
Testosterone Enanthate
Testosterone Isocaproate
Testosterone Phenylpropionate
Testosterone Propionate
Testosterone Propionate, Micronized
Testosterone Undecanoate

C) Orphan Drug Status

1) Testosterone

a) This drug has one or more orphan drug designations, which may include approval or withdrawal of status; Access citation for FDA Orphan Drug Information [52]

2) Testosterone Cypionate

a) This drug has one or more orphan drug designations, which may include approval or withdrawal of status; Access citation for FDA Orphan Drug Information [52]

3) Testosterone Enanthate

a) This drug has one or more orphan drug designations, which may include approval or withdrawal of status; Access citation for FDA Orphan Drug Information [52]

D) Physicochemical Properties

1) Testosterone

a) Molecular Weight

1) 288.4 [85]; 288.42 [28]

2) Testosterone Cypionate

a) Molecular Weight

1) 412.61 [83]

b) Solubility

1) Testosterone cypionate is freely soluble in alcohol, chloroform, dioxane, ether, and vegetable oils, and is insoluble in water [83].

3) Testosterone Enanthate

a) Molecular Weight

1) 400.6 [73]

4) Testosterone Undecanoate

a) Molecular Weight

1) 456.7 [59]

Storage & Stability

A) Testosterone

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the compounding and administration of a hazardous topical drug, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator, and use eye/face and respiratory protection if not prepared in a control device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection, and if there is inhalation potential use respiratory protection [50].

b) Buccal mucosa route

1) Administration

a) The rounded side of the buccal system surface should be placed against the gum and held firmly in place with a finger over the lip for 30 seconds to ensure adhesion [23].

b) If the buccal system falls off during the first 8 hours after application, replace with a new system that should be retained until a total of 12 hours have elapsed from placement of the first system; then continue usual dosing schedule. If the buccal system falls off 8 or more hours after application, apply a new buccal system that may be retained for 12 hours; then continue usual dosing schedule [23].

c) The buccal system should not be chewed or swallowed. Remove system prior to oral care and apply a new system after [23].

c) Nasal route

1) Preparation

a) Prime the pump prior to the first use by depressing the pump 10 times, discarding initial drug delivered. Wash off the gel with warm water then wipe tip with clean, dry tissue. If the product comes into contact with hands, wash hands with soap and water [22].

2) Administration

a) Completely depress the pump 1 time in each nostril; do not apply to any other part of the body. To administer, blow nose, uncap pump, and place the finger on the actuator. Then insert pump until the finger reaches the bottom of the nose. Apply gel to lateral nasal wall and remove pump once fully depressed, wiping the tip along the inside of the lateral nostril. Press on the nostrils just below the bridge of the nose and lightly massage the applied product. Do not blow nose or sniff for 1 hour [22].

d) Topical application route

1) Axiron(R)

a) If using antiperspirant or deodorant stick, roll-on, or spray, apply these 2 minutes prior to the application of testosterone topical solution as part of a normal, consistent, daily routine [20].

b) When using for the first time, prime the pump by depressing the pump-actuated or by twisting the dose dial 3 times; discard product dispensed directly into a basin, sink, or toilet and then wash the liquid away thoroughly [20].

c) Pump actuated: After priming, depress the pump completely only 1 time each time (1 pump actuation equals 30 mg) [20].

d) Pump actuated: Apply using the applicator provided. Position the nozzle over the applicator cup and depress the pump fully once. Do not fill the cup with more than 30 mg (1 pump actuation) [20].

e) Twist actuated: After priming, completely twist (180 degree turn) the dose dial 1 time (1 twist actuation equals 30 mg). The applicator should be filled with no more than 30 mg (1 twist actuation). Dosing that requires greater than 1 twist actuation must be applied in increments of 30 mg [20]

f) Keep the applicator upright. Place it up into the axilla and wipe steadily down and up into the axilla. If the solution drips or runs, wipe it back up with the applicator cup. Do not rub the solution into the skin with fingers or hand [20].

g) Apply each morning to clean, dry, intact skin of the axilla. Do not apply to any other parts of the body. Allow each application site to dry completely prior to the next application (for higher doses) or dressing [20].

h) 30 mg, 1 pump or twist actuation: Apply once to 1 axilla only (left or right) [20].

i) 60 mg, 2 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla [20].

j) 90 mg, 3 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left or right axilla [20].

k) 120 mg, 4 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left axilla and 1 actuation to the right axilla [20].

l) After use, rinse the applicator under room temperature, running water, and then pat dry with a tissue. Place the applicator and cap on the bottle for storage [20].

m) Wash hands thoroughly with soap and water after applying testosterone topical solution [20].

n) Cover the application site with clothing or dressing after the solution has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [20].

o) Wait at minimum 2 hours prior to washing the application site or swimming [20].

p) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [20].

2) AndroGel(R)

a) Prime the AndroGel(R) pump by depressing the actuator 3 times while canister is in upright position. Safely discard the gel dispensed from the first 3 actuations. Priming is only necessary before the first dose [27][49].

b) Apply to clean, dry, intact skin of shoulder or upper arm that will be covered by clothing. For the 40.5 mg (2.5-g packets), squeeze a portion of the gel from the packet into the palm of hand and apply to application sites (as this size packet needs to be split between the left and right shoulder) and repeat until entire contents have been applied. The gel may be delivered from the actuator into the palm of one hand, then applied to the intended site, or may be applied directly from the pump to the intended application site [24][27][49].

c) Apply AndroGel(R) 1.62%, to the shoulder or upper arm (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to any other part of the body, including abdomen or genitals. Wait a minimum of 2 hours prior to washing the application site or swimming [49].

d) AndroGel(R) 1%, apply to the shoulder and upper arm and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to genitals. Avoid swimming or showering for at least 5 hours after application [51].

e) Patients should wash hands thoroughly with soap and water immediately after applying testosterone topical gel [27][49].

f) Cover the application site with clothing or dressing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [27][49].

g) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [27][49].

h) Children and women should avoid contact with unwashed or unclothed application site [27] [49].

i) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [27][49].

j) Application recommendations for AndroGel(R) 1.62% for pump or packets are in the table below [15]:

AndroGel(R) 1.62%						
Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Upper Arm and Shoulder		Total Packets *	Gel Applications per Upper Arm and Shoulder *	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0	One 1.25-g packet	One 1.25-g packet	0
40.5 mg	2	1	1	One 2.5-g packet	Half the contents of one 2.5-g packet	Half the contents of one 2.5-g packet
60.75 mg	3	2	1	One 1.25-g AND one 2.5-g packet	One 2.5-g packet	One 1.25-g packet
81 mg	4	2	2	Two 2.5-g packets	One 2.5-g packet	One 2.5-g packet
* Weight given as gel content of packet.						

k) Application recommendations for AndroGel(R) 1% 75-g pump are in the table below [5]:

Dosing Guidelines for the AndroGel(R) 1% 75-g Multi-Dose Pump	
Prescribed Testosterone Dose	Number of Pump Actuations
50 mg daily	4 pumps once daily
75 mg daily	6 pumps once daily
100 mg daily	8 pumps once daily

3) Fortesta(TM)

a) Prime the pump by depressing the actuator 8 times while canister is in upright position; safely discard the gel dispensed from the first 8 actuations; only necessary to prime pump before the first dose [21].

b) Apply to clean, dry, intact skin of the front and inner thighs; do not apply to genitals or other parts of the body; use one finger to apply gel [21].

c) After the application site is dry, site should be covered with clothing (with sufficient length to cover application site); wash hands thoroughly with soap and water after applying gel [21].

d) Children and women should avoid contact with unwashed or unclothed application site [21].

e) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [21].

f) If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [21].

g) Application recommendations for Fortesta(TM) are in the table below [21]:

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Thigh	
		Thigh #1	Thigh #2
10 mg	1	1	0
20 mg	2	1	1
30 mg	3	2	1
40 mg	4	2	2
50 mg	5	3	2
60 mg	6	3	3
70 mg	7	4	3

4) Testim(R)

a) Apply to clean, dry, intact skin of shoulder or upper arm; do not apply to genitals or abdomen. Wash hands thoroughly with soap and water immediately after applying [24].

b) Do not wash application site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [24].

c) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [24].

d) Children and women should avoid contact with unwashed or unclothed application site [24].

e) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [24].

5) Vogelxo(TM)

a) With multidose bottle, prime the pump 3 times before first use (discard any product released). Depress pump 4 times or empty entire contents of 1 unit-dose tube or packet into palm of the hand and immediately apply to clean, dry, intact skin of shoulder and upper arm. When the daily dosage is 100 mg, repeat on the opposite shoulder [25].

b) Do not apply to abdomen or genitals. Wash hands thoroughly with soap and water immediately after applying [25].

c) Do not wash site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [25].

d) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [25].

e) Children and women should avoid contact with unwashed or unclothed application site [25].

f) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [25].

e) Transdermal route

1) Administration

a) Immediately after opening the pouch, apply the adhesive side of the Androderm(R) system to the back, abdomen, upper arm, or thigh in a clean, dry area of the skin. Press system firmly in

place, ensuring good contact with the skin, especially around the edges. Avoid application to oily, damaged, or irritated skin. Do not apply to the scrotum, and avoid bony prominences or areas of prolonged pressure during sitting or sleeping [19].

b) Avoid swimming, showering, or washing the administration site for at least 3 hours after application [19].

c) Rotate application sites, with at least 7 days between applications to the same site [19].

B) Testosterone Cypionate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle; it is not for IV injection [83].

b) If crystals formed because product was stored at lower than recommended temperatures, they can be dissolved by warming or shaking the vial [83].

C) Testosterone Enanthate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle, avoiding intravascular injection. Crystals formed during storage at lower than recommended temperatures can be dissolved by warming or shaking the vial. A wet syringe or wet needle may turn the solution cloudy but does not affect product potency [73].

c) Subcutaneous route

1) Administration

a) Xyosted(TM) is for subQ injection in the abdominal region only. Avoid IM or intravascular injection. Do not use if the liquid in the syringe is cloudy or if visible particles are present; an air bubble is normal. Do not use if the seal is broken [74].

D) Testosterone Undecanoate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Preparation

a) Carefully remove gray plastic cap from vial; leave the aluminum metal ring and crimp seal around the gray rubber stopper [63].

b) Using an 18-gauge needle at a 45-degree angle with the bevel oriented upward, inject 3 mL of air through the gray rubber stopper to create positive pressure in the vial, and then withdraw 3 mL (750 mg) of solution [64].

c) Expel any air bubbles from the syringe and change the syringe needle to a new IM needle [63].

d) .

2) Administration

a) For IM use only [63]

b) Slowly (over 60 to 90 seconds) inject IM deep into the gluteal muscle; care must be taken to avoid intravascular administration as this may lead to pulmonary oil microembolism; also avoid the superior gluteal arteries and sciatic nerve [63].

c) Discard any unused portion [63].

d) Alternate injection sites between left and right buttock between consecutive injections [63].

c) Oral route

1) Administration

a) Give with food [53][57].

E) Testosterone

1) Buccal mucosa route

a) Patch, Extended Release

1) Store at 20 to 25 degrees C (68 to 77 degrees F). Protect from heat and moisture [108].

2) Intramuscular route

a) Solution

1) Store at room temperature. Warming and rotating the vial between hands will redissolve any crystals that may have formed when stored at lower temperatures [88].

3) Nasal route

a) Gel/Jelly

1) Store at a controlled room temperature between 20 and 25 degree C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [22].

4) Oral route

a) Capsule

1) Refrigerate between 2 and 8 degrees C before dispensing. Do not refrigerate after dispensing. The shelf life is 3 years before opening when stored between 2 and 8 degrees C and 90 days at room temperature after the container has been opened [208].

5) Topical application route

a) Gel/Jelly/Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [28][25]. Do not freeze [21].

2) Store upright at a controlled room temperature of 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [209][183].

6) Transdermal route

a) Patch, Extended Release

1) Store at 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [182].

F) Testosterone Cypionate

1) Injection route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F); protect from light [83].

G) Testosterone Enanthate

1) Intramuscular route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F). If crystals form, warm and rotate vial between palms of hands to dissolve [73].

2) Subcutaneous route

a) Solution

1) Store in original carton at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F). Protect from light; do not refrigerate or freeze [74].

H) Testosterone Undecanoate

1) Intramuscular route

a) Solution

1) Store in original carton at a controlled room temperature of 25 degrees C (77 degrees F) , with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Discard any unused portion [59].

2) Oral route

a) Capsule

1) Store at a temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Store in a dry place and protect from moisture [57].

b) Capsule, Liquid Filled

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [53].

Trade Names

No results available

Regulatory Status

No results available

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TAB 175-26

ESTRADIOL

DRUGDEX Evaluations

DOSING/ADMINISTRATION

Adult Dosing

Normal Dosage

Estradiol

Insertion, vaginal

Dyspareunia, Moderate to severe - Menopause

1) Imvexxy(TM)

a) Use lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Reevaluate periodically as clinically appropriate to determine if treatment is still necessary [5].

b) Initial dosage: 4 mcg intravaginally once daily at the same time each day for 2 weeks [5]

c) Maintenance dosage: 4 or 10 mcg intravaginally twice weekly (every 3 to 4 days); adjust dose based on clinical response [5]

d) Concomitant medication: Consider a progestin in postmenopausal women with a uterus to reduce the risk of endometrial cancer [5].

Oral route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The initial dose of oral estradiol for the treatment of moderate to severe vasomotor symptoms is 1 to 2 mg orally daily in a cyclical pattern (3 weeks on followed by 1 week off). Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [7].

Atrophic vulva (Moderate to Severe) - Menopause

1) The recommended initial dosing regimen is 1 to 2 mg orally daily in a cyclical pattern (3 weeks on, 1 week off). Adjust to the lowest dose as needed to control symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Attempt to taper or discontinue therapy at 3 to 6 month intervals [7].
2) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [7].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Initial dosage: 1 to 2 mg orally daily in a cyclical pattern (3 weeks on, 1 week off) [7]
2) Titration: Adjust dose as needed to control symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Attempt to taper or discontinue therapy at 3 to 6 month intervals [7].
3) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [7].
4) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [7].

Breast cancer, Metastatic; for palliation only

1) The dose of oral estradiol for the palliative treatment of breast cancer in appropriately selected women and men with metastatic disease is 10 mg orally 3 times daily for at least 3 months [7].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

1) The initial dose of oral estradiol for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is 1 to 2 mg orally daily. Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [7].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 2 to 6 mg orally daily with or without antiandrogens or gonadotropin-releasing hormone agonist [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Pl. Trial Ex. 026

Postmenopausal osteoporosis; Prophylaxis

1) The dose of oral estradiol for the prevention of postmenopausal osteoporosis is 0.5 mg orally daily for 23 days of a 28-day cycle. The lowest effective dose has not been established [7].
2) Postmenopausal women require an average of 1500 mg/day of elemental calcium. When calcium supplementation is not contraindicated, it may be useful for women with suboptimal dietary intake. Additionally, vitamin D supplementation of 400 to 800 international units daily may also be required to ensure adequate daily intake [7].
See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy

Prostate cancer, Advanced, Androgen-dependent; for palliation only

1) The dose of oral estradiol for the palliative treatment of advanced androgen-dependent prostate cancer is 1 to 2 mg orally 3 times daily. Determine the effectiveness of therapy by phosphatase levels as well as by symptomatic improvement [7].

Transdermal route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) Emulsion

a) The initial dose of estradiol topical emulsion for the treatment of moderate to severe vasomotor symptoms is one foil patch (1.74 g each) applied topically to clean, dry skin on each thigh daily for a total dose of 3.48 g (delivering 0.05 mg estradiol per day) [35].

2) Gel

a) Divigel(R)

1) Initial dosage: One 0.25 gram packet applied topically once daily, alternating between the right and left upper thigh. Apply to a 5x7-inch surface area and allow to dry before dressing. Do not wash application site within 1 hour after application [33].

2) Maximum dosage: Adjust dosage up to a MAX of 1.25 mg topically once daily as needed [33].

3) Treatment duration: Use the lowest effective dose for the shortest duration consistent with therapy goals [33]

b) Elestrin(R)

1) Initial dosage: Apply 0.87 g (1 pump, which delivers 0.52 mg estradiol) topically once daily via the metered-dose pump in a thin layer to the upper arm and shoulder area (approximately 320 cm(2)); adjust dose based on clinical response [34].

2) Treatment duration: Use the lowest effective dose for the shortest duration consistent with therapy goals [34]

c) Estrogel(R)

1) The initial dose of estradiol topical gel 0.06% (Estrogel(R)) for the treatment of moderate to severe vasomotor symptoms is 1.25 g/day (which delivers 0.75 mg estradiol) applied topically via the metered-dose pump to clean, dry, unbroken skin on the arm. Apply in a thin layer from wrist to shoulder and allow gel to dry for up to 5 minutes before dressing [13].

3) Patch
Initial dose: Outlined in the following table [29][19][8][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Minivelle(R)	0.0375 mg/day applied to the skin twice weekly	lower abdomen (below the umbilicus) or buttocks
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen

Dosage titration: Adjust dose based on clinical response, use lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10].
Alternative dose schedule: Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][12].

a) Switching from other formulations: Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be

initiated 1 week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than 1 week [8][12].

4) Spray

a) The initial dose of transdermal estradiol spray for the treatment of moderate to severe vasomotor symptoms is one spray (delivering 1.53 mg estradiol) applied to the forearm every morning. Dosage adjustment should be guided by the clinical response of the patient. If needed, the dose may be increased to 2 or 3 sprays daily based upon clinical response [36].

Atrophic vulva (Moderate to Severe) - Menopause

1) Gel

a) Apply 1.25 g/day (which delivers 0.75 mg estradiol) topically via the metered-dose pump to clean, dry, unbroken skin on the arm. The gel should be applied in a thin layer from wrist to shoulder and allowed to dry for up to 5 minutes before dressing. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [13].

b) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [13].

2) Patch

The initial dose of transdermal estradiol patches for the treatment of vulvar atrophy is outlined in the following table [19][8][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust dose based on clinical response, use the lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10][8][9][11][12].

Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [9][11][12].

a) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19] [8][9][11][12].

b) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Gel

a) Usual dosage: Apply 1.25 g/day (which delivers 0.75 mg estradiol) topically via the metered-dose pump to clean, dry, unbroken skin on the arm. The gel should be applied in a thin layer from wrist to shoulder and allowed to dry for up to 5 minutes before dressing. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [13].

b) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [13].

c) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [13].

2) Patch

Initial dosage is provided in the following table [19][8][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip

Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust dose based on clinical response, use the lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10][9][11][12].
Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [9][11][12].

a) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19][8][9][11][12].

b) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [19][8][9][11][12].

c) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

The initial dose of transdermal estradiol patches for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is outlined in the following table [19][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen

Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [19][8][9][11][12]. Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][9][11][12].
1) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 0.025 to 0.2 mg/day transdermally with or without antiandrogens or gonadotropin-releasing hormone agonist; replace patch every 3 to 5 days [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Postmenopausal osteoporosis; Prophylaxis

Initial dose: Outlined in the following table [29][19][8][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.025 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks

Minivelle(R)	0.025 mg/day applied to the skin twice weekly	lower abdomen (below umbilicus) or buttocks
Vivelle-Dot(R)	0.025 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust according to severity of symptoms, response of the patient, biochemical markers, and measurements of bone mineral density. Adjust to lowest dose that will provide effective control [8][12].
May be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][12].
1) Concomitant therapy: Postmenopausal women require an average of 1500 mg/day of elemental calcium. When calcium supplementation is not contraindicated, it may be useful for women with suboptimal dietary intake. Additionally, vitamin D supplementation of 400 to 800 international units daily may also be required to ensure adequate daily intake [8][12].
2) Switching from other formulations: Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated 1 week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than 1 week [8][12].
See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy

Vaginal route

Atrophic vulva (Moderate to Severe) - Menopause

1) The recommended dose of estradiol vaginal cream is 2 to 4 g vaginally daily for 1 or 2 weeks, then gradually reduced to 50% of initial dose for a similar period. A maintenance dose of 1 g, administered 1 to 3 times a week, may be used after vaginal mucosa has been restored. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [14].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Vaginal Cream

a) Initial dosage: 2 to 4 g vaginally daily for 1 or 2 weeks, then gradually reduced to 50% of initial dose for a similar period [14].

b) Maintenance dosage: 1 g, administered 1 to 3 times a week, may be used after vaginal mucosa has been restored. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [14].

c) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [14].

2) Vaginal Ring

a) Usual dosage: 1 ring inserted as deeply as possible into the upper one-third of the vagina vault. The ring is to remain in place continuously for 3 months and then be removed. Replace with a new ring if additional therapy is appropriate. Attempt to taper or discontinue at 3 to 6 month intervals [15].

b) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [15].

3) Vaginal Insert

a) Initial dosage: 1 vaginal insert (10 mcg) inserted vaginally once daily for 2 weeks, preferably at the same time each day. The recommended maintenance dose is 1 vaginal insert 10 mcg twice weekly. Reevaluate treatment, and attempt to taper or discontinue periodically [16].

Menopause - Urethral atrophy (Moderate to Severe)

1) The recommended dose of estradiol vaginal ring is 1 ring (contains 2 mg estradiol) inserted as deeply as possible into the upper one-third of the vagina vault. The ring is to remain in place continuously for 3 months and then be removed. Replace with a new ring if additional therapy is appropriate. Attempt to taper or discontinue at 3- to 6-month intervals [15].

General Dosage Information

a) In postmenopausal women with a uterus, initiate progestin with estrogen to reduce the risk of endometrial cancer [34][19][8][12][7][38][13][14][15][35][36]; women with a history of hysterectomy and endometriosis may need a progestin [34][16][29].

b) Use estrogen, alone or with a progestin, at the lowest effective dose and for the shortest duration consistent with individual treatment goals and risks; reevaluate periodically (generally at 3 to 6 month intervals) to determine if treatment is still necessary [34][16][29][19][8][12][7][38][13][14][15][35][36].

Estradiol Acetate

Vaginal route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) Usual dose: 0.05 mg/day inserted intravaginally every 3 months, dose adjusted based on clinical response [59]
2) Use the lowest effective dose for the shortest duration consistent with treatment goals; reevaluate periodically to determine if treatment is necessary [59].
3) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. Women without a uterus generally do not need progestin therapy [59].

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

1) Usual dose: 0.05 mg/day ring inserted intravaginally every 3 months and dose adjust based on clinical response [59]
2) Use the lowest effective dose for the shortest duration consistent with treatment goals, and reevaluate periodically to determine if treatment is necessary [59].
3) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. Women without a uterus generally do not need progestin therapy [59].

Estradiol Cypionate

Intramuscular route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The usual dose of estradiol cypionate for the treatment of moderate to severe vasomotor symptoms associated with menopause is 1 to 5 milligrams injected intramuscularly every 3 to 4 weeks [55].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [55].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [55].

Decreased estrogen level - Female hypogonadism syndrome

1) The dose of estradiol cypionate for the treatment of hypoestrogenism due to hypogonadism is 1.5 to 2 milligrams injected intramuscularly at monthly intervals [55].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [55].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [55].

Gender dysphoria - Male-to-female transsexual

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Estradiol Valerate

Intramuscular route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The dose of estradiol valerate for the treatment of moderate to severe vasomotor symptoms associated with menopause is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

1) The usual dose for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals

and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

1) The dose of estradiol valerate for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 5 to 30 mg IM every 2 weeks OR 2 to 10 mg IM every week with or without antiandrogens or gonadotropin-releasing hormone agonist [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hormone sensitive prostate cancer, Advanced, for palliation only

1) The dose of estradiol valerate for the palliative treatment of advanced androgen-dependent prostate cancer is 30 milligrams or more injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 1 or 2 weeks [57].

Dosage in Renal Failure

A) No specific recommendations are available [10].

Dosage in Hepatic Insufficiency

A) Use is contraindicated in patients with hepatic impairment or disease [10].

Dosage in Other Disease States

A) Cardiovascular Disorders

1) Immediately discontinue estrogen with or without progesterone therapy immediately if DVT, pulmonary embolism, stroke, or myocardial infarction occurs [10].

B) Cholestatic Jaundice

1) Discontinue use if reoccurs [10]

C) Fluid Retention

1) Discontinue use if medically concerning [10]

D) Hypercalcemia

1) Discontinue use if occurs [10]

E) Pancreatitis

1) Discontinue use if occurs [10]

F) Visual Abnormalities

1) Permanently discontinue use if papilledema or retinal vascular lesions occur [10].

Pediatric Dosing

Normal Dosage

Estradiol

Oral route

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage, Adolescents

a) Induction of female puberty: Initial, 5 mcg/kg/day orally for 6 months; increase dose by 5 mcg/kg/day every 6 months to an adult dosage of 2 to 6 mg/day [1]

b) Postpubertal transgender female: Initial, 1 mg/day orally for 6 months, then 2 mg/day [1]

c) Maintenance dosage: Adjust to mimic physiological estradiol levels [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Transdermal route

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage, Adolescents

a) Induction of female puberty: Initial, 6.25 to 12.6 mcg/24 hours applied every 3.5 days; increase dosage by 12.5 mcg/24 hours every 6 months to adult dosage of 50 to 200 mcg/24 hours to mimic physiological estradiol levels [1]

b) Maintenance dosage: Adjust to mimic physiological estradiol levels [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

General Dosage Information

a) Safety and efficacy in pediatric patients have not been established [34][16][29][19][41][7][13][38][8][12][35][36][14][15].

Estradiol Acetate

1) Safety and efficacy of the vaginal ring and oral tablets has not been established in pediatric patients [59][61].

Estradiol Valerate

1) Safety and efficacy not established in pediatric patients [58].

FDA Uses

Estradiol

Abnormal vasomotor function (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral tablets, topical gel and emulsion, transdermal patch and spray); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol oral tablets, transdermal patches, transdermal spray, topical gel, and topical emulsion are indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause [34][33][29][19][7][8][12][36][13][35].

Evidence

Estradiol oral tablets, transdermal patches, transdermal spray, topical gel, and topical emulsion have been shown to be effective [34][33][29][19][7][8][12][36][13][35] Transdermal estrogen use in postmenopausal women was not associated with an increased risk of VTE compared with oral estrogen in the ESTHER study [37].

c) Adult:

1) Transdermal versus Oral

a) Results from the Estrogen and Thromboembolism Risk (ESTHER) study indicate that transdermal estrogen use is not associated with an increased risk of VTE among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy. The multicenter, case-control study enrolled 271 consecutive cases of first documented episodes of idiopathic VTE and 610 matched community and hospital controls. The majority of current users of estrogen received 17-beta-estradiol. After adjusting for confounding factors, the odds ratios (OR) of VTE in current users of oral estrogen was 4.2 (95% CI, 1.5 to 11.6) compared with nonusers. The OR in current users of transdermal estrogen was 0.9 (95% CI, 0.4 to 2.1) compared with nonusers. Additionally, there was no significant association of VTE with the use of micronized progesterone or pregnane derivatives (including medroxyprogesterone acetate) while there was a 4-fold increase in OR of VTE (OR 3.9; 95% CI, 1.5 to 10) among users of norpregnane derivatives (nomegestrol acetate or promegestone). Stratification by dose and duration of estrogen therapy revealed similar

results. There was no association between past estrogen use and VTE risk (OR, 1.1; 95% CI, 0.6 to 1.7) [37].

2) Transdermal Emulsion

a) Estradiol topical emulsion was statistically better than placebo at 4 and 12 weeks for relief of both the frequency and severity of moderate to severe vasomotor symptoms [35]. Postmenopausal women (n=200; mean age 52 years) were randomized to receive estradiol topical emulsion 3.45 g (containing 2.5 mg of estradiol per g) or placebo daily for 12 weeks. Mean change in the number of hot flashes and mean change in severity score from baseline is summarized below:

	EstraSorb(R) 3.45 g/day	Placebo
Number of Daily Hot Flushes (Intent-to-Treat Population)		
Baseline Mean	13.05	13.63
Week 4 Mean	4.42	7.46
Mean Change at Week 4	-8.56 p less than 0.001	-5.97
Week 12 Mean	2	5.88
Mean Change at Week 12	-11.11 p less than 0.001	-7.2
Severity Score of Daily Hot Flushes (Intent-to Treat-Population, Most Recent Value Carried Forward)		
Baseline Mean	2.36	2.44
Week 4 Mean	1.47	1.99
Mean Change at Week 4	-0.89 p less than 0.001	-0.45
Week 12 Mean	0.92	1.88
Mean Change at Week 12	-1.44 p less than 0.001	-0.55

3) Transdermal Gel

a) Significant reductions in the daily mean frequency and severity of moderate to severe hot flushes were observed at 5 and 12 weeks with estradiol topical gel (Elestrin(R)) 0.87 g/day compared with placebo during a randomized 12-week trial involving postmenopausal women (n=484; mean age, 54 years; age range, 28 to 74 years). Following amendment to identify the lowest effective dose, patients were randomized to Elestrin(R) 0.87 g (containing 0.52 mg estradiol), 1.7 g (containing 1.04 mg estradiol) or placebo topically once daily for 12 weeks. The change from baseline in the mean daily frequency and severity of hot flushes is summarized in the following table [34].

	Elestrin(R) 0.87 g/day (n=136)	Elestrin(R) 1.7 g/day (n=142)	Placebo (n=137)
Frequency of Daily Hot Flushes			
Baseline (mean)	13.3	13.1	13.5
Week 4 (mean change)	-6.5*	-8	-5.1
Week 5 (mean change)	-7.5	-8.8	-5.1
Week 12 (mean change)	-8.5	-10	-5.4
Severity Score of Daily Hot Flushes			
Baseline Mean	2.4	2.4	2.4
Week 4 (mean change)	-0.5*	-0.7	-0.2
Week 5 (mean change)	-0.5	-0.8	-0.2
Week 12 (mean change)	-0.8	-1.2	-0.3
Key: *p-value non-significant			

b) Statistically significant reductions in the daily median frequency and severity of moderate to severe hot flushes were observed in patients receiving estradiol 0.1% topical gel (Divigel(R)) compared with placebo during a randomized, double-blind, 12-week trial involving postmenopausal women (n=495; mean age 54.6 years) [38]. Patients were randomized to Divigel(R) 0.25 g, 0.5 g, 1 g (containing 0.25, 0.5, and 1 mg estradiol, respectively) or placebo once daily to the thigh for 12 weeks. The change from baseline in the median daily frequency and severity of hot flushes is summarized in the following table:

	Divigel(R) 0.25 g/day	Divigel(R) 0.5 g/day	Divigel(R) 1 g/day	Placebo
Frequency of Daily Hot Flushes				
Baseline Median	9.72	9.24	9.64	9.32
Median Change at Week 4	-5 p=0.132	-5.73 p=0.011	-7.2 p less than 0.001	-3.63
Median Change at Week 7	-6.62 p less than 0.001	-7.14 p less than 0.001	-7.71 p less than 0.001	-4.37
Median Change at Week 12	-6.88 p less than 0.001	-7.29 p less than 0.001	-8.35 p less than 0.001	-4.48
Severity of Daily Hot Flushes				
Baseline Median	2.52	2.51	2.52	2.54
Median Change at Week 4	-0.07 p=0.283	-0.18 p less than 0.001	-0.47 p less than 0.001	-0.04
Median Change at Week 7	-0.24 p less than 0.001	-0.46 p less than 0.001	-1.06 p less than 0.001	-0.06
Median Change at Week 12	-0.33 p=0.021	-0.56 p=0.002	-1.69 p less than 0.001	-0.13

c) Statistically significant reductions in the daily mean frequency and severity of moderate to severe hot flushes were observed at 4 and 12 weeks in patients receiving estradiol 0.06% topical gel (EstroGel(R)) compared with placebo during a randomized 12-week trial involving postmenopausal women (n=145) [13]. Patients were randomized to EstroGel(R) 1.25 g (containing 0.75 mg estradiol) or placebo once daily for 12 weeks. The change from baseline in the mean daily frequency and severity of hot flushes is summarized in the following table:

	EstroGel(R) 1.25 g/day	Placebo
Frequency of Daily Hot Flushes		
Baseline Mean	10.33	11.01
Week 4 Mean	4.43	5.95
Mean Change at Week 4	-5.91 p=0.019	-5.06
Week 12 Mean	2.79	5.17
Mean Change at Week 12	-7.55 p=0.043	-5.84
Severity Score of Daily Hot Flushes		
Baseline Mean	2.36	2.3
Week 4 Mean	1.73	2
Mean Change at Week 4	-0.63 p=0.005	-0.31
Week 12 Mean	1.33	1.76
Mean Change at Week 12	-1.03 p less than 0.001	-0.54

4) Transdermal Patch

a) Transdermal estradiol patches (Alora(R)) were superior to placebo at 4 and 12 weeks for relief of the frequency and severity of vasomotor symptoms in a randomized, double-blind trial involving 268 postmenopausal women [8]. Women having estradiol and follicle stimulating hormone (FSH) serum concentrations in the postmenopausal range and who experienced an average of at least 60 moderate to severe hot flushes per week were randomized to either Alora(R) 0.05 or 0.01 milligram/day twice a week or placebo for 12 weeks. The mean changes in frequency of vasomotor symptoms from baseline are summarized below:

Week of Therapy	Alora(R) 0.05 mg/day	Alora(R) 0.1 mg/day	Placebo
Baseline mean frequency of moderate to severe vasomotor symptoms	90	85	92
4 Week mean change from baseline*	-57	-70	-45
8 Week mean change from baseline	-65	-77	-49
12 Week mean change from baseline*	-68	-79	-54

* Indicates a statistically significant difference between both treatment groups and placebo using an ANCOVA model

b) Transdermal estradiol (Climara(R)) 0.05 and 0.1 mg patches were statistically superior to placebo for the relief of the frequency of hot flushes in a randomized controlled trial involving 214 postmenopausal women. Women who experienced a minimum of 5 moderate to severe hot flushes per week or a minimum of 15 hot flushes of any severity per week, for 2 consecutive weeks, were randomized to treatment with 0.05 mg estradiol patch, 0.1 mg estradiol patch, or placebo in a cyclical regimen for 11 weeks. Data were available from 191 patients for efficacy analysis. In the 0.05 mg estradiol group, the mean weekly hot flush rate across all treatment cycles decreased from 46 at baseline to 20. In the 0.1 mg estradiol group, the mean weekly hot flush rate across all treatment cycles decreased from 52 at baseline to 16. The mean weekly hot flush rate in the placebo group declined from 53 at baseline to 46. Compared with placebo, both estradiol treatment groups demonstrated a statistically significant greater mean decrease in hot flushes across all treatment cycles (p less than 0.05) [19].

c) Transdermal estradiol (Climara(R)) 0.025 mg/day was superior to placebo at 4 and 12 weeks for relief of the frequency and severity of moderate to severe vasomotor symptoms in a randomized, double-blind trial involving 187 postmenopausal women. Women were randomized to Climara(R) 0.025 mg/day or placebo continuously for up to three 28-day cycles. The mean changes in frequency of vasomotor symptoms from baseline are summarized below [19]:

Week of Therapy	Climara(R) 0.025 mg/day	Placebo
4 Week Mean Change*	-6.45 (p less than 0.002)	-5.11
8 Week Mean Change*	-7.69	-5.98
12 Week Mean Change*	-7.56 (p less than 0.003)	-5.98
*: from baseline in the number of moderate-to-severe vasomotor symptoms		

d) Transdermal estradiol (Vivelle(R)) 0.075 and 0.1 mg patches were superior to placebo in relieving vasomotor symptoms at week 4 and in maintaining relief through weeks 8 and 12 during two controlled trials (n=356) [11][12]. The original study demonstrated that the 0.0375 and 0.05 mg patches did not differ from placebo until approximately week 6, therefore, an additional 12-week placebo-controlled trial involving 255 postmenopausal women was performed with the intention of identifying the efficacy of the 0.0375 mg patch. The 0.0375 mg patch was superior to placebo in reduction of frequency and severity of hot flushes at week 4 and maintained efficacy through weeks 8 and 12. Results with regard to the mean change in mean number of daily hot flushes are summarized in the following table:

Mean change number of hot flushes	Vivelle(R) 0.0375 mg/day	Placebo
Week 4	-8.4 p less than 0.05	-4.9
Week 8	-9.4 p less than 0.05	-5.8
Week 12	-9.8 p less than 0.05	-6.6

e) Transdermal estradiol (Estraderm(R)) was compared with conjugated estrogens in a controlled study involving 124 postmenopausal patients [20]. All patients were receiving conjugated estrogens prior to admission to the study; patients were then randomized to either continue conjugated estrogens or receive 0.1 mg daily of estradiol transdermally for 3 weeks. Doses of conjugated estrogens ranged from 0.625 to 1.25 mg daily. The estradiol system appeared equally effective as conjugated estrogens in controlling postmenopausal symptoms (hot flashes, sweating, headache, insomnia, vaginal discomfort, urge to urinate). Spotting or bleeding tendencies and breast tenderness were similar in both groups, and side effects were similar (less than 10%). However, skin irritation and rash occurred in several patients receiving the transdermal estradiol system, resulting in withdrawal of 13 patients from the study. No clinically significant differences were found in hemostatic parameters between women receiving transdermal estradiol or oral conjugated estrogens [21]. Similar results were observed with oral conjugated estrogens 0.3 mg per day or an estradiol patch delivering 0.025 mg/day for 12 weeks in 193 postmenopausal women [22].

5) Transdermal Spray

a) Estradiol transdermal spray was found to be an effective treatment for vasomotor symptoms in a 12-week, double-blind, randomized trial involving 454 postmenopausal women (mean age, 53 years) [36]. Patients were randomized to at least one dose of the transdermal spray (1, 2, or 3 sprays delivering 1.53 mg of estradiol/spray) or placebo. At baseline, the mean total frequency of moderate to severe vasomotor symptoms was 56 or more per week (8 or more per day). Efficacy was considered clinically and statistically significant when a difference of at least 2/day or 14/week reduction in hot flush frequency was achieved and when a statistically significant

reduction in severity occurred with estradiol spray compared with placebo. At weeks 4 and 12, 1 to 3 sprays of estradiol was superior to placebo in terms of frequency and severity of hot flushes.

	1 spray/day	2 sprays/day	3 sprays/day
Frequency of Daily Hot Flushes			
Baseline Median (estradiol, placebo)	11.81, 12.41	12.66, 12.13	10.78, 12.55
Mean Change at Week 4 (estradiol, placebo)	-6.26, -3.64 p=0.001	-7.30, -4.74 p=0.0027	-6.64, -4.54 p=0.0002
Mean Change at Week 12 (estradiol, placebo)	-8.10, -4.76 p=0.0004	-8.66, -6.19 p=0.0099	-8.44, -5.32 p less than 0.0001
Severity of Weekly Hot Flushes			
Baseline Median (estradiol, placebo)	2.53, 2.55	2.54, 2.54	2.58, 2.54
Mean Change at Week 4 (estradiol, placebo)	-0.47, -0.19 p=0.0573	-0.57, -0.25 p=0.016	-0.43, -0.13 p=0.0031
Mean Change at Week 12 (estradiol, placebo)	-1.04, -0.26 p less than 0.0001	-0.92, -0.54 p=0.0406	-1.07, -0.31 p less than 0.0001

6) Vaginal

a) An estradiol vaginal ring delivering 50 or 100 mcg of estradiol daily was effective in reducing the number and severity of vasomotor symptoms and improving urogenital symptoms, compared with placebo. In a double-blind trial, women with moderate to severe vasomotor symptoms were randomized to a vaginal ring delivering 50 mcg estradiol (n=113), or 100 mcg estradiol (n=112), or a placebo vaginal ring (n=108) daily for 13 weeks. Vasomotor symptoms significantly improved in both treatment groups compared with placebo (p less than 0.05). There was a trend toward greater improvement in patient assessment of urogenital signs with active treatment compared with placebo. For women with vaginal atrophy, the maturation index improved significantly in both the 50 and 100 mcg treatment groups compared with placebo (p=0.008 and p=0.003, respectively). Scores for climacteric symptoms also improved significantly (p less than 0.05) for both treatment groups compared with placebo. The vaginal rings were well tolerated [39]. Similar results were noted in a prospective, multicenter, randomized, double-blind trial comparing estradiol vaginal ring (delivering 50 mcg/day) with oral estradiol (1 mg/day). A total of 159 postmenopausal women were randomized to treatment for 24 weeks. Significant improvement in climacteric symptoms scores were noted at 12 and 24 weeks in both treatment groups (p less than 0.05). There was also significant improvement in scores of anxiety, depression, and sexual dysfunction for both groups (p less than 0.05). The frequency of hot flushes was significantly reduced (p less than 0.001) for both groups at 12 and 24 weeks. No significant between-group differences were noted [40].

Atrophic vulva (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral tablet, EstroGel(R), transdermal patch, vaginal cream); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol oral tablets, EstraGel(R), transdermal patches, and vaginal cream are indicated for the treatment of moderate to severe symptoms of vulvar atrophy associated with menopause [19][7][13][8][9][11][12][14]

Limitation of Use

When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19][7][13][8][9][11][12]

Atrophy of vagina (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral tablet, EstroGel(R), transdermal patch, vaginal formulations); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol oral tablets, topical gel EstroGel(R), transdermal patches, and vaginal cream, ring, and inserts are indicated for the treatment of moderate to severe symptoms of vaginal atrophy associated with menopause [16][19][7][13][8][9][11][12][14][15].

Limitation of Use

When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19][7][13][8][9][11][12]

c) Adult:

1) Transdermal

a) Transdermal estradiol (Alora(R)) improved vaginal atrophy in a placebo-controlled trial. Postmenopausal women were treated with transdermal estradiol 0.05 mg/day (n=54), transdermal estradiol 0.1 mg/day (n=45), or placebo (n=46). Vaginal cytology was obtained before treatment and at the last visit. The mean increase in superficial cells was 18.7%, 23.7%, and 8.7% for the estradiol 0.05 mg/day, 0.1 mg/day, and placebo groups, respectively. Additionally, corresponding reductions in basal/parabasal and intermediate cells were also noted [8].

b) Transdermal estradiol (Estraderm(R)) was compared with conjugated estrogens in a controlled study involving 124 postmenopausal patients [20]. All patients were receiving conjugated estrogens prior to admission to the study; patients were then randomized to either continue conjugated estrogens or receive 0.1 mg daily of estradiol transdermally for 3 weeks. Doses of conjugated estrogens ranged from 0.625 to 1.25 mg daily. The estradiol system appeared equally effective as conjugated estrogens in controlling postmenopausal symptoms (hot flashes, sweating, headache, insomnia, vaginal discomfort, urge to urinate). Spotting or bleeding tendencies and breast tenderness were similar in both groups, and side effects were similar (less than 10%). However, skin irritation and rash occurred in several patients receiving the transdermal estradiol system, resulting in withdrawal of 13 patients from the study. No clinically significant differences were found in hemostatic parameters between women receiving transdermal estradiol or oral conjugated estrogens [21]. Similar results were observed with oral conjugated estrogens 0.3 mg per day or an estradiol patch delivering 0.025 mg/day for 12 weeks in 193 postmenopausal women [22].

2) Vaginal

a) After 12 weeks of treatment, estradiol 10 mcg vaginal inserts were significantly superior to placebo in decreasing the severity of a composite score of most bothersome symptoms associated with atrophic vaginitis (vaginal dryness, vaginal and/or vulvar irritation or itch, vaginal soreness, dysuria, dyspareunia, and vaginal bleeding associated with intercourse). A 12-month, randomized study enrolled 309 postmenopausal women who inserted one 10 mcg estradiol insert (or placebo) intravaginally daily for 14 days. They then used 1 insert twice weekly for 50 weeks. There was a significant increase in the percentage of vaginal superficial cells at week 12 with estradiol compared with placebo (13.2% compared with 3.8%), a significant decrease in parabasal cells at week 12 (-37% compared with -9.3%), and a significant mean reduction between baseline and week 12 in vaginal pH score (-1.3 compared with -0.4) [16].

b) The efficacy of estradiol vaginal ring (Estring(R)) for the treatment of postmenopausal vaginal atrophy was demonstrated in two controlled trials that compared estradiol vaginal ring with conjugated estrogens vaginal cream. Both studies concluded there was no difference in efficacy between the two treatments with respect to the physicians' and patients' assessment of vaginal symptom improvement after 12 weeks of treatment. In both studies, the treatments demonstrated similar efficacy in reduction of vaginal pH levels and maturation of vaginal mucosa after 12 weeks. Endometrial overstimulation occurred in 11% of patients receiving conjugated estrogens vaginal cream compared with 0% in patients receiving estradiol vaginal ring. Patients preferred the estradiol ring over the conjugated estrogens cream due to comfort and ease of use [15].

c) Women (n=176) with postmenopausal urogenital atrophy were evaluated for safety and efficacy using an estrogen vaginal ring or oestrogen cream. The 12-week treatment period consisted of a vaginal ring that uniformly released estradiol 5 to 10 mcg/24 hours or nightly use of conjugated estrogen cream 0.625 mg for 3 weeks followed by one drug-free week; the conjugated estrogen cycle was repeated twice. Equivalence was demonstrated for vaginal dryness, dyspareunia, vaginal mucosal atrophy, and intercurrent vaginal bleeding. At the end of the treatment period, no statistically

significant difference was observed in the incidence of bleeding following the progestogen challenge test. Therapy with the estradiol vaginal ring was preferred over conjugated estrogen cream [23].

d) Although estradiol vaginal cream and conjugated estrogen vaginal cream are similarly effective in treating postmenopausal vaginal atrophy, estradiol may be preferred because of decreased undesirable effects [24]. Conjugated estrogens, given intravaginally, were found to cause a significant elevation in estrone and estradiol levels and an increase in sex hormone binding globulin (SHBG) capacity. Estradiol induced no such changes. Histological examination in 2 patients from each group showed no evidence of endometrial hyperplasia in the patients receiving estradiol, while moderate hyperplasia was found in both patients receiving conjugated estrogens.

e) In a double-blind trial involving 29 females with postmenopausal syndrome, estradiol vaginal cream (0.01%) was compared with conjugated estrogens vaginal cream, both given daily at bedtime for 2 weeks. Marked improvement in vaginal and vasomotor symptoms was noted with both drugs after 7 to 14 days. Plasma estrone and estradiol concentrations were significantly increased after both drugs, although the increase was more marked with estradiol than with the conjugated estrogens. The maturational indices of the parabasal and superficial cells were also significantly improved with both drugs. Adverse effects were mild (primarily breast tenderness and abdominal bloating), occurring in 7 of 20 patients receiving estradiol and 2 of 9 patients receiving conjugated estrogens. The authors concluded that both preparations were effective in the treatment of postmenopausal symptoms [25].

Breast cancer, Metastatic; for palliation only

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral only); Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol oral tablets are indicated as palliative treatment of metastatic breast cancer in appropriately selected men and women [7]

c) Adult:

1) A randomized study involving 328 patients with stage II/IIIA breast cancer found no improvements in relapse-free or overall survival when ethinyl estradiol was used to prime cancer cells prior to chemotherapy (Bontenbal et al, 2000). Patients received 4 cycles of fluorouracil 500 mg/meter squared, doxorubicin 50 mg/meter squared, and cyclophosphamide 500 mg/meter squared once every 4 weeks. Of the 328 patients, 162 received no estrogenic recruitment and 166 received 2 doses of 0.5 mg ethinyl estradiol, 24 hours prior to and at the time of chemotherapy. Within a median follow-up of 6.8 years, 177 patients relapsed, of which 123 died. There were no significant differences between the treatment groups related to relapse-free, local recurrence-free, distant metastasis-free, and survival. This conclusion supports the findings of other randomized studies.

2) Oral micronized estradiol 1 mg 3 times daily for days 0 through 20 every other month alternating with tamoxifen 20 mg twice daily for days 0 through 27, in addition to chemotherapy, resulted in an objective response rate of 39% (28% complete response and 11% partial response) among 25 patients with metastatic breast cancer [26]. This study protocol did not evaluate the role of estradiol in the priming of tumor cell proliferation in vivo nor its ultimate clinical effect by comparison with a control group. Overall, the treatment was nonaggressive and well-tolerated, suggesting that estradiol may play a useful role in the treatment of metastatic, estrogen receptor-positive breast cancer; however, further study is needed to define its optimal use.

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral tablets and transdermal patches); Pediatric, no

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class I; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol oral tablets and transdermal patches are indicated for the treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure [19][7][8][9][11][12]

c) Adult:

1) Transdermal estradiol has been shown to be effective in inducing puberty in a study of 15 hypogonadal women [41]. The following protocol was used: transdermal estradiol 25 mcg/day patch applied twice weekly for 3 weeks of each month for 6 months, later adding oral medroxyprogesterone acetate 5 to 10 mg daily during the third week of each cycle, and finally increasing the estradiol dose of days 15 to 25 by substituting the 50 mcg/day patch. The patients ranged in age from 14 to 27 years, with the treatment period ranging from 0.5 to 3 years. No adverse effect on lipoprotein levels was seen. Transdermal estradiol appears to be safe and effective in this setting.

d) Pediatric:

1) Transdermal estradiol has been shown to be effective in inducing puberty in a study of 15 hypogonadal women [41]. The following protocol was used: transdermal estradiol 25 mcg/day patch applied twice weekly for 3 weeks of each month for 6 months, later adding oral medroxyprogesterone acetate 5 to 10 mg daily during the third week of each cycle, and finally increasing the estradiol dose of days 15 to 25 by substituting the 50 mcg/day patch. The patients ranged in age from 14 to 27 years, with the treatment period ranging from 0.5 to 3 years. No adverse effect on lipoprotein levels was seen. Transdermal estradiol appears to be safe and effective in this setting.

Dyspareunia, Moderate to severe - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (Imvexxy(TM) vaginal insert); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol vaginal insert (Imvexxy(TM)) is indicated for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause [5].

Evidence

In a randomized trial, estradiol vaginal inserts significantly improved dyspareunia severity scores at week 12 compared with placebo. The percentages of superficial and parabasal cells and vaginal pH were also significantly improved; as well as vaginal dryness and vulvar and/or vaginal irritation or itching [6].

c) Adult:

1) In a randomized trial (REJOICE), estradiol vaginal inserts significantly improved dyspareunia severity scores at week 12 compared with placebo in postmenopausal women with vulvar and vaginal atrophy (N=764). Mean change from baseline of the dyspareunia severity scores was -1.52, -1.69, and -1.69 for 4-, 10-, and 25-mcg doses vs -1.28 for placebo. At week 12, the percentage of vaginal superficial cells significantly increased for all doses (17% to 23% vs 6% for placebo), the percentage of vaginal parabasal cells significantly decreased (41% to 46% vs 7% for placebo), and vaginal pH was significantly improved. Vaginal dryness and vulvar and/or vaginal irritation or itching were also significantly improved. Dyspareunia was identified as the most bothersome symptom and was associated with vulvar and vaginal atrophy. Included women also had 5% or less superficial cells on vaginal smear and a vaginal pH of greater than 5. Headache was the most commonly reported treatment-emergent adverse event. Patients self-administered digitally a 4-, 10-, or 25- mcg insert into the vagina once daily for 2 weeks, then twice weekly for 10 weeks [6].

Menopause - Urethral atrophy (Moderate to Severe)

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (vaginal ring); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol vaginal ring is indicated for the treatment of urogenital symptoms associated with postmenopausal atrophy of the lower urinary tract (urinary urgency and dysuria) [15].

c) Adult:

1) Women (n=176) with postmenopausal urogenital atrophy were evaluated for safety and efficacy using an estrogen vaginal ring or oestrogen cream. The 12-week treatment period consisted of a vaginal ring which uniformly released estradiol 5 to 10 mcg/24 hours or nightly use of conjugated estrogen cream 0.625 mg for 3 weeks followed by one drug-free week; the conjugated estrogen cycle was repeated twice. Equivalence was demonstrated for vaginal dryness, dyspareunia, vaginal mucosal atrophy, and intercurrent vaginal bleeding. At the end of the treatment period no statistically significant difference was observed in the incidence of bleeding following the progestogen challenge test. Therapy with the estradiol vaginal ring was preferred over conjugated estrogen cream [23].

Postmenopausal osteoporosis; Prophylaxis

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral tablets and transdermal patches); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol transdermal patch is indicated for the prevention of postmenopausal osteoporosis [10][29][7][8][12].

Limitation of Use

Consider therapy only for women at significant risk of osteoporosis and for whom nonestrogen medications are not appropriate [29][19][7][8][12].

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy [7][8][12].

See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy
See Drug Consult reference: Canadian: Management of Osteoporosis in Men and Women

c) Adult:

1) General Information

a) Investigators looked at 670 white women in the Framingham Study cohort, with a mean age of 76 years, to determine whether bone mass in elderly women was affected by earlier estrogen, and how long women needed to take estrogen to have a beneficial effect on bone density as they get older. The bone mineral density of these women was measured at the femur, spine, shaft of the radius, and ultradistal radius. Density of the radius and ultradistal radius was significantly higher in women who had taken estrogen for at least 10 years. Bone mineral density of the spine was significantly higher only in women who had taken estrogen for 7 to 9 years; femoral bone density values were higher (but not significantly) in women who had used estrogen for 7 to 9 years, or 10 or more years. The women younger than 75 years old who had taken estrogen for at least 7 years had significantly higher bone mineral density than the women who had never taken estrogen. In the women older than 75 years who had taken estrogen for a comparable duration, the overall bone density was only slightly higher than in women who had never taken estrogen, although the bone mineral density in the shaft of the radius of estrogen takers was significantly higher. Among women younger than 75 years old, the bone mineral density was positively correlated with the duration of estrogen therapy; however, both the correlation and the benefits seem to be lost in women older than 75 years. This study suggests that for long-term preservation of bone mineral density, women should take estrogen for at least 7 years after menopause. This duration may still not be adequate to protect women 75 years and older from fracture [30].

2) Oral

a) Loss of vertebral bone mass was prevented in postmenopausal women who received oral estradiol during a randomized, double-blind, dose-ranging study. Patients were randomized to estradiol 0.5 mg daily or placebo for 23 days of a 28-day cycle for a total of 2 years. After estradiol was discontinued, bone mass declined at a rate similar to the immediate postmenopausal period. There was no evidence that treatment with estradiol was able to restore bone mass to premenopausal levels [7].

b) A 3-year study of early postmenopausal women (n=153) concluded that thinness and smoking are important risk factors for the development of osteoporosis, but are counteracted by hormone replacement therapy (Bjarnason and Christiansen, 2000). In the study, patients were randomized to receive 1 or 2 mg of oral estradiol daily or placebo. Baseline BMI was significantly (p less than 0.01) associated with bone resorption with a subsequent association between BMI and bone mineral density (BMD). A low BMI was associated with an increased rate of loss (p less than 0.01), while response to either 1 or 2 mg estradiol treatment was independent of BMI. Smoking was associated with a 4% lower BMD at baseline compared with that of nonsmokers and this effect was additive with that of BMI. The increase in serum estradiol during treatment for smokers was half that of nonsmokers. Serum follicle-stimulating hormone (FSH) was significantly less suppressed in smokers in the estradiol 1 mg treatment group, while the FSH serum concentrations were similar among smokers and nonsmokers in the placebo and 2 mg treatment group. The data suggest that osteoporosis screening strategies may benefit from including these risk factors.

c) Oral micronized estradiol 0.5 to 2 mg daily in cyclic fashion for 18 months was significantly better than placebo for prevention of bone loss in postmenopausal women in a double-blind, placebo-controlled study. During the double-blind phase, no significant increases in bone density were seen. Further data were obtained after switching the placebo group to treatment with 1 mg daily for an additional 18 months, during which time significant increases in bone density were seen (4.3% annually). Significant net gains in vertebral bone density with micronized estradiol were also reported (Munk-Jensen, 1988); however, estradiol was given continuously in this study rather than cyclically, a regimen less favored due to possible increased risk of endometrial cancer [31].

3) Transdermal

a) Treatment with transdermal estradiol (Alora(R)) patch was superior to placebo with regard to effects on bone mineral density (BMD) during a 2-year, randomized, double-blind study involving 355 hysterectomized, nonosteoporotic, postmenopausal women (mean age, 53.2 years). The study participants were randomized to transdermal estradiol (Alora(R)) 0.025, 0.05, or 0.075 mg/day every 3 or 4 days or placebo. Additionally, all patients received oral elemental calcium 1000 mg daily. The primary endpoint was the percent change in BMD from baseline to year 2. The average lumbar spine T-score at baseline was 0.64. A total of 196 patients were included in the completer population while 258 patients were included in the intent-to-treat, last observation carried forward (LOCF) population. All doses of transdermal estradiol were statistically superior to placebo in terms of percent change in BMD from baseline. The mean percent changes in BMD at 2 years (LOCF) were 1.45%, 3.39%, 4.24%, and -0.8% for estradiol 0.025, 0.05, 0.075 mg/day and placebo, respectively [8].

b) Treatment with transdermal estradiol (Climara(R)) was superior to placebo with regard to effects on bone mineral density (BMD) during a 2-year, randomized study involving 175 hysterectomized, nonosteoporotic, postmenopausal women. The study participants were randomized to transdermal estradiol (Climara(R)) 0.025, 0.05, 0.06, or 0.1 mg/day (n=129) or placebo (n=46). The primary endpoint was the percent change in anterior-posterior lumbar spine BMD from baseline to year 2. Of the patients randomized, a total of 134 contributed to the last observation carried forward (LOCF) population. All doses of transdermal estradiol demonstrated a statistically significant overall treatment effect at each timepoint compared with placebo, which implied bone preservation versus bone loss for all active treatment groups. The percent change in total hip BMD was statistically significant for all estradiol treatment groups compared with placebo [19].

c) Treatment with transdermal estradiol (Vivelle(R)) was superior to placebo with regard to effects on bone mineral density (BMD) during a 2-year, randomized, double-blind study involving 261 hysterectomized and nonhysterectomized, postmenopausal women with no evidence of osteoporosis (mean age, 52 years). The study participants were randomized to transdermal estradiol (Vivelle(R)) 0.025, 0.0375, 0.05, or 0.1 mg/day (n=194) or placebo (n=67). Additionally, all patients received oral elemental calcium 1000 mg daily and nonhysterectomized women received oral medroxyprogesterone acetate 2.5 mg daily. The primary endpoint was the percent change in BMD of the AP lumbar spine from baseline to year 2. Of the 261 women randomized, 232 contributed to the last observation carried forward (LOCF) population. All doses of transdermal estradiol were associated with an increase in BMD of the AP lumbar spine while placebo was associated with a decrease in BMD. All estradiol doses, with the exception of 0.05 mg/day, were significantly superior to placebo (p less than 0.05) at all time points and the highest dose of transdermal estradiol was superior to the 3 lower doses. Additionally, all doses of transdermal estradiol were significantly superior to placebo (p less than 0.05) with regard to percent change in BMD of the femoral neck from baseline to year 2, a secondary efficacy endpoint. Again, the highest transdermal estradiol dose was superior to the 3 lower doses for the secondary endpoint [11][12].

d) Transdermal estradiol 0.025 to 0.1 mg daily demonstrated efficacy in the prevention of postmenopausal bone loss. A multicenter, randomized, placebo-controlled, parallel-group study evaluated the efficacy, safety, and tolerability of an estradiol transdermal system over 2 years for the prevention of postmenopausal bone loss. Postmenopausal women (n=261) were randomized to apply the estradiol transdermal system (0.025,

0.0375, 0.05, or 0.1 mg per day) or matching placebo twice a week for 2 years. After 2 years of treatment, there were significant differences at all doses of estradiol in bone mineral density of the L1-L4 anteroposterior lumbar spine when compared to placebo (0.1 and 0.05 mg/day, p less than 0.001; 0.0375 mg/day, p equal to 0.024; 0.025 mg/day, p equal to 0.002). There were also significant differences in the bone mineral density of the femoral neck (all, p less than or equal to 0.044). All doses of the transdermal estradiol system were well tolerated [32].

Prostate cancer, Advanced, Androgen-dependent; for palliation only

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral only); Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol oral tablets are indicated for palliative treatment of advanced androgen-dependent prostate cancer [7].

In the multicenter, randomized, open-label, phase 2 Prostate Adenocarcinoma: TransCutaneous Hormones versus luteinizing-hormone-releasing hormone agonists (PATCH) trial (n=254), 92% of patients with locally advanced or metastatic prostate cancer who received transdermal estrogen achieved castrate testosterone concentrations at 3 months. Cardiovascular events occurred in 10.1% of patients at a median of 19 months [27].

Transdermal estradiol produced an effective tumor response, was associated with minimal cardiovascular toxicity, prevented andropause symptoms, and improved quality-of-life scores [28].

c) Adult:

1) Transdermal Patch

a) In the multicenter, randomized, open-label, phase 2 Prostate Adenocarcinoma: TransCutaneous Hormones versus luteinizing-hormone-releasing hormone agonists (PATCH) trial (n=254), 92% of patients with locally advanced or metastatic prostate cancer who received transdermal estrogen achieved castrate testosterone concentrations at 3 months, with cardiovascular events occurring in 10.1% of patients at a median of 19 months. Men (median age, 74 years; interquartile range, 69 to 79 years; metastatic disease, 36%) with testosterone levels of 6 nanomoles/liter (nmol/L) or higher were randomized 1:2 to receive a luteinizing-hormone-releasing hormone agonist (LHRHa) prescribed according to local practice (n=85) or transdermal estrogen 3 patches (100 mcg/24 hours) changed twice weekly for 4 weeks, then (if serum testosterone levels were 1.7 nmol/L or lower) 2 patches changed twice weekly (regimen 1; n=33) or 4 patches changed twice weekly for 4 weeks followed by 3 patches changed twice weekly when castrate testosterone levels were reached (regimen 2; n=136). Radical radiotherapy to the prostate was initially not permitted in the study but was later allowed to demonstrate changes in practice. Second-line therapy was permitted in cases of disease progression, including changing to the nonassigned study treatment. At 3 months, 93% and 92% of patients in the LHRHa group and estrogen group, respectively, achieved testosterone levels of 1.7 nmol/L or lower; at 6 months, the percentages were 88% and 95%, respectively. After a median followup of 19 months, cardiovascular events (primary endpoint) occurred in 7.1% (95% CI, 2.7% to 14.9%) of patients who received LHRHa and 10.1% (95% CI, 6% to 15.6%) of patients who received estrogen. The rate of cardiovascular events was 2.9% higher (95% CI, -4.2 to 10.1) in the estrogen group compared with LHRHa; however, this study was not powered to detect a difference between treatment groups. At 6 months, among patients still receiving the study drug and who did not receive additional therapy, mean fasting glucose and mean fasting cholesterol levels were increased in the LHRHa group by 2% and 7.6% and decreased in the estrogen group by 2.1% and 1.2%, respectively (p less than 0.035 and p less than 0.0001, respectively). Other adverse events included gynecomastia, which occurred more frequently in the estrogen group compared with LHRHa, and hot flushes, which occurred more often in the LHRHa group [27].

b) Data from a pilot study involving 20 men with advanced prostate cancer who received transdermal estradiol indicate transdermal therapy produced an effective tumor response, was associated with minimal cardiovascular toxicity, prevented andropause symptoms, and improved quality-of-life scores. The men applied 6 transdermal estradiol (7.8 mg) patches weekly for 8 weeks and then reduced the number of patches to maintain castrate levels of testosterone. Median follow-up was 15 months. All patients achieved castrate levels of testosterone within 3 weeks and had biochemical evidence of disease regression. One patient died of disease at 14 months, and only 1 cardiovascular

complication (fluid retention) occurred. Mild to moderate gynecomastia occurred in 80% of patients. No patient reported hot flashes [28].

Estradiol Acetate

Abnormal vasomotor function (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence

Estradiol acetate vaginal ring 0.05 mg/day or 0.1 mg/day significantly decreased the frequency and severity of moderate to severe vasomotor menopause symptoms compared with placebo at weeks 4 and 12 in a randomized trial (N=333) [59].

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (vaginal ring); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence

Efficacy of estradiol acetate vaginal ring for the treatment of vulvar and vaginal atrophy in postmenopausal women was demonstrated in a randomized trial (N=333). At week 13, vaginal superficial cells increased by a mean of 16.0% and 18.9% for estradiol acetate vaginal ring 0.05 mg/day and 0.1 mg/day, respectively, compared with 1.11% for placebo, and there was a reduction in parabasal cells. Vaginal pH decreased by a mean of 0.73 and 0.60 for estradiol acetate vaginal ring 0.05 mg/day and 0.1 mg/day, respectively, compared with mean decrease of 0.25 for placebo [60][59].

Estradiol Cypionate

Abnormal vasomotor function (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol cypionate is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause [55]

Decreased estrogen level - Female hypogonadism syndrome

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol cypionate is indicated for the treatment of female hypoestrogenism due to hypogonadism [55]

Estradiol Valerate

Abnormal vasomotor function (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol valerate is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause [57]

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol valerate injection is indicated for treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause [57]

When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with estrogen therapy [57]

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure [57]

Hormone sensitive prostate cancer, Advanced, for palliation only

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only) [57]

Non-FDA Uses

Estradiol

Alzheimer's disease; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A cohort-based study (n=221,406) with an average follow-up of more than 5 years demonstrated that current estrogen replacement therapy in postmenopausal women did not reduce the risk of developing Alzheimer disease (Seshardri et al, 2001)

The Baltimore Longitudinal Study of Aging, a prospective study of postmenopausal or perimenopausal women (n=472), showed a reduced risk of Alzheimer disease in women who had reported the use of estrogen [45]

An observational, cohort study of elderly women (n=1124) demonstrated that estrogen may delay the onset and decrease the risk of developing Alzheimer disease (AD) [46]

A case-control study nested within a prospective cohort study of postmenopausal women (n=8877) demonstrated that estrogen replacement therapy may be useful for preventing or delaying the onset of Alzheimer disease (Paganini-Hill and Henderson, 1996)

c) Adult:

1) A cohort-based study with an average follow-up of more than 5 years demonstrated that current estrogen replacement therapy (ERT) in postmenopausal women did not reduce the risk of developing Alzheimer disease (AD). The population-based nested case-control study involved 2 base cohorts, one of women who received (ERT) (n=112,481) and another who did not (n=108,925). Fifty-nine newly diagnosed cases of AD and 221 matched control subjects were identified from the 2 cohorts. The risk for developing AD was determined to be equal for women who received ERT for at least 1 year and for nonusers, as 25% of the newly diagnosed AD patients and 24% of controls currently used ERT (relative risk estimate (OR) of 1.18; 95% CI, 0.59 to 2.37). Smoking (current and past) was not an independent risk factor for AD but body mass index was and appropriate adjustments in the relative risks were made. When past ERT recipients and current users were combined, the risk of developing AD did not significantly change (OR, 1.19; 95% CI, 0.62 to 2.27). Additionally, the duration of ERT use did not account for significant differences in the risk as users for 5 years or longer were compared with nonusers (OR 1.05; 95% CI, 0.32 to 3.44). There was also no difference for estrogen recipients who received estrogen alone or combined with a progestin (Seshardri et al, 2001).

2) The Baltimore Longitudinal Study of Aging was a prospective study of 472 postmenopausal or perimenopausal women that showed a reduced risk of Alzheimer disease (AD) in women who had reported the use of estrogen. Of the 472 women enrolled, 45% had used oral or transdermal estrogen replacement therapy (ERT) at any time (excluding premenopausal oral contraceptives). Thirty-four cases of AD were diagnosed during the 16-year follow-up, which included 9 ERT users. The relative risk for AD in ERT users versus nonusers was 0.46 (95% CI, 0.209 to 0.997), which indicates a reduced risk of AD for women who had reported the use of estrogens. Level of education, age at menopause and menarche, years of natural cyclic estrogen exposure, menopause duration, and surgical menopause did not affect the results of the study, and there was no effect related to duration of ERT therapy [45].

3) An observational, cohort study of elderly (mean age 74 years) women (n=1124) demonstrated that estrogen may delay the onset and decrease the risk of developing

Alzheimer disease (AD). Initially, all of the women were free of AD but during follow-up (1 to 5 years), 167 women developed the disease. Women who developed AD were older and had fewer years of education than those who did not, but age at menopause was similar for both groups. Estrogen use after the onset of menopause was reported in 156 of the 1124 enrolled women, with an average duration of 6.8 years. The age at onset of AD was significantly later in women who had taken estrogen than those who did not (p less than 0.01). The relative risk (RR) of AD associated with a history of estrogen use was 0.40 (95% CI, 0.22 to 0.85; p=0.01). Adjustment for ethnicity, years of education, apolipoprotein-E genotype, and participation group (senior housing versus Medicare sample) did not significantly change the RR. In addition, women who received estrogen for longer than 1 year (average, 13.6 years) had a greater reduction in risk (RR 0.13, 0.02 to 0.92; p less than 0.01) [46].

4) A case-control study nested within a prospective cohort study of 8,877 women demonstrated that estrogen replacement therapy (ERT) may be useful for preventing or delaying the onset of Alzheimer disease (AD) in postmenopausal women. Of the 8,777 cohort patients, 248 women who died with AD or other dementia diagnoses were identified and 5 controls were matched to each case based on year of death and year of birth (+/-1 year). The risk of AD and related dementia was significantly reduced in estrogen users (both oral and nonoral preparations) compared with nonusers (odds ratio (OR), 0.65; 95% CI, 0.49 to 0.88). Both increasing dosage and duration of conjugated estrogen were associated with a significant decrease in risk (p equal to 0.01 for both). The lowest observed risk was observed in long-term (at least 15 years) users who received high doses (at least 1.25 mg daily) (OR, 0.48; 95% CI, 0.19 to 1.17) (Paganini-Hill and Henderson, 1996).

Dementia

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence

Results from Women's Health Initiative Memory Study (WHIMS) demonstrated that conjugated equine estrogen therapy alone did not reduce the incidence of dementia or mild cognitive impairment and increased the risk for both end points combined [47]

Guidelines

Do not use estrogen alone for the primary prevention of chronic conditions in asymptomatic postmenopausal women. There is moderate certainty that estrogen-only prophylaxis provides no net benefit or that the harms outweigh the benefits in postmenopausal women who have had a hysterectomy [43].

c) Adult:

1) Conjugated equine estrogen (CEE) therapy alone did not reduce the incidence of dementia or mild cognitive impairment (MCI) and increased the risk for both end points combined. The Women's Health Initiative Memory Study (WHIMS), a double-blind ancillary study of the Women's Health Initiative, randomized 2947 postmenopausal women (aged 65 to 79 years) to CEE 0.625 mg daily or placebo. All women were free of probable dementia at baseline and incidence of probable dementia and MCI was measured by the Modified Mine-Mental State Examination (3MSE) at baseline and annually thereafter. After a period of 5.21 years, 47 patients were diagnosed with probable dementia, of whom 28 were assigned to CEE and 19 to placebo (hazard ratio (HR), 1.49; 95% CI, 0.83 to 2.66) [47]; this correlates to an estimated event rate difference of 12 per 10,000 woman-years with estrogen-only versus placebo (95% CI, -4 to 41) [43]. The incidence rates for probable dementia in the estrogen-alone trial were not significantly different from those in the estrogen plus progestin trial (45 vs 22 per 10000 person-years for CEE plus progestin versus placebo). When data for estrogen alone and estrogen plus progestin were pooled, the risk of probable dementia was significantly increased versus placebo (HR, 1.76; 95% CI, 1.19 to 2.60). In the estrogen-alone trial, 76 patients in the CEE group were diagnosed with MCI versus 58 in the placebo group (HR, 1.34; 95% CI, 0.95 to 1.89). In the combined data, the HR was similar (HR, 1.25; 95% CI, 0.97 to 1.6). In the estrogen-alone trial, 93 patients in the CEE group were diagnosed with either probable dementia or MCI compared to 69 in the placebo group (HR, 1.38; 95% CI, 1.01 to 1.89) [47].

Disorder of cardiovascular system; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence

There was no significant difference in coronary events with estrogen versus placebo in pooled analysis of the EPAT, PEPI, and WHI trials of postmenopausal women who had undergone hysterectomy [42]

The risk of stroke was significantly greater with estrogen versus placebo in the WHI study [42].

Guidelines

Do not use estrogen alone for the primary prevention of chronic conditions in asymptomatic postmenopausal women. There is moderate certainty that estrogen-only prophylaxis provides no net benefit or that the harms outweigh the benefits in postmenopausal women who have had a hysterectomy [43].

c) Adult:

1) Coronary Heart Disease

a) Pooled analysis of the Estrogen in the Prevention of Atherosclerosis Trial (EPAT), the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, and Women's Health Initiative (WHI) trial (n=11,310; high quality evidence) reported no significant difference in coronary events with estrogen versus placebo (3.6% vs 3.8%; relative risk [RR], 0.95; 95% CI, 0.79 to 1.14) with a mean follow-up of 6.8 years among women who had undergone hysterectomy. In the WHI trial, there was no significant difference in cardiovascular risk with hormone therapy versus placebo 3.9 years after treatment discontinuation (hazard ratio [HR], 0.97; 95% CI, 0.75 to 1.25) [42].

b) Results from the WHI trial showed no significant difference in cardiovascular risk with hormone therapy versus placebo 3.9 years after treatment discontinuation (hazard ratio [HR], 0.97; 95% CI, 0.75 to 1.25). Estrogen therapy did not significantly affect the risk of coronary heart disease in subgroups based on age, race/ethnicity, hypertension, diabetes, high cholesterol that required medication, coronary risk factors, years since oophorectomy or hysterectomy, or body mass index. The risk for coronary heart disease with estrogen increased with age: Ages 50 to 59 years, HR 0.6 (95% CI, 0.35 to 1.04); ages 60 to 69 years, HR, 0.95 (95% CI, 0.72 to 1.24); ages 70 to 79 years, HR, 1.09 (95% CI, 0.8 to 1.49). Time since menopause also did not have a significant effect on the risk of coronary heart disease with estrogen-only therapy versus placebo [42].

2) Stroke

a) The risk of stroke was significantly higher with estrogen-only therapy versus placebo (3.2% vs 2.4%; hazard ratio [HR], 1.35; 95% CI, 1.07 to 1.7) after a median treatment duration of 7.2 years in the Women's Health Initiative (WHI) study (N=10,739; moderate quality evidence) [42]; this correlated to an estimated event rate difference of 11 per 10,000 woman-years (95% CI, 2 to 23 events) [43]. Stroke risk was similar between arms 3.9 years after treatment discontinuation. At 10.7 years of follow-up, cumulative stroke risk was higher with estrogen-only (4.4% vs 3.8%; HR, 1.15; 95% CI, 0.97 to 1.37). Results on stroke risk from the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) and the Estrogen Replacement and Atherosclerosis (ERA) study were inconclusive due to low event rates [42].

b) In a study of 664 postmenopausal women (mean age, 71 years) who had recently had an ischemic stroke or transient ischemic attack, estradiol 1 mg/day did not reduce mortality or the recurrence of stroke. Over a follow up period of 2.8 years, 48 deaths and 51 nonfatal strokes occurred in the estradiol group versus 41 deaths and 52 nonfatal strokes in the placebo group. During the first 6 months, 3 fatal strokes and 18 nonfatal strokes occurred in women in the estradiol group, compared with 1 fatal stroke and 8 nonfatal strokes in women in the placebo group. Women receiving estradiol were more likely to have vaginal bleeding and endometrial hyperplasia and a more frequent need for hysterectomy [44].

Gender dysphoria - Male-to-female transsexual

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIb; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adolescents)

After puberty suppression with triptorelin, administration of daily oral estrogen to adolescent transgirls (N=28) produced breast development within the first year and increased hip circumference and decreased the waist/hip ratio over 3 years of treatment [2].

Evidence (Adults)

Estradiol, as ethinyl estradiol and 17-beta estradiol, may be effective in changing the physical external appearance for male to female transsexuals [3][4].

Guidelines (Adolescents)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy younger than 16 years, but studies in this population are minimal. Initial therapy to undergo suppression of pubertal development is suggested at Tanner stage G2/B2. Neither puberty suppression nor gender-affirming hormone therapy is recommended in prepubertal children [1].

Guidelines (Adults)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender [1].

Estrogen options include oral or transdermal 17-beta estradiol and oral conjugated estrogens; it is suggested that ethinyl estradiol not be used as it may have a higher risk of VTE than other preparations. Treatment with physiologic doses of estrogen alone does not suppress testosterone levels into the normal range for females; multiple adjunctive medications are available [1].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Pediatric:

1) Administration of daily oral estrogen to 28 adolescent transgirls produced breast development within the first year and increased hip circumference and decreased the waist/hip ratio over 3 years of treatment. Results for selected outcomes are shown in the table below. Subjects had received triptorelin alone for a median of 24.8 months (range, 6.4 to 51.6 months) before initiation of estrogen at a median age of 16 years (range, 13.9 to 18.9 years); estrogen was initiated in 5 patients with tall stature (greater than 180 cm) before 15.5 years. Median Tanner breast development stage was 1 at treatment initiation, 3 after 1 year, 4 after 2 years, and 5 after 3 years. Gonadotropin levels were suppressed in all patients, with the exception of one who was noncompliant with gonadotropin-releasing hormone analog therapy. Estradiol levels increased with increasing doses, and the adult dose of 2 mg administered for a median of 2 years (range, 3 to 30 months) resulted in a median serum estradiol level of 100 picomole/L. There were no significant changes over time in median prolactin levels, Hb, HCT, HbA1c, or liver enzymes. Study subjects had lifelong extreme gender dysphoria, were psychologically stable, and lived in a supportive environment. For transgirls who had started triptorelin before 16 years, the starting dose of estradiol was 5 mcg/kg/day once daily, increased by 5 mg/kg/day every 6 months until an adult dose of 2 mg/day was reached. For transgirls who started triptorelin at 16 years or older and had complete endogenous puberty, the starting estradiol dose was 1 mg orally daily, which was increased to 2 mg after 6 months. Two patients received 200 mcg ethinylestradiol and 4 received estradiol 6 mg to limit growth [2].

Estrogen-Induced Changes in Tanner Stage and Anthropometric Parameters

	Baseline	After 3 Years of Treatment	Standard Deviation at 3 Years (Female Adolescent Reference)
Tanner breast stage, median	1	5 (range, 2 to 5)	-
Testicular volume, median	8 mL	6.5 mL	-
Height, mean	178 cm	180 cm*	1.53 +/- 1.5
Body mass index, mean	20.8 kg/m(2)	21.5 kg/m(2)*	-0

Waist circumference, mean	73.9 cm	73.7 cm	0.22 /- 1.29
Hip circumference, mean	93.9 cm	97.4 cm*	0.42 +/- 0.98
Waist/hip ratio, mean	0.79	0.75*	-0.04 +/- 1.01
Bone age, median	14.3 years (range, 13 to 18 years)	18 years (range, 16 to 19 years)	-
Fat percentage, mean	26%	25.9%	-
Lean body mass percentage, mean	119%	125%	-
*significant difference from baseline			

Impaired cognition

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence

Results from Women's Health Initiative Memory Study (WHIMS) demonstrated that conjugated equine estrogen therapy alone did not reduce the incidence of dementia or mild cognitive impairment and increased the risk for both end points combined [47]

Guidelines

Do not use estrogen alone for the primary prevention of chronic conditions in asymptomatic postmenopausal women. There is moderate certainty that estrogen-only prophylaxis provides no net benefit or that the harms outweigh the benefits in postmenopausal women who have had a hysterectomy [43].

c) Adult:

1) Conjugated equine estrogen (CEE) therapy alone did not reduce the incidence of dementia or mild cognitive impairment (MCI) and increased the risk for both end points combined. The Women's Health Initiative Memory Study (WHIMS), a double-blind ancillary study of the Women's Health Initiative, randomized 2947 postmenopausal women (aged 65 to 79 years) to CEE 0.625 mg daily or placebo. All women were free of probable dementia at baseline and incidence of probable dementia and MCI was measured by the Modified Mine-Mental State Examination (3MSE) at baseline and annually thereafter. After a period of 5.21 years, 47 patients were diagnosed with probable dementia, of whom 28 were assigned to CEE and 19 to placebo (hazard ratio (HR), 1.49; 95% CI, 0.83 to 2.66) [47]; this correlates to an estimated event rate difference of 12 per 10,000 woman-years with estrogen-only versus placebo (95% CI, -4 to 41) [43]. The incidence rates for probable dementia in the estrogen-alone trial were not significantly different from those in the estrogen plus progestin trial (45 vs 22 per 10,000 person-years for CEE plus progestin versus placebo). When data for estrogen alone and estrogen plus progestin were pooled, the risk of probable dementia was significantly increased versus placebo (HR, 1.76; 95% CI, 1.19 to 2.60). In the estrogen-alone trial, 76 patients in the CEE group were diagnosed with MCI versus 58 in the placebo group (HR, 1.34; 95% CI, 0.95 to 1.89). In the combined data, the HR was similar (HR, 1.25; 95% CI, 0.97 to 1.6). In the estrogen-alone trial, 93 patients in the CEE group were diagnosed with either probable dementia or MCI compared to 69 in the placebo group (HR, 1.38; 95% CI, 1.01 to 1.89) [47].

Menstrual migraine

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A double-blind, randomized, crossover trial (n=35) suggested that perimenstrual estradiol supplement can be of benefit in preventing menstrual migraine attacks, but discontinuation of estradiol supplement led to an increase in migraine attacks [50]

c) Adult:

1) In a double-blind, randomized, crossover trial (n=35), the use of perimenstrual estradiol gel 1.5 mg was more effective than placebo in preventing menstrual migraines; however, there was a rise in migraine attacks upon discontinuation of estradiol supplement. Women aged between 29 and 50 years (mean 43 years) were given indistinguishable gels (estradiol or placebo), and instructed to alternate and apply 1.5 mg gel to the upper arms or thighs daily from approximately 6 days before the first full day of bleeding up to and including the second full day of bleeding for 6 cycles. This therapeutic approach resulted in 133 and 171 migraine days while women were using estradiol and placebo, respectively (p=0.03). Estradiol gel was associated with a 22% reduction in migraine days per woman relative to placebo (relative risk (RR) 0.78; 95% CI, 0.62 to 0.99; p=0.04), and the attacks were less severe (RR 0.73; 95% CI, 0.54 to 0.97; p=0.03). However, the occurrence of migraine attack increased by 40% in the 5 days following estradiol use compared with placebo (RR 1.4; 95% CI, 1.03 to 1.92; p=0.03). Although the risk of migraine disappeared 5 to 10 days post estradiol use (RR 1.04; 95% CI, 0.67 to 1.62; p=0.92), the potential benefit of perimenstrual estradiol supplement was offset by the occurrence of deferred post-gel migraine attacks associated with estradiol withdrawal [50].

Mental distress

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Transdermal estradiol reduced response to mental stress in a small, crossover study of postmenopausal women (n=10) [48]

c) Adult:

1) A blinded, crossover study of 10 postmenopausal women demonstrated that transdermal estradiol reduced the response to mental stress, as measured by plasma epinephrine levels, diastolic blood pressure, and the overall cardiac sympathetic tone. The women were randomized to receive transdermal estradiol (50 mcg daily) or placebo for 3 weeks, with a 3-week wash-out between the 2 treatments. At the conclusion of each treatment, the subjects underwent a mental stress test during which circulating levels of catecholamines and other hormonal and biochemical variables were measured. The epinephrine response was less marked during estradiol treatment compared to placebo and the difference in effects of placebo and estradiol on stress-induced epinephrine responses were significantly different (p less than 0.05). While there were no effects of treatment on stress-induced systolic blood pressure, mean diastolic blood pressure was significantly increased from baseline during placebo treatment (p less than 0.002), but not during estrogen treatment (p equal to 0.64). In addition, a decrease in the responses of some measures of stress-induced cardiac sympathetic tone was also measured with estradiol treatment. More studies are warranted to determine the influence of estrogens on sympathoadrenal functioning [48].

Migraine; Prophylaxis

See Drug Consult reference: Migraine Prophylaxis and Treatment in Adults - Clinical Practice Guidelines

Postpartum depression

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A small, open-label study (n=23) showed that depression symptoms may be rapidly reduced in patients with postpartum depression by treatment with estradiol [49]

c) Adult:

1) A small (n=23) open-label study showed that treatment with sublingual estradiol for 8 weeks rapidly reduced depression symptoms in women diagnosed with postpartum depression. All patients were severely depressed and had a low serum estradiol concentration (mean=79.8 picomoles per liter (pmol/L)). Ten patients received psychotherapy and 4 patients received antidepressant medication prior to estradiol therapy without benefit. Micronized estradiol was given sublingually at a dose of 1 mg 3 to 8 times daily depending on daily serum estradiol concentrations. At a mean dose of 3.9 mg during the first week of treatment, significant mood improvement was noted (p less than 0.001) which was measured using a clinician-rated depression symptom scale (the Montgomery-Asberg Depression Rating Scale (MADRS)). Improvement continued at a mean dose of 4.8 mg during the second week, and by the end of the week, the MADRS scores correlated with clinical recovery in 83% of patients. Further studies are needed to determine the optimum treatment duration, dose, and central mechanism of action of estradiol [49].

Urinary tract infectious disease; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol-releasing vaginal ring prolonged the time to next recurrence and decreased the number per year of urinary tract infections among postmenopausal women [51].

c) Adult:

1) The time to next recurrence was prolonged in postmenopausal women with recurrent urinary tract infection using an estradiol-releasing vaginal ring. In a multicenter, randomized, open parallel-group study, women (n=53) were assigned to the estradiol-releasing vaginal ring or to the control group (n=55). Women were included in the study if they were menopausal greater than 2 years and had greater than 3 urinary tract infections treated during the previous 12 months. One ring was carried vaginally for a 12-week period. The duration of treatment was 36 weeks for the estradiol group and 36 weeks or until the first recurrence for the control group. A recurrence of urinary tract infection occurred in 51% (n=27) of the estradiol group and 80% (n=44) in the control group [51].

Estradiol Acetate

Migraine; Prophylaxis

See Drug Consult reference: Migraine Prophylaxis and Treatment in Adults - Clinical Practice Guidelines

Estradiol Cypionate

Gender dysphoria - Male-to-female transsexual

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Estradiol Valerate

Gender dysphoria - Male-to-female transsexual

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adults)

In male-to-female transsexual adults, hormone treatment with estradiol valerate and goserelin acetate for 2 years before sex reassignment surgery significantly increased body mass index, total fat mass, and lumbar spine bone mineral density and significantly decreased lean mass [56].

Guideline (Adults)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender [1].

Estradiol valerate or cypionate or transdermal preparations are options to oral estradiol that may have an advantage in older transgender females who may have a higher risk of VTE. it is suggested that ethinyl estradiol not be used as it may have a higher risk of VTE than other preparations. Treatment with physiologic doses of estrogen alone does not suppress testosterone levels into the normal range for females; multiple adjunctive medications are available [1].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) In male-to-female transsexual adults (N=84), hormone treatment with estradiol valerate and goserelin acetate for 2 years before sex reassignment surgery significantly increased body mass index, total fat mass, and lumbar spine bone mineral density and significantly decreased lean mass. There were significant increases in median levels of estrogen and sex hormone-binding globulin and significant decreases in median levels of luteinizing hormone, follicle-stimulating hormone, and testosterone, with no significant change in median prolactin and dehydroepiandrosterone sulphate levels. Results for selected hormonal and anthropometric outcomes are shown in the table below. There were no significant changes in triglycerides, cholesterol, and LDL, but HDL was significantly increased from 54 to 70.1 mg/dL. One 49-year-old patient developed a DVT. Estradiol valerate 10 mg IM was administered every 10 days, and goserelin acetate 3.8 mg subQ was administered every 4 weeks to suppress androgen secretion [56].

Hormone-Induced Changes in Median Anthropometric and Endocrine Parameters

	Baseline	24 Months
BMI (kg/m(2))	22.3	23.3*
Fat mass (kg)	10.7	14.3*
Lean mass (kg)	59.6	55.4*
Femur BMD (g/cm(2))	1.09	1.09
L2-L4 BMD (g/cm(2))	1.20	1.30*
LH (international units/L)	2.9	0.2*
FSH (international units/L)	2.8	0.2*
Testosterone (nanomoles/L)	13.0	0.7*
Estrogen (picomoles/L)	55.5	697.8*
Prolactin (milli-international units/L)	230.2	244.4
DHEAS (micromoles/L)	7.0	4.3
SHBG (nanomoles/L)	37.2	118.0*

*significant change from baseline

BMD, bone mineral density; BMI, body mass index; DHEAS, dehydroepiandrosterone sulphate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin

Dose Adjustments

Adult Dosage

Normal Dosage

Estradiol

Insertion, vaginal

Dyspareunia, Moderate to severe - Menopause

1) Imvexxy(TM)

a) Use lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Reevaluate periodically as clinically appropriate to determine if treatment is still necessary [5].

b) Initial dosage: 4 mcg intravaginally once daily at the same time each day for 2 weeks [5]

c) Maintenance dosage: 4 or 10 mcg intravaginally twice weekly (every 3 to 4 days); adjust dose based on clinical response [5]

d) Concomitant medication: Consider a progestin in postmenopausal women with a uterus to reduce the risk of endometrial cancer [5].

Oral route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The initial dose of oral estradiol for the treatment of moderate to severe vasomotor symptoms is 1 to 2 mg orally daily in a cyclical pattern (3 weeks on followed by 1 week off). Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [7].

Atrophic vulva (Moderate to Severe) - Menopause

1) The recommended initial dosing regimen is 1 to 2 mg orally daily in a cyclical pattern (3 weeks on, 1 week off). Adjust to the lowest dose as needed to control symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Attempt to taper or discontinue therapy at 3 to 6 month intervals [7].
2) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [7].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Initial dosage: 1 to 2 mg orally daily in a cyclical pattern (3 weeks on, 1 week off) [7]
2) Titration: Adjust dose as needed to control symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Attempt to taper or discontinue therapy at 3 to 6 month intervals [7].
3) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [7].
4) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [7].

Breast cancer, Metastatic; for palliation only

1) The dose of oral estradiol for the palliative treatment of breast cancer in appropriately selected women and men with metastatic disease is 10 mg orally 3 times daily for at least 3 months [7].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

1) The initial dose of oral estradiol for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is 1 to 2 mg orally daily. Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [7].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 2 to 6 mg orally daily with or without antiandrogens or gonadotropin-releasing hormone agonist [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Postmenopausal osteoporosis; Prophylaxis

1) The dose of oral estradiol for the prevention of postmenopausal osteoporosis is 0.5 mg orally daily for 23 days of a 28-day cycle. The lowest effective dose has not been established [7].
2) Postmenopausal women require an average of 1500 mg/day of elemental calcium. When calcium supplementation is not contraindicated, it may be useful for women with suboptimal dietary intake. Additionally, vitamin D supplementation of 400 to 800 international units daily may also be required to ensure adequate daily intake [7].
See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy

Prostate cancer, Advanced, Androgen-dependent; for palliation only

1) The dose of oral estradiol for the palliative treatment of advanced androgen-dependent prostate cancer is 1 to 2 mg orally 3 times daily. Determine the effectiveness of therapy by phosphatase levels as well as by symptomatic improvement [7].

Transdermal route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) Emulsion

a) The initial dose of estradiol topical emulsion for the treatment of moderate to severe vasomotor symptoms is one foil patch (1.74 g each) applied topically to clean, dry skin on each thigh daily for a total dose of 3.48 g (delivering 0.05 mg estradiol per day) [35].

2) Gel

a) Divigel(R)

1) Initial dosage: One 0.25 gram packet applied topically once daily, alternating between the right and left upper thigh. Apply to a 5x7-inch surface area and allow to dry before dressing. Do not wash application site within 1 hour after application [33].

2) Maximum dosage: Adjust dosage up to a MAX of 1.25 mg topically once daily as needed [33].

3) Treatment duration: Use the lowest effective dose for the shortest duration consistent with therapy goals [33]

b) Elestrin(R)

1) Initial dosage: Apply 0.87 g (1 pump, which delivers 0.52 mg estradiol) topically once daily via the metered-dose pump in a thin layer to the upper arm and shoulder area (approximately 320 cm(2)); adjust dose based on clinical response [34].

2) Treatment duration: Use the lowest effective dose for the shortest duration consistent with therapy goals [34]

c) Estrogel(R)

1) The initial dose of estradiol topical gel 0.06% (Estrogel(R)) for the treatment of moderate to severe vasomotor symptoms is 1.25 g/day (which delivers 0.75 mg estradiol) applied topically via the metered-dose pump to clean, dry, unbroken skin on the arm. Apply in a thin layer from wrist to shoulder and allow gel to dry for up to 5 minutes before dressing [13].

3) Patch

Initial dose: Outlined in the following table [29][19][8][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Minivelle(R)	0.0375 mg/day applied to the skin twice weekly	lower abdomen (below the umbilicus) or buttocks
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen

Dosage titration: Adjust dose based on clinical response, use lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10].

Alternative dose schedule: Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][12].

a) Switching from other formulations: Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated 1 week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than 1 week [8][12].

4) Spray

a) The initial dose of transdermal estradiol spray for the treatment of moderate to severe vasomotor symptoms is one spray (delivering 1.53 mg estradiol) applied to the forearm every morning. Dosage adjustment should be guided by the clinical response of the patient. If needed, the dose may be increased to 2 or 3 sprays daily based upon clinical response [36].

Atrophic vulva (Moderate to Severe) - Menopause

1) Gel

a) Apply 1.25 g/day (which delivers 0.75 mg estradiol) topically via the metered-dose pump to clean, dry, unbroken skin on the arm. The gel should be applied in a thin layer from wrist to shoulder and allowed to dry for up to 5 minutes before dressing. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [13].

b) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [13].

2) Patch

The initial dose of transdermal estradiol patches for the treatment of vulvar atrophy is outlined in the following table [19][8][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust dose based on clinical response, use the lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10][8][9][11][12].

Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [9][11][12].

a) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19][8][9][11][12].

b) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Gel

a) Usual dosage: Apply 1.25 g/day (which delivers 0.75 mg estradiol) topically via the metered-dose pump to clean, dry, unbroken skin on the arm. The gel should be applied in a thin layer from wrist to shoulder and allowed to dry for up to 5 minutes before dressing. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [13].

b) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [13].

c) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [13].

2) Patch

Initial dosage is provided in the following table [19][8][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust dose based on clinical response, use the lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10][9][11][12].

Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [9][11][12].

a) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19][8][9][11][12].

b) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [19][8][9][11][12].

c) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

The initial dose of transdermal estradiol patches for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is outlined in the following table [19][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen

Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [19][8][9][11][12]. Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][9][11][12].

1) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 0.025 to 0.2 mg/day transdermally with or without antiandrogens or gonadotropin-releasing hormone agonist; replace patch every 3 to 5 days [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Postmenopausal osteoporosis; Prophylaxis

Initial dose: Outlined in the following table [29][19][8][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.025 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Minivelle(R)	0.025 mg/day applied to the skin twice weekly	lower abdomen (below umbilicus) or buttocks
Vivelle-Dot(R)	0.025 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust according to severity of symptoms, response of the patient, biochemical markers, and measurements of bone mineral density. Adjust to lowest dose that will provide effective control [8][12].
May be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][12].

1) Concomitant therapy: Postmenopausal women require an average of 1500 mg/day of elemental calcium. When calcium supplementation is not contraindicated, it may be useful for women with suboptimal dietary intake. Additionally, vitamin D supplementation of 400 to 800 international units daily may also be required to ensure adequate daily intake [8][12].

2) Switching from other formulations: Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated 1 week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than 1 week [8][12].
See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy

Vaginal route

Atrophic vulva (Moderate to Severe) - Menopause

1) The recommended dose of estradiol vaginal cream is 2 to 4 g vaginally daily for 1 or 2 weeks, then gradually reduced to 50% of initial dose for a similar period. A maintenance dose of 1 g, administered 1 to 3 times a week, may be used after vaginal mucosa has been restored. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [14].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Vaginal Cream

a) Initial dosage: 2 to 4 g vaginally daily for 1 or 2 weeks, then gradually reduced to 50% of initial dose for a similar period [14].

b) Maintenance dosage: 1 g, administered 1 to 3 times a week, may be used after vaginal mucosa has been restored. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [14].

c) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [14].

2) Vaginal Ring

a) Usual dosage: 1 ring inserted as deeply as possible into the upper one-third of the vagina vault. The ring is to remain in place continuously for 3 months and then be removed. Replace with a new ring if additional therapy is appropriate. Attempt to taper or discontinue at 3 to 6 month intervals [15].

b) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [15].

3) Vaginal Insert

a) Initial dosage: 1 vaginal insert (10 mcg) inserted vaginally once daily for 2 weeks, preferably at the same time each day. The recommended maintenance dose is 1 vaginal insert 10 mcg twice weekly. Reevaluate treatment, and attempt to taper or discontinue periodically [16].

Menopause - Urethral atrophy (Moderate to Severe)

1) The recommended dose of estradiol vaginal ring is 1 ring (contains 2 mg estradiol) inserted as deeply as possible into the upper one-third of the vagina vault. The ring is to remain in place continuously for 3 months and then be removed. Replace with a new ring if additional therapy is appropriate. Attempt to taper or discontinue at 3- to 6-month intervals [15].

General Dosage Information

a) In postmenopausal women with a uterus, initiate progestin with estrogen to reduce the risk of endometrial cancer [34][19][8][12][7][38][13][14][15][35][36]; women with a history of hysterectomy and endometriosis may need a progestin [34][16][29].

b) Use estrogen, alone or with a progestin, at the lowest effective dose and for the shortest duration consistent with individual treatment goals and risks; reevaluate periodically (generally at 3 to 6 month intervals) to determine if treatment is still necessary [34][16][29][19][8][12][7][38][13][14][15][35][36].

Estradiol Acetate

Vaginal route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) Usual dose: 0.05 mg/day inserted intravaginally every 3 months, dose adjusted based on clinical response [59]
2) Use the lowest effective dose for the shortest duration consistent with treatment goals; reevaluate periodically to determine if treatment is necessary [59].
3) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. Women without a uterus generally do not need progestin therapy [59].

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

1) Usual dose: 0.05 mg/day ring inserted intravaginally every 3 months and dose adjust based on clinical response [59]
2) Use the lowest effective dose for the shortest duration consistent with treatment goals, and reevaluate periodically to determine if treatment is

necessary [59].
3) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. Women without a uterus generally do not need progestin therapy [59].

Estradiol Cypionate

Intramuscular route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The usual dose of estradiol cypionate for the treatment of moderate to severe vasomotor symptoms associated with menopause is 1 to 5 milligrams injected intramuscularly every 3 to 4 weeks [55].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [55].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [55].

Decreased estrogen level - Female hypogonadism syndrome

1) The dose of estradiol cypionate for the treatment of hypoestrogenism due to hypogonadism is 1.5 to 2 milligrams injected intramuscularly at monthly intervals [55].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [55].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [55].

Gender dysphoria - Male-to-female transsexual

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Estradiol Valerate

Intramuscular route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The dose of estradiol valerate for the treatment of moderate to severe vasomotor symptoms associated with menopause is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

1) The usual dose for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

1) The dose of estradiol valerate for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 5 to 30 mg IM every 2 weeks OR 2 to 10 mg IM every week with or without antiandrogens or gonadotropin-releasing hormone agonist [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hormone sensitive prostate cancer, Advanced, for palliation only

1) The dose of estradiol valerate for the palliative treatment of advanced androgen-dependent prostate cancer is 30 milligrams or more injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 1 or 2 weeks [57].

Dosage in Renal Failure

A) No specific recommendations are available [10].

Dosage in Hepatic Insufficiency

A) Use is contraindicated in patients with hepatic impairment or disease [10].

Dosage in Other Disease States

A) Cardiovascular Disorders

1) Immediately discontinue estrogen with or without progesterone therapy immediately if DVT, pulmonary embolism, stroke, or myocardial infarction occurs [10].

B) Cholestatic Jaundice

1) Discontinue use if reoccurs [10]

C) Fluid Retention

1) Discontinue use if medically concerning [10]

D) Hypercalcemia

1) Discontinue use if occurs [10]

E) Pancreatitis

1) Discontinue use if occurs [10]

F) Visual Abnormalities

1) Permanently discontinue use if papilledema or retinal vascular lesions occur [10].

Pediatric Dosage

Normal Dosage

Estradiol

Oral route

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage, Adolescents

a) Induction of female puberty: Initial, 5 mcg/kg/day orally for 6 months; increase dose by 5 mcg/kg/day every 6 months to an adult dosage of 2 to 6 mg/day [1]

b) Postpubertal transgender female: Initial, 1 mg/day orally for 6 months, then 2 mg/day [1]

c) Maintenance dosage: Adjust to mimic physiological estradiol levels [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Transdermal route

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage, Adolescents

a) Induction of female puberty: Initial, 6.25 to 12.6 mcg/24 hours applied every 3.5 days; increase dosage by 12.5 mcg/24 hours every 6 months to adult dosage of 50 to 200 mcg/24 hours to mimic physiological estradiol levels [1]

b) Maintenance dosage: Adjust to mimic physiological estradiol levels [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

General Dosage Information

a) Safety and efficacy in pediatric patients have not been established [34][16][29][19][41][7][13][38][8][12][35][36][14][15].

Estradiol Acetate

1) Safety and efficacy of the vaginal ring and oral tablets has not been established in pediatric patients [59][61].

Estradiol Valerate

1) Safety and efficacy not established in pediatric patients [58].

Administration

A) Estradiol

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: Use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package is recommended [52].

3) NIOSH: In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, use double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [52].

4) NIOSH: In the compounding and administration of a hazardous topical drug, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator, and use eye/face and respiratory protection if not prepared in a control device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection, and if there is inhalation potential use respiratory protection [52].

b) Transdermal route

1) Emulsion

a) Apply and rub emulsion into thighs and calves for 3 minutes on each side until thoroughly absorbed. Rub excess on both hands and buttocks and allow to dry completely before covering with clothing. Wash hands after application [35].

2) Gel

a) Divigel(R)

1) Apply entire contents of the single-dose packet to clean, dry skin of left or right upper thigh. The gel should not be applied to face, breasts, in or around vagina, or to irritated skin. Avoid contact with eyes. Allow to dry before dressing and do not wash application site within 1 hour after application. Wash hands with soap and water after application [38].

b) Estrogel(R)

1) Prime the metered dose pump by fully depressing the spout 2 times for the 93 g pump or 3 times for the 50 and 25 g pumps prior to the first use. Collect gel into palm of hand and apply directly onto dry, clean, unbroken skin of the upper arm and shoulder area. The gel should not be applied directly to breast. Apply gel gently from wrist to shoulder and allow to dry for up to 5 minutes before dressing. It is not necessary to massage or rub in the ge. Wash hands with soap and water after application [13].

c) Elestrin(R)

1) To prime the pump, push the head down slowly and allow it to spring back automatically; repeat until gel comes out. Throw away the first amount of gel (not a full dose) into the trash. Once the pump head has come all the way back up, the pump is ready to use [34].

2) If taking a bath or shower or using a sauna, apply dose afterwards. Dry skin completely before application. Apply dose at the same time each day [34].

3) Hold the pump with the tip facing clean, dry, unbroken skin of the application area of the arm, and press the pump firmly and fully for each pump needed. Gently spread the gel over the entire area of the upper arm and shoulder using 2 fingers. Do not apply to the breast or in or around the vagina. Wash hands after application [34].

4) Allow the gel to dry for at least 5 minutes before dressing, and keep the area dry for as long as possible. Avoid fire, flame, or smoking until the gel has dried. Do not allow others to come in contact with the application area for at least 2 hours. If swimming, wait at least 2 hours before going into the water. Do not apply sunscreen to the area where the gel was applied for at least 25 minutes, and do not apply for 7 or more consecutive days [34].

5) If a dose is missed, do not double the dose. If the next dose is less than 12 hours away, wait and apply the dose the next day. If it is more than 12 hours until the next dose, apply the missed dose and resume normal dosing the next day [34].

3) Transdermal System

a) Place system on clean, dry skin, preferably on the lower abdomen, upper quadrant of the buttock, or outer aspect of the hip. Do not apply to the breasts or waistline. Rotate sites of application with 1 week allowed between applications to a particular site [29][19][8][12].

b) Press Climara (R) system firmly in place for at least 10 seconds, making sure there is good contact, especially around the edges [10]

c) If Climara(R) or Minivelle(R) system falls off reapply to different site; if reapplication not possible, apply new patch to another location for remainder of dosing interval [29][19]

d) Swimming, bathing, or using a sauna may decrease the adhesion of the Climara (R) system and the delivery of estradiol [10]

e) Remove Climara(R) system carefully and slowly, fold it in half, and throw it away. If any adhesive remains on the skin, allow the area to dry for 15 minutes, then gently rub with an oil-based cream or lotion to remove residue [10].

4) Spray

a) Prior to initial application, prime pump by spraying 3 sprays with the cover on. With container being held vertically upright, apply to adjacent, nonoverlapping areas on the inner surface of the forearm, starting near the elbow. Allow to dry for 2 minutes before covering with clothing, and do not wash the site for 1 hour after application. Women should cover the application site with clothing if another person may come into contact with that area of the skin after the spray dries [53].

c) Vaginal route

1) Cream

a) The prescribed dose should be measured using the supplied applicator. Gently insert applicator with measured dose deeply into vagina and press plunger downward to original position. Clean the applicator with mild soap and warm water after use [14].

2) Ring

a) The vaginal ring should be inserted as deeply as possible into the upper one-third of the vaginal vault; the exact position is not critical. To remove the ring, hook a finger through the ring and pull. If the ring is removed or falls out any time during the 90-day treatment period, rinse the ring in lukewarm water and reinsert [15].

3) Insert

a) Using the supplied applicator for Vagifem(R), gently insert into the vagina as far as it can comfortably go without force, or until half of the applicator is inside the vagina, whichever is less [16].

b) Insert Imvexxy(TM) intravaginally with the smaller end up for a depth of about 2 inches into the vaginal canal [5].

B) Estradiol Acetate

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: Use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package is recommended [52].

3) NIOSH: In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, use double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [52].

b) Vaginal route

1) Administration

a) Wash hands thoroughly before and after inserting vaginal ring [59]

b) Press the opposite sides of the vaginal ring and insert into the vagina [59]

c) The patient may reposition estradiol acetate vaginal ring with finger if needed. If the ring is totally expelled from the vagina, it should be rinsed with lukewarm water and reinserted [59].

d) To remove, wash hands and hook finger through ring and gently pull downward [59].

C) Estradiol Cypionate

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if

the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [52].

b) Intramuscular route

1) Preparation

a) If crystals form because estradiol cypionate vials had been stored at lower temperatures than what is recommended, they may be redissolved by warming and shaking the vial [55].

D) Estradiol Valerate

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [52].

b) Intramuscular route

1) Administration

a) Estradiol valerate injection may be administered with a small gauge needle due to its low viscosity. A dry needle and syringe should be used since use of a wet needle or syringe may cause the solution to become cloudy [57].

b) Inject deep into the upper, outer quadrant of the gluteal muscle [57]

c) If crystals form because estradiol valerate vials had been stored at lower temperatures than what is recommended, they may be redissolved by warming [57].

d) Since the 40-milligram vial provides a high concentration in a low volume, particular care should be taken to administer the full prescribed dose [57].

E) Estradiol

1) Oral route

a) Tablet

1) Store at a controlled room temperature, 20 to 25 degrees C (68 to 77 degrees F); protect from light and close lid tightly [62].

2) Topical application route, Transdermal route

a) Gel/Jelly

1) Store at a controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [74][520][65].

3) Transdermal route

a) Patch, Extended Release

1) Store between 20 and 25 degrees C (66 and 77 degrees F). Store in the protective pouch and apply immediately after removal [29][67][66][521][19]. Excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [29][521][19].

b) Spray

1) Store at room temperature, between 20 and 25 degrees C (68 and 77 degrees F); do not freeze. Excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [69].

4) Vaginal route

a) Cream

1) Store at room temperature; protect from temperatures above 40 degrees C (104 degrees F) [73].

b) Insert, Extended Release

1) Store at a controlled room temperature between 15 and 25 degrees C (59 and 77 degrees F) [5][142], with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [5].

c) Insert, Extended Release

1) Store at a controlled room temperature, 25 degrees C (77 degrees F); do not refrigerate. Excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [16].

F) Estradiol Acetate

1) Oral route

a) Tablet

1) Store estradiol acetate tablets at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) [170].

2) Vaginal route

a) Insert, Extended Release

1) Store estradiol acetate vaginal ring at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) [60].

G) Estradiol Cypionate

1) Intramuscular route

a) Oil

1) Store estradiol cypionate injection at controlled room temperature (20 to 25 degrees Celsius or 68 to 77 degrees Fahrenheit) [55].

H) Estradiol Valerate

1) Intramuscular route

a) Oil

1) Store estradiol valerate injection at room temperature [57].

Comparative Efficacy

Conjugated Estrogens

Abnormal vasomotor function (Moderate to Severe) - Menopause

a) Transdermal estradiol was compared with conjugated estrogens in a controlled study involving 124 postmenopausal patients [20]. All patients were receiving conjugated estrogens prior to admission to the study; patients were then randomized to either continue conjugated estrogens or receive 0.1 mg daily of estradiol transdermally for 3 weeks. Doses of conjugated estrogens ranged from 0.625 to 1.25 mg daily. The estradiol system appeared equally effective as conjugated estrogens in controlling postmenopausal symptoms (hot flashes, sweating, headache, insomnia, vaginal discomfort, urge to urinate). Spotting or bleeding tendencies and breast tenderness were similar in both groups, and side effects were similar (less than 10%). However, skin irritation and rash occurred in several patients receiving the transdermal estradiol system, resulting in withdrawal of 13 patients from the study. No clinically significant differences were found in hemostatic parameters between women receiving transdermal estradiol or oral conjugated estrogens [21]. Similar results were observed with oral conjugated estrogens 0.3 mg per day or an estradiol patch delivering 0.025 mg/day for 12 weeks in 193 postmenopausal women [22].

b) Percutaneous estradiol (Oestrogel(R), a topical gel available in Europe) applied to the abdomen or thighs daily provided relief of menopausal symptoms equal to that of oral conjugated estrogens in a randomized, comparative study (Dupont et al, 1991). The topical gel resulted in a ratio of estradiol to estrone comparable to physiologic levels in the luteal phase of premenopausal women while oral conjugated estrogens did not (1.2 versus 0.1, respectively).

c) In a double-blind trial involving 29 females with postmenopausal syndrome, estradiol vaginal cream (0.01%) was compared with conjugated estrogens vaginal cream, both given daily at bedtime for 2 weeks [25]. Marked improvement in vaginal and vasomotor symptoms was noted with both drugs after 7 to 14 days. Plasma estrone and estradiol concentrations were significantly increased after both drugs, although the increase was more marked with estradiol than with the conjugated estrogens. The maturational indices of the parabasal and superficial cells were also significantly improved with both drugs. Adverse effects were mild (primarily breast tenderness and abdominal bloating), occurring in 7 of 20 patients receiving estradiol and 2 of 9 patients receiving conjugated estrogens. The authors concluded that both preparations were effective in the treatment of postmenopausal symptoms.

Atrophic vulva - Atrophy of vagina - Menopause

a) A 12-week comparison study involving the use of estradiol vaginal tablets (25 micrograms (mcg)) with conjugated estrogen cream (1 gram) daily in postmenopausal women with urogenital symptoms demonstrated that both treatments improved urogenital symptoms as well as vaginal health index and cytology. The improvements were noted after 4 weeks of treatment. Conjugated estrogen cream was superior in alleviating vaginal dryness and dyspareunia. Endometrial proliferation was noted in 2 patients after 12 weeks, but no hyperplasia or cancer was identified [522].

b) Transdermal estradiol (Estraderm(R)) was compared with conjugated estrogens in a controlled study involving 124 postmenopausal patients [20]. All patients were receiving conjugated estrogens prior to admission to the study; patients were then randomized to either continue conjugated estrogens or receive 0.1 mg daily of estradiol transdermally for 3 weeks. Doses of conjugated estrogens ranged from 0.625 to 1.25 mg daily. The estradiol system appeared equally effective as conjugated estrogens in controlling postmenopausal symptoms (hot flashes, sweating, headache, insomnia, vaginal discomfort, urge to urinate). Spotting or bleeding tendencies and breast tenderness were similar in both groups, and side effects were similar (less than 10%). However, skin irritation and rash occurred in several patients receiving the transdermal estradiol system, resulting in withdrawal of 13 patients from the study. No clinically significant differences were found in hemostatic parameters between women receiving transdermal estradiol or

oral conjugated estrogens [21]. Similar results were observed with oral conjugated estrogens 0.3 mg per day or an estradiol patch delivering 0.025 mg/day for 12 weeks in 193 postmenopausal women [22].

c) Women (n=176) with postmenopausal urogenital atrophy were evaluated for safety and efficacy using an estrogen vaginal ring or estrogen cream. The 12-week treatment period consisted of a vaginal ring which uniformly released estradiol 5 to 10 mcg/24 hours or nightly use of conjugated estrogen cream 0.625 mg for 3 weeks followed by one drug-free week; the conjugated estrogen cycle was repeated twice. Equivalence was demonstrated for vaginal dryness, dyspareunia, vaginal mucosal atrophy, and intercurrent vaginal bleeding. At the end of the treatment period no statistically significant difference was observed in the incidence of bleeding following the progestogen challenge test. Therapy with the estradiol vaginal ring was preferred over conjugated estrogen cream [23].

d) Although estradiol vaginal cream and conjugated estrogen vaginal cream are similarly effective in treating postmenopausal vaginal atrophy, estradiol may be preferred because of decreased undesirable effects [24]. Conjugated estrogens, given intravaginally, were found to cause a significant elevation in estrone and estradiol levels and an increase in sex hormone binding globulin (SHBG) capacity. Estradiol induced no such changes. Histological examination in 2 patients from each group showed no evidence of endometrial hyperplasia in the patients receiving estradiol, while moderate hyperplasia was found in both patients receiving conjugated estrogens.

e) In a double-blind trial involving 29 females with postmenopausal syndrome, estradiol vaginal cream (0.01%) was compared with conjugated estrogens vaginal cream, both given daily at bedtime for 2 weeks [25]. Marked improvement in vaginal and vasomotor symptoms was noted with both drugs after 7 to 14 days. Plasma estrone and estradiol concentrations were significantly increased after both drugs, although the increase was more marked with estradiol than with the conjugated estrogens. The maturational indices of the parabasal and superficial cells were also significantly improved with both drugs. Adverse effects were mild (primarily breast tenderness and abdominal bloating), occurring in 7 of 20 patients receiving estradiol and 2 of 9 patients receiving conjugated estrogens. The authors concluded that both preparations were effective in the treatment of postmenopausal symptoms.

Disorder of cardiovascular system; Prophylaxis

a) Plasminogen-activator inhibitor type 1 (PAI-1), which is an antagonist of fibrinolysis and inhibits tissue plasminogen activator and urokinase plasminogen activator, was reduced in postmenopausal women who received conjugated estrogen alone or in combination with medroxyprogesterone. Women (n=30) in group 1 were assigned conjugated estrogen 0.625 mg daily alone or in combination with medroxyprogesterone 2.5 mg daily for 1 month and then received the alternate therapy for 1 month. Women (n=20) in group 2 received transdermal estradiol 0.1 mg daily alone or in combination with medroxyprogesterone 2.5 mg daily. Plasma levels of PAI-1 were reduced from 32 ng/mL to 14 ng/mL following 1 month of conjugated estrogen therapy (p less than 0.001). One month after conjugated estrogen and medroxyprogesterone therapy, PAI-1 levels decreased from 31 ng/mL to 15 ng/mL (p=0.003). No significant differences in PAI-1 levels or in the degree of reduction from baseline were observed between the conjugated estrogen and the conjugated estrogen with medroxyprogesterone groups. LDL cholesterol levels decreased and HDL cholesterol levels increased in both groups. In the transdermal estradiol alone and estradiol with medroxyprogesterone groups there was no significant change in the PAI-1 levels from base line [525].

Postmenopausal osteoporosis; Prophylaxis

a) An 18-month trial comparing the effects of transdermal estradiol or oral conjugated estrogens vs placebo showed both active drug treatments to be associated with significant increases in bone mineral density (BMD) compared to no therapy. There were no significant differences in BMD between the two treatment groups [523].

b) Similar efficacy of micronized 17 beta-estradiol (Estrace(R)) 1 mg daily and conjugated estrogens (Premarin(R)) 0.625 mg daily in preventing bone loss in postmenopausal women (51 to 80 years of age) has been reported [524]. As protection from bone loss was demonstrated to persist as long as estrogen therapy with either compound was continued, these investigators recommend the early and continued use of hormonal replacement for life in postmenopausal women to prevent accelerated bone loss.

Adverse Effects

a) CARDIOVASCULAR EVENTS: In a case-control study of postmenopausal women (N=384), current use of oral conjugated equine estrogens (CEE) was associated with a significant 108% increase in the risk of venous thrombosis (VT) compared with current use of oral estradiol. Myocardial infarction (MI) risk was 87% higher, but the difference was not significant. Ischemic stroke risk was similar between groups. The women had no prior history of VT, MI, or ischemic stroke. Results were not influenced by age, daily estrogen dose, concomitant progestogen use, or timing of initiation of hormone therapy. CEE users had a greater likelihood of clotting than estradiol users, based on a 68% higher level of normalized activated protein C sensitivity ratio (nAPCsr). The difference in nAPCsr provided a possible biological mechanism for the observed difference in cardiovascular event risk [526].

Venlafaxine

Abnormal vasomotor function - Menopausal symptom

a) In the MsFLASH trial (N=339, midlife women), low-dose oral estradiol or low-dose venlafaxine decreased the mean frequency of vasomotor symptoms (VMS) associated with menopause at week 8 by 53% and 48%, respectively, a difference that was statistically significant compared with placebo (29%). Patients were randomized in a 2:2:3 ratio to 17-beta-estradiol 0.5-mg/day orally, venlafaxine XR 75 mg/day orally (titrated from 37.5 mg/day up to 75 mg/day over 1 week), or placebo for 8 weeks. The mean VMS frequency at baseline was 8.1/day [527].

Place In Therapy

A) Estradiol

1) Primary Prevention of Chronic Conditions in Postmenopausal Women

a) Use of estrogen alone has no net benefit for primary prevention of chronic conditions in most postmenopausal women who have had a hysterectomy and is therefore not recommended. These recommendations are applicable to the use of hormone therapy for primary prevention of chronic conditions in asymptomatic postmenopausal women. The statements do not apply in women considering hormone therapy to manage menopausal symptoms or in women who have had premature menopause (primary ovarian insufficiency) or surgical menopause. Decisions regarding therapy should be individualized to the specific patient or situation [43].

b) The following table summarizes evidence from randomized, placebo-controlled trials about the benefits and harms of estrogen-alone hormone therapy for prevention of chronic conditions in postmenopausal women [42]:

Outcome	Relative Benefit/Harm of HT	Relative Risk (95% Confidence Interval)*	Number of Trials	Number of Women	Strength of Evidence
Breast cancer (invasive)	NS	0.79 (0.61 to 1.01)	1^	10,739	Moderate
Colorectal cancer	NS	1.15 (0.81 to 1.63)	1^	10,739	Low
Lung cancer	NS#	1.04 (0.73 to 1.48)	1^	10,739	Low
Coronary heart disease	NS	0.95 (0.79 to 1.14)	3	11,310	High
Dementia (probable)	NS	1.49 (0.84 to 2.66)	1^	2947	Low
Diabetes, prevention	Benefit	0.87 (0.77 to 0.98)	1^	9917	Moderate
Fractures, prevention	Benefit	0.73 (0.65 to 0.8)	1^	10,739	High
Gallbladder disease	Harm	1.51 (1.32 to 1.73)	1^	8376	Moderate
Stroke	Harm	1.33 (1.06 to 1.67)	1^	10,739	Moderate
Urinary incontinence	Harm	1.53 (1.37 to 1.71)	1^	3073	Moderate
VTE	Harm	1.43 (1.11 to 1.85)	1^	10,739	Moderate
All-cause mortality	NS	1.01 (0.88 to 1.17)	3	11,961	High

KEY: HT=hormone therapy; NS=non-significant finding; VTE=venous thromboembolism

*Treatment with estrogen alone versus control.

^Estimates are based on the best available single study.

#Event rates were low, such that firm conclusions could not be made regarding difference between harm and benefit.

The absolute event rate difference for potential harms per 10,000 woman-years were estimated per each outcome as: Dementia (probable, 65 years or older), 12; gallbladder disease, 30; stroke, 11; VTE (DVT or pulmonary embolism), 11; urinary incontinence, 1261 [43].
The absolute event rate difference for potential benefits per 10,000 woman-years were estimated per each outcome as: Diabetes, -19; all fractures, -53; invasive breast cancer, -7 [43].

c) Although the review of randomized trials found no significant increase in the risk of invasive breast cancer with estrogen-only menopausal hormone therapy (MHT) [42], a meta-analysis of worldwide epidemiological data showed a significant increase in the risk of breast cancer in current estrogen users (except vaginal estrogens) compared with nonusers (RR, 1.37; 95% CI, 1.33 to 1.41). Results are based on 24 prospective studies and 61,383 cases of breast cancer; randomized studies did not have sufficient breast cancer cases for inclusion. The risk of breast cancer was greater with 5 through 14 years of estrogen use (RR, 1.33; 95% CI, 1.28 to 1.37) than with 1 through 4 years of use (RR, 1.17; 95% CI 1.1 to 1.26). Starting at age 50 years, the absolute 20-year breast cancer incidence rates were 7.4% with 10 years of estrogen use and 6.8% with 5 years

use versus 6.3% with no MHT use. There was no difference in risk between equine estrogen and estradiol or between oral and transdermal administration. In past users, excess duration-dependent risks continued for more than 10 years after MHT discontinuation. Of women who used estrogen-only MHT, 84% had received a hysterectomy [121].

2) Estrogen Replacement Therapy

a) Estrogen replacement therapy (ERT) increases bone mineral density, reduces the risk of osteoporotic fracture, and relieves postmenopausal vasomotor symptoms and symptoms of vaginal and vulval atrophy. When used solely for vulvar and vaginal atrophy, topical estrogens, such as vaginal creams, should be used. Nonestrogen products should be used for the prevention of osteoporosis and estrogen should be used only in cases of significant risk of osteoporosis and the benefit outweighs the risks associated with estrogen use. Estrogens (alone or combined with progestins) should not be used for the prevention of cardiovascular disease or dementia. Proven risks associated with estrogen monotherapy includes stroke, deep vein thrombosis, and development of probable dementia. Proven risks of estrogen/progestin therapy include myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, deep vein thrombosis, and development of probable dementia [16][7][13][38][8][92][12][36][14][15].

3) Estradiol Preparations

a) Oral estradiol is indicated for the treatment of moderate to severe menopausal vasomotor symptoms, moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause, hypoestrogenism due to hypogonadism, castration or primary ovarian failure, breast cancer in men and women with metastatic disease (palliation only), androgen-dependent prostate cancer (palliation only), and for the prevention of postmenopausal osteoporosis [7].

b) When prescribing oral estradiol solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women who are at a significant risk of developing osteoporosis and for whom non-estrogen medications are not considered to be appropriate [7].

c) Topical estradiol gel 0.06% (EstraGel(R)) is indicated for the treatment of moderate to severe menopausal vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause [13] while topical estradiol gel 0.1% (Divigel(R)) is indicated only for the treatment of moderate to severe menopausal vasomotor symptoms [38].

d) Estradiol is available as several different transdermal systems which vary by strength and whether they are applied once or twice weekly. All are to be applied to the lower abdomen or buttocks. The various estradiol transdermal systems are indicated for the treatment of moderate to severe menopausal vasomotor symptoms, moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause, hypoestrogenism due to hypogonadism, castration or primary ovarian failure, and/or for the prevention of postmenopausal osteoporosis [29][8][92][12].

e) Estradiol is also available as a transdermal spray. The spray is approved for the treatment of moderate to severe menopausal vasomotor symptoms [36].

f) Estradiol may also be given vaginally using any of the following formulations: estradiol vaginal cream, estradiol vaginal ring, or estradiol vaginal inserts. The vaginal cream is indicated for the treatment of vulvar and vaginal atrophy [14], while the vaginal ring is indicated for the treatment of moderate to severe urogenital symptoms associated with postmenopausal atrophy of the vagina and/or the lower urinary tract [15]. The vaginal insert Vagifem(R) is indicated for the treatment of atrophic vaginitis [16]. The vaginal insert Imvexxy(TM) is indicated for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause [5].

See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy
See Drug Consult reference: Canadian: Management of Osteoporosis in Men and Women

B) Estradiol Acetate

1) Estrogen Replacement Therapy

a) Estrogen replacement therapy (ERT) relieves postmenopausal symptoms and vaginal atrophy. When used solely for vulvar and vaginal atrophy, topical estrogens, such as vaginal creams, should be used. Estrogens (alone or combined with progestins) should not be used for the prevention of cardiovascular disease or dementia. Proven risks associated with estrogen monotherapy includes stroke, deep vein thrombosis, and development of probable dementia. Proven risks of estrogen/progestin therapy include myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, deep vein thrombosis, and development of probable dementia [170][60].

b) Many authorities recommend cyclical estrogen/progestin therapy for postmenopausal women. While this will decrease the risk of endometrial carcinoma, progestins may reverse the beneficial effects of estrogens on lipoproteins and risk of coronary atherosclerosis. Cyclic progestins may also affect compliance due to the return of withdrawal bleeding. There is no published data to suggest that women treated with cyclic estrogen/progestin regimens have a better overall mortality (or morbidity) than women treated with cyclic estrogens alone. There is also no basis for recommending that women without a uterus receive cyclic estrogen/progestin therapy, since these women have no risk of developing endometrial carcinoma.

c) There is no evidence that, in equipotent estrogenic doses, any one estrogen is superior to the others for treatment of menopausal symptoms or prevention of osteoporosis. The largest clinical experience, however, is with conjugated estrogens, followed by estradiol.

d) Use of estrogens for other menopausal problems such as skin or mood changes has not been proven effective.

2) Estradiol Acetate

a) Oral estradiol acetate is indicated for the treatment of moderate to severe menopausal vasomotor symptoms while estradiol acetate vaginal ring is indicated for the treatment of moderate to severe menopausal vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. However, if prescribing solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should always be considered first [170][60].

C) Estradiol Cypionate

1) Estrogen Replacement Therapy

a) Estrogen replacement therapy (ERT) increases bone mineral density, reduces the risk of osteoporotic fracture, and relieves postmenopausal symptoms and vaginal atrophy. Estrogens (alone or combined with progestins) should not be used for the prevention of cardiovascular disease or dementia. Proven risks associated with estrogen monotherapy includes stroke, deep vein thrombosis, and development of probable dementia. Proven risks of estrogen/progestin therapy include myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, deep vein thrombosis, and development of probable dementia [55]. When used solely for vulvar and vaginal atrophy, topical estrogens, such as vaginal creams, should be used. Nonestrogen products should be used for the prevention of osteoporosis and estrogen should be used only in cases of significant risk of osteoporosis and the benefit outweighs the risks associated with estrogen use.

b) Many authorities recommend cyclical estrogen/progestin therapy for postmenopausal women. While this will decrease the risk of endometrial carcinoma, progestins may reverse the beneficial effects of estrogens on lipoproteins and risk of coronary atherosclerosis. Cyclic progestins may also affect compliance due to the return of withdrawal bleeding. There is no published data to suggest that women treated with cyclic estrogen/progestin regimens have a better overall mortality (or morbidity) than women treated with cyclic estrogens alone. There is also no basis for recommending that women without a uterus receive cyclic estrogen/progestin therapy, since these women have no risk of developing endometrial carcinoma.

c) There is no evidence that, in equipotent estrogenic doses, any one estrogen is superior to the others for treatment of menopausal symptoms or prevention of osteoporosis. The largest clinical experience, however, is with conjugated estrogens, followed by estradiol.

d) Use of estrogens for other menopausal problems such as skin or mood changes has not been proven effective.

2) Estradiol Cypionate

a) Estradiol cypionate injection is indicated for the treatment of moderate to severe menopausal vasomotor symptoms associated with menopause and hypoestrogenism due to hypogonadism [55].

D) Estradiol Valerate

1) Estrogen Replacement Therapy

a) Estrogen replacement therapy (ERT) increases bone mineral density, reduces the risk of osteoporotic fracture, and relieves postmenopausal symptoms and vaginal atrophy. When used solely for vulvar and vaginal atrophy, topical estrogens, such as vaginal creams, should be used. Nonestrogen products should be used for the prevention of osteoporosis and estrogen should be used only in cases of significant risk of osteoporosis and the benefit outweighs the risks associated with estrogen use. Estrogens (alone or combined with progestins) should not be used for the prevention of cardiovascular disease or dementia. Proven risks associated with estrogen monotherapy includes stroke, deep vein thrombosis, and development of probable dementia. Proven risks of estrogen/progestin therapy include myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, deep vein thrombosis, and development of probable dementia [57].

b) Many authorities recommend cyclical estrogen/progestin therapy for postmenopausal women. While this will decrease the risk of endometrial carcinoma, progestins may reverse the beneficial effects of estrogens on lipoproteins and risk of coronary atherosclerosis. Cyclic progestins may also affect compliance due to the return of withdrawal bleeding. There is no published data to suggest that women treated with cyclic estrogen/progestin regimens have a better overall mortality (or morbidity) than women treated with cyclic estrogens alone. There is also no basis for recommending that women without a uterus receive cyclic estrogen/progestin therapy, since these women have no risk of developing endometrial carcinoma.

c) There is no evidence that, in equipotent estrogenic doses, any one estrogen is superior to the others for treatment of menopausal symptoms or prevention of osteoporosis. The largest clinical experience, however, is with conjugated estrogens, followed by estradiol.

d) Use of estrogens for other menopausal problems such as skin or mood changes has not been proven effective.

2) Estradiol Valerate

a) Estradiol cypionate injection is indicated for the treatment of moderate to severe menopausal vasomotor symptoms associated with menopause, moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause, hypoestrogenism due to hypogonadism, castration, or primary ovarian failure, and treatment of advanced androgen-dependent carcinoma of the prostate (palliation only) [57].

MEDICATION SAFETY

Contraindications

A) Estradiol

1) Known anaphylactic reaction, angioedema, or hypersensitivity to estradiol or any component of the product [70][71][64][72][66][74][75][76][19][69]

2) Active arterial thromboembolic disease (eg, stroke, myocardial infarction) or history of these conditions [70][64][5][72][66][74][69][76][7][14][75][19][8]

3) Breast cancer, whether known, suspected, or history of this condition [70][64][5][72][66][74][69][19][75]; except in appropriately selected patients being treated for metastatic disease [76][7][14][8]

4) Active DVT, pulmonary embolism, or history of these conditions [70][64][5][72][66][74][69][76][7][14][75][19][8]

5) Estrogen-dependent neoplasia, whether known or suspected [70][64][5][72][66][74][76][7][14][75][19][8]

6) Hepatic impairment or disease [70][64][5][72][66][74][69][76][7][14][75][19][8]

7) Pregnancy, whether known or suspected [72][69][76][7][14][75][8]

8) Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders [70][64][5][72][66][74][69][75][76][19]

9) Undiagnosed abnormal genital bleeding [70][64][5][72][66][74][69][76][7][14][75][19][8]

B) Estradiol Acetate

1) Active or history of arterial thromboembolic disease (eg, stroke, myocardial infarction) [59][61]

2) Active or history of DVT or pulmonary embolism [59][61]

3) Anaphylactic reaction or angioedema to Femring(R) [59]

4) Breast cancer (known, suspected, or history of) [59][61]

5) Estrogen-dependent neoplasia [59][61]

6) Hypersensitivity to estradiol acetate or product ingredients [59][61]

7) Liver dysfunction or disease [59][61]

8) Pregnancy [59][61]

9) Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders [59]

10) Undiagnosed abnormal genital bleeding [59][61]

C) Estradiol Cypionate

1) Arterial thromboembolic disease (stroke, myocardial infarction) (active or recent) [55]

2) Breast cancer (known, suspected or history of) [55]

3) Deep vein thrombosis/pulmonary embolism (active or a history of these conditions) [55]

4) Estrogen-dependent neoplasia (known or suspected) [55]

5) Genital bleeding, undiagnosed abnormal [55]

6) Hypersensitivity to estradiol cypionate or product ingredients [55]

7) Liver dysfunction or disease [55]

8) Pregnancy (known or suspected) [55]

D) Estradiol Valerate

1) Undiagnosed abnormal genital bleeding [58]

2) Known, suspected, or history of breast cancer [58]

3) Known or suspected estrogen-dependent neoplasia [58]

4) Active or history of deep vein thrombosis or pulmonary embolism [58]

5) Active or recent (within the past year) arterial thromboembolic disease (eg, myocardial infarction, stroke) [58]

6) Liver disease or dysfunction [58]

7) Known hypersensitivity to estradiol valerate [58]

8) Known or suspected pregnancy [58]

Precautions

A) Estradiol

1) Angioedema: Hereditary angioedema; estrogens may exacerbate symptoms of angioedema [16][29][66][74][69][75][76][19]

2) Application: Fire, flame, and smoking should be avoided until applied alcohol-based products are

dried [74][69][76][75]

3) Cardiovascular: Arterial vascular disease risk factors (eg, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, obesity) increase the risk of cardiovascular disorders [5][16][29][72][66][74][69][76][7][14][75][19][8]; discontinue therapy in all patients if pulmonary embolism, DVT, stroke or myocardial infarction are suspected [68][10][33] or occur [71]

4) Cardiovascular: VTE risk factors (eg, personal or family history of VTE, obesity, systemic lupus erythematosus) increase the risk of cardiovascular disorders [68][10][5][29][72][74][69][76][7][14][75][8]; discontinue therapy in all patients if pulmonary embolism, DVT, stroke or myocardial infarction are suspected [68][10][33] or occur [71].

5) Cardiovascular: Men given large doses of estrogen (conjugated estrogens 5 mg/day) may have increased risk of myocardial infarction, pulmonary embolism, or thrombophlebitis [7][14][8]

6) Cardiovascular: Elevated blood pressure may occur [5][29][74]; monitoring recommended [19]

7) Cardiovascular: Hypertension may occur or worsen; monitoring recommended [72][66][76][7][14][15][75][19][8]

8) Endocrine and metabolic: Severe hypercalcemia may occur in women with bone metastases from breast cancer; discontinue [5][16][29][72][66][74][69][76][7][14][14][75][19][8]

9) Endocrine and metabolic: Triglyceride elevation leading to pancreatitis or other complications may occur in patients with preexisting hypertriglyceridemia [5][16][29][72][66][74][69][76][7][14][75][8]; discontinue if pancreatitis occurs [63][71][68][10]

10) Endocrine and metabolic: Hypothyroidism; estrogen increases thyroid-binding globulin levels which may require a dosage increase in thyroid replacement therapy; monitoring recommended [5][16][29][72][66][74][69][76][7][14][75][19][8]

11) Endocrine and metabolic: Premature puberty/breast development (females) and gynecomastia (males) have been reported in children from inadvertent skin exposure to transdermal spray; contact with unwashed or unclothed application sites should be avoided [69]

12) Endocrine and metabolic: Fluid retention may be exacerbated in patients with conditions affected by fluid retention (cardiac or renal dysfunction); monitoring recommended [63][68][10][5][16][29][72][69][76][7][14][75][8]; discontinuation may be necessary [10][33]. Discontinue estrogen-alone therapy with evidence of medically concerning fluid retention [63][71][68].

13) Endocrine and metabolic: Hypocalcemia may occur in patients with hypoparathyroidism [5][16][29][72][66][74][69][75][76][19]

14) Endocrine and metabolic: Diabetes mellitus exacerbation may occur [5][16][29][72][66][74][69][76][7][14][75][19][8]

15) Endocrine and metabolic: Prepubertal boys; estrogen treatment may modify the normal pubertal process and induce gynecomastia [7][14][8][12]

16) Endocrine and metabolic: Prepubertal children; large and repeated doses of estrogen over an extended time period may accelerate epiphyseal closure, which could result in short adult stature [66][7][14][8]

17) Gastrointestinal: Gallbladder disease requiring surgery; estrogens reported to increase risk in postmenopausal women [5][16][29][72][66][74][69][76][7][14][75][19][8]

18) Hematologic: Surgeries associated with an increased risk of thromboembolism or periods of prolonged immobilization; discontinuation at least 4 to 6 weeks prior to surgery recommended [5][16][29][72][66][74][69][76][7][14][75][19][8]

19) Hematologic: Porphyria may be exacerbated [5][16][29][72][66][74][69][76][7][14][75][19][8]

20) Hepatic: Hepatic impairment or history of cholestatic jaundice with past estrogen use or pregnancy; discontinue if cholestatic jaundice recurs [5][16][29][72][66][74][69][76][7][14][75][19][8]

21) Hepatic: Hepatic hemangiomas may be exacerbated [5][16][29][72][66][74][69][76][7][14][75][19][8]

22) Immunologic: Anaphylaxis and angioedema have been reported [29][66]

23) Immunologic: Systemic lupus erythematosus may be exacerbated [5][16][29][72][66][74][69][76][7][14][75][19][8]

24) Immunologic: Tartrazine (FD&C Yellow No. 5) sensitivity, especially with aspirin sensitivity; oral tablets may cause allergic-type reaction [7]

25) Neurologic: Epilepsy or migraines may be exacerbated [5][16][29][72][66][74][69][76][7][14][75][19][8]

26) Ophthalmic: Retinal vascular thrombosis has been reported; discontinuation may be necessary [5][16][29][72][66][74][69][76][7][14][75][19][8]

27) Ophthalmic: Visual abnormalities may occur; discontinue therapy if papilledema or retinal vascular lesions occur [63][71][68][10]

28) Reproductive: Prolonged therapy; increased risk of breast or endometrial [5][29][16] or ovarian cancer with duration of use [29][72][66][74][69][76][7][14][75][19][8]

29) Reproductive: Ovarian cancer; estrogens with or without progestin may increase risk [5][29][16][29][72][66][74][69][76][7][14][75][19][8]

30) Reproductive: Endometriosis may be exacerbated in patients with residual, post-hysterectomy endometriosis treated with estrogen alone; consider adding a progestin [5][29][16][29][72][66][74][69][76][7][14][75][19][8]

31) Reproductive: Prepubertal girls; estrogen treatment induces premature breast development and vaginal cornification, and may induce vaginal bleeding [66][7][14][8]

32) Reproductive: Abrasions induced by the Vagifem(R) applicator have been reported, particularly in women with severely atrophic vaginal mucosa [16]

33) Reproductive: Vaginal infection; treat before initiating or continuing therapy with vaginal ring or vaginal insert [72]

34) Reproductive: Vaginal irritation (narrow, short or stenosed vagina); irritation or ulceration may occur with vaginal ring use [72]

35) Respiratory: Asthma exacerbations may occur [5][29][16][29][72][66][74][69][76][7][14][75][19][8]

36) Sunscreen use: Absorption of transdermal and topical formulations may be affected [69][76][13][75]

37) Systemic absorption: May occur with vaginal insert use; precautions associated with systemic estrogen alone therapy should be taken into account [5]

B) Estradiol Acetate

1) Angioedema: Hereditary angioedema may be exacerbated [59][61]

2) Cardiovascular: Monitor patients with risk factors for arterial vascular disease (eg, hypertension, diabetes, tobacco use, hypercholesterolemia, obesity) or VTE (eg, personal or family history of VTE, obesity, systemic lupus erythematosus) due to increased risk of cardiovascular disorders with use of estrogen mono- or combination therapy [59][61]

3) Cardiovascular: Significant blood pressure increases have occurred with estrogen use [59][61]

4) Cardiovascular: Conditions affected by fluid retention (eg, cardiac or renal dysfunction) may worsen; monitoring recommended [59][61]

5) Endocrine and metabolic: Hypothyroid patients treated with thyroid hormone replacement therapy require monitoring and possible thyroid hormone dose adjustment due to increased thyroid-binding globulin levels [59][61]

6) Endocrine and metabolic: Severe hypercalcemia may occur in women with breast cancer and bone metastases; discontinue if condition develops [59][61]

7) Endocrine and metabolic: Triglyceride elevations have been reported, which may progress to pancreatitis in women with preexisting hypertriglyceridemia; discontinuation may be required [59][61]

8) Endocrine and metabolic: Hypoparathyroidism; use with caution as hypocalcemia may occur with estrogen use [59][61]

9) Endocrine and metabolic: Diabetes may be exacerbated; use with caution [59][61]

10) Gastrointestinal: A 2 to 4-fold increased risk of gallbladder disease requiring surgery has been reported in postmenopausal women with estrogen use [59][61]

11) Hematologic: Porphyria may be exacerbated; use with caution [59][61]

12) Hepatic: Liver impairment; poor estrogen metabolism may occur [59][61]

13) Hepatic: Use caution in patients with a history of cholestatic jaundice and discontinue if condition recurs [59][61]

14) Hepatic: Hepatic hemangioma may be exacerbated; use with caution [59][61]

15) Immunologic: Systemic lupus erythematosus may be exacerbated; use with caution [59][61]

16) Neurologic: Epilepsy may be exacerbated; use with caution [59][61]

17) Neurologic: Migraines may be exacerbated; use with caution [59][61]

18) Ophthalmic: Retinal vascular thrombosis has been reported; interrupt therapy if condition is suspected and permanently discontinue if confirmed [59][61]

19) Reproductive: Estrogen mono- or combination therapy may increase risk of ovarian cancer [59][61]

20) Reproductive: Vaginal form may not be suitable for women susceptible to vaginal irritation or ulceration or with conditions that increase the risk of expulsion (eg, vaginal stenosis, narrow vagina, vaginal infection, cervical prolapse, rectoceles, cystoceles) [59][61]

21) Reproductive: Endometriosis exacerbation may occur with estrogen alone; consider adding a progestin in patients known to have residual endometriosis posthysterectomy [59][61]

22) Respiratory: Asthma may be exacerbated; use with caution [59][61]

23) Surgery: If possible, discontinue estrogens at least 4 to 6 weeks before prolonged bedrest or elective surgery associated with thromboembolism risk [59][61]

C) Estradiol Cypionate

1) Endometrial cancer; unopposed estrogen use increases the risk in women with intact uteri [55]

2) Cardiovascular disorders; estrogens with or without progestins should not be used for the prevention of cardiovascular disease [55]

3) Myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, deep vein thrombosis; conjugated estrogens plus progestin increased the risk in postmenopausal women aged 50 to 79 years; risk should be assumed to be similar with all doses of conjugated estrogens with medroxyprogesterone acetate and with other combinations and dosage forms of estrogens and progestins [55]

4) Dementia; conjugated estrogens in combination with medroxyprogesterone increased the risk of probable dementia in postmenopausal women aged 65 years and older and should not be used for the prevention of dementia; risk should be assumed to be similar with all doses of conjugated estrogens with medroxyprogesterone acetate and with other combinations and dosage forms of estrogens and progestins [55]

5) Addition of a progestin to estrogen therapy; lowers incidence of endometrial hyperplasia in women with a uterus but may also increase risk of breast cancer, affect lipoprotein metabolism, and impair glucose tolerance [55]

6) Arterial vascular disease risk factors (hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, obesity); increased risk of cardiovascular events [55]

7) Asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas; estrogen therapy may cause exacerbation [55]

8) Breast cancer and bone metastases; increased risk for severe hypercalcemia [55]

9) Conditions affected by fluid retention (cardiac or renal dysfunction); estrogens may exacerbate condition [55]

10) Endometriosis; estrogen therapy may cause exacerbation [55]

11) Gallbladder disease requiring surgery; estrogens increases risk 2- to 4-fold in postmenopausal women [55]

12) Hypertension; estrogen therapy may increase blood pressure [55]

13) Hypertriglyceridemia; may elevate plasma triglycerides leading to pancreatitis and other complications [55]

14) Hypocalcemia, severe; estrogens should be used with caution [55]

15) Hypothyroidism; estrogen increases thyroid-binding globulin levels which may require a dosage increase in thyroid replacement therapy [55]

16) Impaired liver function or history of cholestatic jaundice; decreased estrogen metabolism [55]

17) Ovarian cancer; estrogens with or without progestin may increase risk [55]

18) Prolonged therapy; estrogen-plus-progestin combination therapy increases risk of breast cancer with duration of use [55]

19) Retinal vascular thrombosis has been reported in patients receiving estrogens; discontinue conjugated estrogens if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine [55]

20) Surgeries associated with an increased risk of thromboembolism or periods of prolonged immobilization; increased risk of thromboembolism [55]

21) Venous thromboembolism risk factors (personal or family history, obesity, systemic lupus erythematosus); increased risk of developing venous thromboembolism [55]

D) Estradiol Valerate

1) Cardiovascular: Blood pressure elevations may occur; monitoring recommended [58]

2) Cardiovascular: Fluid retention may occur. Use caution in patients with conditions affected by fluid retention (eg, cardiac or renal dysfunction); monitoring recommended [58]

3) Endocrine and metabolic: Exacerbation of diabetes mellitus may occur [58]

4) Endocrine and metabolic: Exercise caution in patients with severe hypocalcemia [58]

5) Endocrine and metabolic: Increased doses of thyroid replacement therapy may be required in patients dependent on thyroid hormone replacement therapy; monitoring recommended [58]

6) Endocrine and metabolic: Preexisting hypertriglyceridemia increases risk of triglyceride elevations leading to pancreatitis [58]

7) Endocrine and metabolic: Severe hypercalcemia may occur in the presence of breast cancer and bone metastases; discontinue use [58]

8) Gastrointestinal: Increased risk of gallbladder disease requiring surgery has been reported [58]

9) Hematologic: Exacerbation of porphyria may occur [58]

10) Hematologic: Hypercoagulability, primarily related to decreased antithrombin activity, may occur [58]

11) Hepatic: Exacerbation of hepatic hemangiomas may occur [58]

12) Hepatic: Impaired liver function; poor metabolism of estrogens may occur [58]

13) Hepatic: Use caution in patients with a history of cholestatic jaundice associated with past estrogen use or pregnancy; if reoccurrence occurs discontinue use [58]

14) Immunologic: Exacerbation of systemic lupus erythematosus may occur [58]

15) Neurologic: Exacerbation of epilepsy may occur [58]

16) Neurologic: Exacerbation of migraine may occur [58]

17) Neurologic: Increased risk of stroke among women 50 years of age or older; discontinue if stroke occurs or is suspected [58]

18) Ophthalmic: Retinal vascular thrombosis has been reported; discontinuation may be necessary [58]

19) Reproductive: Abnormal uterine bleeding and/or mastodynia may occur [58]

20) Reproductive: Addition of a progestin during estrogen administration when a woman has not had a hysterectomy may decrease incidence of endometrial hyperplasia [58]

21) Reproductive: Exacerbation of endometriosis may occur and lead to malignant transformation of residual implants post-hysterectomy with estrogen therapy alone; consider addition of progestin therapy [58]

22) Reproductive: Increased risk of ovarian cancer [58]

23) Respiratory: Exacerbation of asthma may occur [58]

24) Surgery: Discontinue 4 to 6 weeks before surgery that is associated with increased risk of VTE, or during prolonged immobilization [58]

Adverse Effects

Cardiovascular Effects

Estradiol

Coronary arteriosclerosis

a) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): 59% decreased risk of coronary artery disease in ever-users of unopposed estrogen or estrogen plus progestin therapy compared with never-users [103]

Edema

a) Incidence: Transdermal system, 0.5% to 13% [19]

b) General Information

1) Edema has been reported with estrogen and/or progestin therapy [76][7][38][35][8][19][11][12][36][14][15].

c) Adult Clinical Studies

1) Estrogen replacement (transdermal route): 0.5% to 13% vs 6% with placebo [19]

Heart disease

a) General Information

1) No cardiovascular benefit occurred with estrogen mono- or combination therapy [29][69]

2) No overall effect on coronary heart disease events was reported with estrogen monotherapy [29][69]

b) Prevention and Management

1) Appropriately manage risk factors for arterial vascular disease (eg, obesity, high cholesterol, tobacco use, diabetes, hypertension) [29][69]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69]

3) Do not use estrogen alone or with progestin to prevent cardiovascular disease [29][69]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Risk of all coronary heart disease (CHD) events (ie, nonfatal myocardial infarction, CHD death) with conjugated estrogen plus medroxyprogesterone acetate was increased non-significantly vs placebo. In a subgroup analysis, a nonsignificant reduction in CHD events was seen in women treated less than 10 years after menopause [29][69]

2) Hormone replacement therapy (oral route): No cardiovascular benefit was seen in postmenopausal women with heart disease with conjugated estrogen plus medroxyprogesterone acetate therapy. There were more cardiovascular heart disease (CHD) events in the first year compared with placebo, but not after year 1 [69][76][7][13][38][35][8][19][11][12][14][15].

Hypertension

a) General Information

1) May produce or exacerbate hypertension in some women, especially with higher-dose estrogens used in contraceptives, in older menopause-treatment regimens, and in cancer treatment [97][98][99][100][101]

2) Substantial increases in blood pressure were reported as idiosyncratic reactions to estrogens in some cases, but a generalized effect of estrogen on blood pressure was not demonstrated in a large randomized trial [29][76][7][38][35][8][19][11][12][36][14][15]

Ischemic heart disease, Mortality

a) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): death due to ischemic heart disease, 1% in current users, 3% in former users, and 3.7% in never users [104]

Myocardial infarction

a) General Information

1) Increased risk with estrogen and progestin combination therapy [29][69][74]

2) Risk for myocardial infarction or coronary death was reduced by 39% with estrogen monotherapy among women aged 50 to 59 years and 14% among women aged 60 to 69 years; 10% increased risk among women aged 70 to 79 years [93].

3) Risk of all coronary heart disease (CHD) events (ie, nonfatal myocardial infarction, CHD death) was not significantly higher with estrogen alone vs placebo [29][69]

4) A nonsignificant reduction in CHD events was seen in women treated less than 10 years after menopause [29][69]

5) Increased risk of nonfatal myocardial infarction in men with larger doses of conjugated estrogens for palliative care [7][13][38][35][8][11][12][14][15][94].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [86].

b) Prevention and Management

1) Appropriately manage risk factors for arterial vascular disease (eg, obesity, high cholesterol, tobacco use, diabetes, hypertension) [69][74][76][19]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69]

3) Oral administration was associated with a more than 2-fold increase in C-reactive protein (CRP) levels in 1 study; transdermal administration had no effect on CRP [95]

4) Discontinue immediately if condition occurs or is suspected [29][69][74][76][19]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route), Non-fatal myocardial infarction, estrogen monotherapy: Risk was 9% lower with conjugated estrogens vs placebo [69][74]

2) Hormone replacement therapy (oral route), Non-fatal myocardial infarction, estrogen-progestin therapy: Risk was 28% higher with conjugated estrogens plus medroxyprogesterone acetate vs placebo [29][69][74]

3) Estrogen replacement (oral, transdermal routes), C-reactive protein levels: Oral conjugated estrogen was linked to a more than 2-fold increase in highly sensitive C-reactive protein levels from baseline; transdermal estrogen had no effect [95]

4) Estrogen replacement: The prothrombin 20210 G A variant increased myocardial infarction risk among hypertensive women treated with hormone replacement therapy (HRT) compared with HRT-treated women without the prothrombin variant [96]

Myocardial ischemia

a) Postmarketing

1) Has been reported [74]

Raynaud's phenomenon

a) Incidence: 19.1% [102]
b) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): 19.1% with unopposed estrogen replacement therapy; 9.8% with estrogen plus progesterone; 8.4% with no estrogen therapy [102]

Thrombophlebitis

a) Postmarketing

1) Has been reported [66][72]

Estradiol Acetate

Edema

a) Edema has been reported with estrogen and/or progestin therapy [170].

Heart disease

a) Final reports from the Women's Health Initiative (WHI) Estrogen Alone trial indicate that estrogen only provided no overall protection against myocardial infarction or coronary death, however, there seemed to be a trend toward lowering the risk of coronary heart disease in women who were 50 to 59 years of age at baseline. The estrogen only study was halted after 6.8 years of follow-up [93][143][144].
b) At an average of 5.2 years follow-up, results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicated conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone acetate 2.5 mg daily lead to a significant increase in coronary heart disease (hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.02 to 1.63). After an average follow-up of 6.8 years in the WHI Estrogen-alone substudy, the relative risk of conjugated estrogens therapy versus placebo was 0.95 (95% CI 0.79 to 1.16) [170][145].
c) A secondary analysis of the Women's Health Initiative (WHI) Estrogen Plus Progestin trial identified a nonsignificant reduction in risk of coronary heart disease (CHD) among women who initiated hormone therapy closer to menopause compared with women who initiated hormone therapy more distant from onset of menopause. The hazard ratio (HR) for CHD in women who initiated hormone therapy within 10 years since menopause was 0.76 (95% confidence interval (CI), 0.50 to 1.16) compared to 1.10 (95% CI, 0.84 to 1.45) and 1.28 (95% CI, 1.03 to 1.58) for women who initiated therapy within 10 to 19 years and 20 or more years, respectively (p=0.02). The estimated absolute risk for CHD was -6 per 10,000 person-years for women within 10 years of menopause, 4 per 10,000 person-years for 10 to 19 years since menopause, and 17 per 10,000 person-years for 20 or more years from menopause. When the risk of CHD was analyzed by age, the number of events increased with age but there was no statistically significant additional effect of hormone therapy by age. The HR for CHD in women aged 50 to 59 years was 0.93 (95% CI, 0.65 to 1.33) compared with 0.98 (95% CI, 0.79 to 1.21) for women aged 60 to 69 years and 1.26 (95% CI, 1.00 to 1.59) in women aged 70 to 79 years (p=0.16). There was, however, a reduction in total mortality in women aged 50 to 59 years (HR, 0.70; 95% CI, 0.51 to 0.96) and a nonsignificant trend for increasing HRs across age groups was noted (p=0.06). The risk of stroke was increased with hormone therapy (HR, 1.32; 95% CI, 1.12 to 1.56) but the risk did not vary significantly by age or time since menopause [146].
d) Results from the Heart and Estrogen/progestin Replacement Study (HERS) indicated that treatment with conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily provided no cardiovascular benefit in postmenopausal women with documented heart disease (n=2763, mean age 66.7 years). During an average follow-up of 4.1 years, treatment did not reduce the overall rate of coronary heart disease (CHD) events. In year one, there were more CHD events in the estrogen/progestin treated group compared with placebo but this was not the case in subsequent years. In the open-label extension of HERS (HERS II, n=2321), after an additional follow-up of 2.7 years (6.8 years total), rates of CHD events were comparable among women in the estrogen/progestin group and the placebo group in the HERS, HERSII, and overall [170].

Hypertension

a) In a small number of cases, substantial increases in blood pressure were reported as idiosyncratic reactions to estrogens. However, in a large, randomized, controlled trial, a generalized effect of estrogen on blood pressure was not demonstrated [170].
b) Estrogen therapy can produce or exacerbate hypertension in some women. This effect is consistently found with the higher doses of estrogens used in contraceptives, in older menopause-treatment regimens, and in treatment of cancer [101][100]; [99][98][97].

Myocardial infarction

a) Summary

1) The data on risk of myocardial infarction (MI) in postmenopausal women receiving estrogen replacement is not definitive. The Women's Health Initiative (WHI) Estrogen Alone trial comparing estrogen to placebo was unable to demonstrate a significant difference in the risk of myocardial infarction or coronary death [93][144]. However, data from the WHI Estrogen Plus Progestin trial

involving estrogen plus progestin demonstrated an increased risk of nonfatal myocardial infarction after an average follow-up of 5.2 years (hazard ratio 1.32, 95% confidence interval 1.02 to 1.72) in postmenopausal women with a uterus who received estrogen and progestin therapy [170][145].

b) Final results from the Women's Health Initiative (WHI) Estrogen Alone trial involving unopposed estrogen therapy for coronary prevention, demonstrated no overall protection against myocardial infarction (MI) or coronary death in postmenopausal women without a uterus. The subjects (n=10,739, mean age 63.6 years) were randomized to oral conjugated equine estrogens (CEE) 0.625 milligrams or placebo daily. After a mean duration follow-up of 7.1 years, there were 201 coronary heart disease (CHD) events among women using CEE compared with 217 events among women receiving placebo (hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.79 to 1.16). The primary outcome (MI or coronary death) hazard ratios for patients aged 50 to 59 years, 60 to 69 years, and 70 to 79 years at baseline were 0.61 (95% CI, 0.25 to 1.50), 0.86 (95% CI, 0.60 to 1.25), and 1.10 (95% CI, 0.69 to 1.73), respectively. Additionally, coronary revascularization was less frequent in women aged 50 to 59 years who were receiving CEE (HR, 0.55; 95% CI, 0.35 to 0.86). This group was also associated with less frequent composite outcomes, such as HR for MI, coronary death, coronary revascularization, and confirmed angina (HR, 0.66; 95% CI, 0.45 to 0.96) [93].

c) Results of a population-based, case-control study indicated there was no difference in risk of myocardial infarction (MI) or stroke associated with the use of oral conjugated equine estrogen (CEE) or esterified estrogens (EE), but there was a suggested higher risk of ischemic stroke associated with CEE use alone and higher risk of MI associated with recent initiation of CEE. A total of 2724 postmenopausal women (mean age 67 to 70 years) with an incident MI (n=1644) or stroke (n=1080) were identified. The control group was comprised of a random sample of age-matched postmenopausal women without MI or stroke (n=4205). Compared with no use of hormone therapy, use of CEE or EE, with or without progestin, demonstrated little or no difference in risk of MI, ischemic stroke, or hemorrhagic stroke. When CEE and EE were compared, the use of CEE was not associated with any increased risk of MI (adjusted odds ratio (OR), 0.93; 95% confidence interval (CI), 0.65 to 1.31) or ischemic stroke (adjusted OR, 1.31; 95% CI, 0.88 to 1.97). The additional adjustment for progestin use had little impact on OR for either therapy. When CEE and EE use (without progestin) were compared to each other, there was no difference in risk for MI, but there was a suggestion of higher risk of ischemic stroke associated with the use of CEE alone (OR, 1.57; 95% CI, 0.98 to 2.53; p=0.06). There was also a suggestion of higher risk of MI and ischemic stroke associated with CEE when high daily doses (greater than 0.625 milligrams) of CEE and EE were compared, however, the number of subjects was small and the CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

d) Larger doses of estrogen (5 milligrams conjugated estrogens daily) used in palliation therapy of prostate and breast cancer have been shown to increase the risk of nonfatal myocardial infarction during a large prospective clinical trial involving men [170].

e) Oral conjugated estrogens (CEE) but not transdermal estradiol was found to increase C-reactive protein (CRP) levels in a randomized, crossover, placebo-controlled trial. Postmenopausal women (n=29) were randomized to CEE 0.625 milligrams/day, transdermal estradiol 100 micrograms/day, or placebo for 8 weeks. CRP, a marker of systemic inflammation and predictor of myocardial infarction and cardiovascular mortality, was measured before and after 8 weeks of therapy. Oral estrogen therapy caused a more than two-fold increase in highly sensitive CRP (p less than 0.01 versus baseline and placebo). In the same women, transdermal estrogen had no effect on CRP. The data suggests the route of estrogen replacement therapy may be an important consideration in minimizing the adverse effects of estrogen therapy on cardiovascular outcomes [95].

f) In a population-based, case-control study of 232 postmenopausal hypertensive women, the association between hormone replacement therapy (HRT) and myocardial infarction (MI) risk differed between those with and without the prothrombin 20210 G A variant. The prothrombin variant was a risk factor for MI among hypertensive women. In addition, there was a significant interaction between the use of HRT and the prothrombin variant on the risk of MI among women with hypertension. These findings need to be confirmed in other settings [96].

Raynaud's phenomenon

a) Incidence: 19.1% [102]

b) There was an association between postmenopausal patients using unopposed estrogen replacement therapy and Raynaud's phenomenon (19.1%) in women from the Framingham Offspring Cohort. The incidence was 9.8% among women receiving estrogen plus progesterone and 8.4% among those women not receiving estrogen. It has been suggested that estrogens may affect the pathogenesis of certain vascular disorders [102].

Estradiol Cypionate

Edema

a) Edema has been reported with estrogen and/or progestin therapy [55].

Heart disease

a) Final reports from the Women's Health Initiative (WHI) Estrogen Alone trial indicate that estrogen only provided no overall protection against myocardial infarction or coronary death, however, there seemed to be a trend toward lowering the risk of coronary heart disease in women who were 50 to 59 years of age at baseline. The estrogen only study was halted after 6.8 years of follow-up [93][143][144].

b) At an average of 5.2 years follow-up, results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicated conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone acetate 2.5 mg daily lead to a significant increase in coronary heart disease (hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.02 to 1.63). After an average follow-up of 6.8 years in the WHI Estrogen-alone substudy, the relative risk of conjugated estrogens therapy versus placebo was 0.95 (95% CI 0.79 to 1.16) [55][145].

c) A secondary analysis of the Women's Health Initiative (WHI) Estrogen Plus Progestin trial identified a nonsignificant reduction in risk of coronary heart disease (CHD) among women who initiated hormone therapy closer to menopause compared with women who initiated hormone therapy more distant from onset of menopause. The hazard ratio (HR) for CHD in women who initiated hormone therapy within 10 years since menopause was 0.76 (95% confidence interval (CI), 0.50 to 1.16) compared to 1.10 (95% CI, 0.84 to 1.45) and 1.28 (95% CI, 1.03 to 1.58) for women who initiated therapy within 10 to 19 years and 20 or more years, respectively (p=0.02). The estimated absolute risk for CHD was -6 per 10,000 person-years for women within 10 years of menopause, 4 per 10,000 person-years for 10 to 19 years since menopause, and 17 per 10,000 person-years for 20 or more years from menopause. When the risk of CHD was analyzed by age, the number of events increased with age but there was no statistically significant additional effect of hormone therapy by age. The HR for CHD in women aged 50 to 59 years was 0.93 (95% CI, 0.65 to 1.33) compared with 0.98 (95% CI, 0.79 to 1.21) for women aged 60 to 69 years and 1.26 (95% CI, 1.00 to 1.59) in women aged 70 to 79 years (p=0.16). There was, however, a reduction in total mortality in women aged 50 to 59 years (HR, 0.70; 95% CI, 0.51 to 0.96) and a nonsignificant trend for increasing HRs across age groups was noted (p=0.06). The risk of stroke was increased with hormone therapy (HR, 1.32; 95% CI, 1.12 to 1.56) but the risk did not vary significantly by age or time since menopause [146].

Increased blood pressure

a) In a small number of cases, substantial increases in blood pressure were reported as idiosyncratic reactions to estrogens. However, in a large, randomized, controlled trial, a generalized effect of estrogen on blood pressure was not demonstrated [55].

b) Estrogen therapy can produce or exacerbate hypertension in some women. This effect is consistently found with the higher doses of estrogens used in contraceptives, in older menopause-treatment regimens, and in treatment of cancer [101][100]; [99][98][97].

Myocardial infarction

a) General Information

1) Final results from the Women's Health Initiative (WHI) Estrogen Alone trial involving unopposed estrogen therapy for coronary prevention, demonstrated no overall protection against myocardial infarction (MI) or coronary death in postmenopausal women without a uterus. The subjects (n=10,739, mean age 63.6 years) were randomized to oral conjugated equine estrogens (CEE) 0.625 milligrams or placebo daily. After a mean duration follow-up of 7.1 years, there were 201 coronary heart disease (CHD) events among women using CEE compared with 217 events among women receiving placebo (hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.79 to 1.16). The primary outcome (MI or coronary death) hazard ratios for patients aged 50 to 59 years, 60 to 69 years, and 70 to 79 years at baseline were 0.61 (95% CI, 0.25 to 1.50), 0.86 (95% CI, 0.60 to 1.25), and 1.10 (95% CI, 0.69 to 1.73), respectively. Additionally, coronary revascularization was less frequent in women aged 50 to 59 years who were receiving CEE (HR, 0.55; 95% CI, 0.35 to 0.86). This group was also associated with less frequent composite outcomes, such as HR for MI, coronary death, coronary revascularization, and confirmed angina (HR, 0.66; 95% CI, 0.45 to 0.96) [93].

2) Results of a population-based, case-control study indicated there was no difference in risk of myocardial infarction (MI) or stroke associated with the use of oral conjugated equine estrogen (CEE) or esterified estrogens (EE), but there was a suggested higher risk of ischemic stroke associated with CEE use alone and higher risk of MI associated with recent initiation of CEE. A total of 2724 postmenopausal women (mean age 67 to 70 years) with an incident MI (n=1644) or stroke (n=1080) were identified. The control group was comprised of a random sample of age-matched postmenopausal women without MI or stroke (n=4205).

Compared with no use of hormone therapy, use of CEE or EE, with or without progestin, demonstrated little or no difference in risk of MI, ischemic stroke, or hemorrhagic stroke. When CEE and EE were compared, the use of CEE was not associated with any increased risk of MI (adjusted odds ratio (OR), 0.93; 95% confidence interval (CI), 0.65 to 1.31) or ischemic stroke (adjusted OR, 1.31; 95% CI, 0.88 to 1.97). The additional adjustment for progestin use had little impact on OR for either therapy. When CEE and EE use (without progestin) were compared to each other, there was no difference in risk for MI, but there was a suggestion of higher risk of ischemic stroke associated with the use of CEE alone (OR, 1.57; 95% CI, 0.98 to 2.53; p=0.06). There was also a suggestion of higher risk of MI and ischemic stroke associated with CEE when high daily doses (greater than 0.625 milligrams) of CEE and EE were compared, however, the number of subjects was small and the CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

3) Larger doses of estrogen (5 milligrams conjugated estrogens daily) used in palliation therapy of prostate and breast cancer have been shown to increase the risk of nonfatal myocardial infarction during a large prospective clinical trial involving men [55].

4) Oral conjugated estrogens (CEE) but not transdermal estradiol was found to increase C-reactive protein (CRP) levels in a randomized, crossover, placebo-controlled trial. Postmenopausal women (n=29) were randomized to CEE 0.625 milligrams/day, transdermal estradiol 100 micrograms/day, or placebo for 8 weeks. CRP, a marker of systemic inflammation and predictor of myocardial infarction and cardiovascular mortality, was measured before and after 8 weeks of therapy. Oral estrogen therapy caused a more than two-fold increase in highly sensitive CRP (p less than 0.01 versus baseline and placebo). In the same women, transdermal estrogen had no effect on CRP. The data suggests the route of estrogen replacement therapy may be an important consideration in minimizing the adverse effects of estrogen therapy on cardiovascular outcomes [95].

5) In a population-based, case-control study of 232 postmenopausal hypertensive women, the association between hormone replacement therapy (HRT) and myocardial infarction (MI) risk differed between those with and without the prothrombin 20210 G A variant. The prothrombin variant was a risk factor for MI among hypertensive women. In addition, there was a significant interaction between the use of HRT and the prothrombin variant on the risk of MI among women with hypertension. These findings need to be confirmed in other settings [96].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [86].

Raynaud's phenomenon

a) Incidence: 19.1% [102]
b) There was an association between postmenopausal patients using unopposed estrogen replacement therapy and Raynaud's phenomenon (19.1%) in women from the Framingham Offspring Cohort. The incidence was 9.8% among women receiving estrogen plus progesterone and 8.4% among those women not receiving estrogen. It has been suggested that estrogens may affect the pathogenesis of certain vascular disorders [102].

Estradiol Valerate

Edema

a) General Information

1) Edema has been reported with estrogen and/or progestin therapy [57].

Heart disease

a) General Information

1) Final reports from the Women's Health Initiative (WHI) Estrogen Alone trial indicate that estrogen only provided no overall protection against myocardial infarction or coronary death, however, there seemed to be a trend toward lowering the risk of coronary heart disease in women who were 50 to 59 years of age at baseline. The estrogen only study was halted after 6.8 years of follow-up [93] [143][144].

2) At an average of 5.2 years follow-up, results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicated conjugated estrogens 0.625

milligrams (mg) plus medroxyprogesterone acetate 2.5 mg daily lead to a significant increase in coronary heart disease (hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.02 to 1.63). After an average follow-up of 6.8 years in the WHI Estrogen-alone substudy, the relative risk of conjugated estrogens therapy versus placebo was 0.95 (95% CI 0.79 to 1.16) [57][145].

3) A secondary analysis of the Women's Health Initiative (WHI) Estrogen Plus Progestin trial identified a nonsignificant reduction in risk of coronary heart disease (CHD) among women who initiated hormone therapy closer to menopause compared with women who initiated hormone therapy more distant from onset of menopause. The hazard ratio (HR) for CHD in women who initiated hormone therapy within 10 years since menopause was 0.76 (95% confidence interval (CI), 0.50 to 1.16) compared to 1.10 (95% CI, 0.84 to 1.45) and 1.28 (95% CI, 1.03 to 1.58) for women who initiated therapy within 10 to 19 years and 20 or more years, respectively (p=0.02). The estimated absolute risk for CHD was -6 per 10,000 person-years for women within 10 years of menopause, 4 per 10,000 person-years for 10 to 19 years since menopause, and 17 per 10,000 person-years for 20 or more years from menopause. When the risk of CHD was analyzed by age, the number of events increased with age but there was no statistically significant additional effect of hormone therapy by age. The HR for CHD in women aged 50 to 59 years was 0.93 (95% CI, 0.65 to 1.33) compared with 0.98 (95% CI, 0.79 to 1.21) for women aged 60 to 69 years and 1.26 (95% CI, 1.00 to 1.59) in women aged 70 to 79 years (p=0.16). There was, however, a reduction in total mortality in women aged 50 to 59 years (HR, 0.70; 95% CI, 0.51 to 0.96) and a nonsignificant trend for increasing HRs across age groups was noted (p=0.06). The risk of stroke was increased with hormone therapy (HR, 1.32; 95% CI, 1.12 to 1.56) but the risk did not vary significantly by age or time since menopause [146].

Increased blood pressure

a) General Information

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2) Estrogen therapy can produce or exacerbate hypertension in some women. This effect is consistently found with the higher doses of estrogens used in contraceptives, in older menopause-treatment regimens, and in treatment of cancer [101][100]; [99][98][97].

Myocardial infarction

a) General Information

1) Final results from the Women's Health Initiative (WHI) Estrogen Alone trial involving unopposed estrogen therapy for coronary prevention, demonstrated no overall protection against myocardial infarction (MI) or coronary death in postmenopausal women without a uterus. The subjects (n=10,739, mean age 63.6 years) were randomized to oral conjugated equine estrogens (CEE) 0.625 milligrams or placebo daily. After a mean duration follow-up of 7.1 years, there were 201 coronary heart disease (CHD) events among women using CEE compared with 217 events among women receiving placebo (hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.79 to 1.16). The primary outcome (MI or coronary death) hazard ratios for patients aged 50 to 59 years, 60 to 69 years, and 70 to 79 years at baseline were 0.61 (95% CI, 0.25 to 1.50), 0.86 (95% CI, 0.60 to 1.25), and 1.10 (95% CI, 0.69 to 1.73), respectively. Additionally, coronary revascularization was less frequent in women aged 50 to 59 years who were receiving CEE (HR, 0.55; 95% CI, 0.35 to 0.86). This group was also associated with less frequent composite outcomes, such as HR for MI, coronary death, coronary revascularization, and confirmed angina (HR, 0.66; 95% CI, 0.45 to 0.96) [93].

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milligrams) of CEE and EE were compared, however, the number of subjects was small and the CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

3) Larger doses of estrogen (5 milligrams conjugated estrogens daily) used in palliation therapy of prostate and breast cancer have been shown to increase the risk of nonfatal myocardial infarction during a large prospective clinical trial involving men [57].

4) Oral conjugated estrogens (CEE) but not transdermal estradiol was found to increase C-reactive protein (CRP) levels in a randomized, crossover, placebo-controlled trial. Postmenopausal women (n=29) were randomized to CEE 0.625 milligrams/day, transdermal estradiol 100 micrograms/day, or placebo for 8 weeks. CRP, a marker of systemic inflammation and predictor of myocardial infarction and cardiovascular mortality, was measured before and after 8 weeks of therapy. Oral estrogen therapy caused a more than two-fold increase in highly sensitive CRP (p less than 0.01 versus baseline and placebo). In the same women, transdermal estrogen had no effect on CRP. The data suggests the route of estrogen replacement therapy may be an important consideration in minimizing the adverse effects of estrogen therapy on cardiovascular outcomes [95].

5) In a population-based, case-control study of 232 postmenopausal hypertensive women, the association between hormone replacement therapy (HRT) and myocardial infarction (MI) risk differed between those with and without the prothrombin 20210 G A variant. The prothrombin variant was a risk factor for MI among hypertensive women. In addition, there was a significant interaction between the use of HRT and the prothrombin variant on the risk of MI among women with hypertension. These findings need to be confirmed in other settings [96].

a) Trangender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [86].

Raynaud's phenomenon

a) Incidence: 19.1% [102]
b) Adult Clinical Trials

1) There was an association between postmenopausal patients using unopposed estrogen replacement therapy and Raynaud's phenomenon (19.1%) in women from the Framingham Offspring Cohort. The incidence was 9.8% among women receiving estrogen plus progesterone and 8.4% among those women not receiving estrogen. It has been suggested that estrogens may affect the pathogenesis of certain vascular disorders [102].

Dermatologic Effects

Estradiol

Application site irritation

a) Incidence: Transdermal spray, 1.3% [36]; transdermal system, 5.7% to 56.7% [29][8]
b) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 1.3% [36]

2) Estrogen replacement (transdermal route): Up to 3.2% [29]

3) Estrogen replacement (transdermal route): 5.7% to 56.7% vs 58.6% with placebo [8]

c) Postmarketing

1) Topical gel: Application site dryness, pain, discoloration, rash, and reaction have been reported [74]

Chloasma

a) General Information

1) May persist after discontinuation of estrogen and/or progestin therapy [76][7] [38][35][8][11][12][36][14][15]

Erythema multiforme

a) Postmarketing

1) Has been reported [76]

Hirsutism

a) General Information

1) Hirsutism has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

Loss of scalp hair

a) General Information

1) Loss of scalp hair has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

Persistent erythema of skin

a) Incidence: Transdermal system, less than or equal to 3.2% [29]
b) Adult Clinical Trials

1) Estrogen replacement (transdermal route): Less than or equal to 3.2% [29]

Pruritus

a) Incidence: Topical emulsion, 4% [35]
b) General Information

1) Pruritus has been reported with estrogen and/or progestin therapy [76][7][38][35][8][92][11][12][36][14][15]

c) Adult Clinical Studies

1) Estrogen replacement (topical route): 4% with estradiol topical emulsion vs 0% with placebo [35]; topical gel, noted in clinical studies [74]

d) Postmarketing

1) Has been reported [29]

Estradiol Acetate

Chloasma

a) Chloasma or melasma that may persist when the drug has been discontinued has been reported during the use of estrogen and/or progestin therapy [170].

Hirsutism

a) Hirsutism has been reported during the use of estrogen and/or progestin therapy [170].

Loss of scalp hair

a) Loss of scalp hair has been reported during the use of estrogen and/or progestin therapy [170].

Pruritus

a) Pruritus has been reported during the use of estrogen and/or progestin therapy [170].

Estradiol Cypionate

Chloasma

a) Chloasma or melasma that may persist when the drug has been discontinued has been reported during the use of estrogen and/or progestin therapy [55].

Hirsutism

a) Hirsutism has been reported during the use of estrogen and/or progestin therapy [55].

Loss of scalp hair

a) Loss of scalp hair has been reported during the use of estrogen and/or progestin therapy [55].

Pruritus

a) Pruritus has been reported during the use of estrogen and/or progestin therapy [55].

Estradiol Valerate

Chloasma

a) Chloasma or melasma that may persist when the drug has been discontinued has been reported during the use of estrogen and/or progestin therapy [57].

Hirsutism

a) Hirsutism has been reported during the use of estrogen and/or progestin therapy [57].

Loss of scalp hair

a) Loss of scalp hair has been reported during the use of estrogen and/or progestin therapy [57].

Pruritus

a) Pruritus has been reported during the use of estrogen and/or progestin therapy [57].

Endocrine/Metabolic Effects

Estradiol

Body fluid retention

a) General Information

1) Estrogens may cause some degree of fluid retention and may exacerbate conditions affected by fluid retention, such as cardiac or renal dysfunction [29][69][76][7][13][38][35][8][19][11][12][14][15][94].

b) Prevention and Management

1) Discontinue with evidence of fluid retention [68]

Galactorrhea

a) General Information

1) Has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

Gynecomastia

a) Adult Case Reports

1) Gynecomastia and impotence have been reported in 2 men after regular use of an estrogen-containing hair lotion (50 mg estradiol/100 mL alcoholic solution). Although one patient had return of libido and regression of the gynecomastia 4 weeks after discontinuing the hair lotion, the other patient had no regression of his gynecomastia. This patient underwent bilateral mastectomy 6 months after discontinuation of the hair product [109].

b) Pediatric Case Reports

1) Three prepubertal boys presented with gynecomastia and elevated estradiol levels as a result from indirect exposure to a custom-compounded preparation of estrogen cream being used by each child's mother. The indirect exposure also resulted in rapid changes in growth and advanced bone age [110].

Hypercalcemia

a) General Information

1) Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases [29][74][76][7][13][38][35][8][19][11][12][36][14][15][94]

b) Prevention and Management

1) Discontinue use [29][76][19] and treat hypercalcemia [29][74].

Hypertriglyceridemia

a) General Information

1) Estrogen therapy may be associated with elevations in plasma triglycerides, possibly leading to pancreatitis [68]

b) Prevention and Management

1) Discontinue if pancreatitis occurs [68]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Triglyceride levels increased with estrogen with or without medroxyprogesterone [111]

2) Hormone replacement therapy (transdermal route): No significant triglyceride elevation with estradiol plus oral progesterone [112]

3) Hormone replacement therapy (IM route): Significant increase in triglyceride levels with estradiol valerate plus dehydroandrosterone enanthate [113]

Hypocalcemia

a) General Information

1) Has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

2) Increased risk in women with hypoparathyroidism [29][69][19]

Syndrome of carbohydrate intolerance

a) General Information

1) Reduced carbohydrate tolerance has been reported with the use of estrogen and/or progestin therapy [76][7][13][38][35][8][11][12][36][14][15].

Thyroid-binding globulin high

a) Prevention and Management

1) Increased doses of thyroid replacement therapy may be required in women receiving estrogens and thyroid hormone therapy [68]

Weight decreased

a) General Information

1) Weight loss has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15].

Weight increased

a) Incidence: Transdermal system, up to 8.5% [29]

b) General Information

1) Weight increase has been reported with estrogen and/or progestin therapy [29] [76][7][38][35][8][19][11][12][36][14][15].

c) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 0% to 8.5% vs 1.9% with placebo [29]

Estradiol Acetate

Body fluid retention

a) Estrogens may cause some degree of fluid retention and may exacerbate conditions affected by fluid retention, such as cardiac or renal dysfunction [170].

Breast cancer

a) Risk Among Healthy Women

1) The overall results of studies are mixed, however, the more recent large-scale and long-term studies identify an increased risk of developing breast cancer with the use of hormone replacement therapy. Estrogen and progestin regimens appear to increase the risk of breast cancer (hazard ratio 1.26, 95% confidence interval 1.00 to 1.59). The risk associated with unopposed estrogen therapy is increased among long-term users (10 years or more) [143][144][145][123].

Final results from the Nurses' Health Study (NHS) reported an increased risk of invasive breast cancer in postmenopausal women without a uterus who had received unopposed estrogen for 10 years or longer. The NHS was an observational, prospective cohort study initially involving a total of 11,508 postmenopausal women who had a hysterectomy and reported information on estrogen use at baseline. With the expansion of the study population every 2 years to include subsequent postmenopausal women without a uterus, the final follow-up period included 28,835 women. Biennial questionnaires were used to assess estrogen use. The primary outcome was invasive breast cancer. During 335,296 person-years of follow-up, 934 invasive breast cancers were diagnosed, which included 226 among women who never used hormones and 708 among current estrogen users. The relative risk (RR) and 95 confidence intervals (95% CI) based on length of use is reported in the following table:

Length of Estrogen Use	RR	95% CI (p for trend less than 0.001)
less than 5 years	0.96	0.75 to 1.22
5 to 9.9 years	0.90	0.73 to 1.12
10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

When analyses were stratified by body mass index (BMI), the risk of invasive breast cancer appeared to be greater in leaner women, however, the difference did not reach statistical significance (p=0.1). The RR for current estrogen use of 20 years or longer in women with a BMI of less than 25 was 1.77 (95% CI, 1.26 to 2.48) while the RR for current estrogen use of 20 years or longer in women with a BMI of 25 or greater was 1.25 (95% CI, 0.91 to 1.71). Additionally, the risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers was increased among current users of estrogen after 15 years of use (RR, 1.48; 95% CI, 1.05 to 2.07). Overall, there did not seem to be a strong dose-response relationship among estrogen use and risk of breast cancer [123].

2) Results from the Women's Health Initiative (WHI) Estrogen-Alone trial indicate treatment with conjugated equine estrogens (CEE) does not increase breast cancer incidence in postmenopausal women without a uterus, however, it was associated with an increased frequency of mammography screening that required short interval follow-up. Women (n=10,739) with similar baseline breast cancer risk were randomized in a double-blind trial to CEE 0.625 milligrams (mg) or placebo daily. After a mean follow-up of 7.1 years, nonsignificant reductions for invasive breast cancer and total breast cancer were observed in women receiving CEE (hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.62 to 1.04; p=0.09 and HR, 0.82; 95% CI, 0.65 to 1.04; p=0.1, respectively) compared with placebo. No effect on in situ disease was evident. Breast cancers with localized disease were diagnosed less frequently in women receiving CEE compared with women receiving placebo (HR, 0.69; 95% CI, 0.51 to 0.95). Advanced stage cancer incidence was comparable between the 2 groups. Compared with placebo, ductal carcinomas were decreased in women receiving CEE (HR, 0.71; 95% CI, 0.52 to 0.99), but the test for interaction by tumor type (ductal versus lobular) was not significant (p=0.054). The interactions between treatment assignment and estimated 5-year breast cancer risk, history of benign breast disease, and number of first-degree relatives with breast cancer were significant (p=0.01, p=0.005, and p=0.01, respectively). The percentage of mammographies requiring follow-up after the first year was significantly higher in the CEE group compared with the placebo group (9.2% versus 5.5%, respectively; p less than 0.001). In addition, the cumulative number

of mammograms over the course of the trial that required follow-up each year thereafter was significantly higher in the CEE group compared with the placebo group (36.2% versus 28.1%; p less than 0.001) [149].

3) Results of the Women's Health Initiative substudy involving 16,608 postmenopausal women who received conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily demonstrated an increased risk of invasive breast cancer in women receiving hormone therapy relative to placebo. After an average follow-up of 5.2 years, the relative risk of invasive breast cancer was 1.26; 95% confidence interval, 1.00 to 1.59) [170].

4) Data from a retrospective cohort study of 46,355 postmenopausal women suggests the risk of developing breast cancer is less with estrogen alone than with estrogen-progestin combined. The data were derived from follow-up (mean=10.2 years) to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. During follow-up, 2082 cases of breast cancer were identified. Relative risks (RR) were adjusted for age, age at menopause, education, body mass index (BMI), and mammographic screening. The RR for current and recent use (previous 4 years) of estrogen only was 1.2 (95% confidence interval (CI), 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin. The RR increase by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users. The RR associated with ever using estrogen or estrogen-progestin was 1.1 (95% CI, 1.0-1.3) and 1.3 (95% CI, 1.0-1.6), respectively. Increases in RR with each year of estrogen-only use and estrogen-progestin-only use among recent users with a BMI of 24.4 kilogram (kg) per meter squared or less were 0.03 (95% CI, 0.01-0.06) and 0.12 (95% CI, 0.02-0.25), respectively. Risk in heavier women did not increase in relation to use of either regimen. A limitation of the study includes retrospective collection and problems of recall in the reporting of hormone use, which does not make it a true prospective cohort study [150][151].

5) Results reported from a prospective, longitudinal study involving 210 postmenopausal women with normal baseline mammograms concluded hormone replacement therapy (HRT) with varying regimens of ESTRADIOL or CONJUGATED EQUINE ESTROGENS (CEE) increased mammographic density while tibolone and ESTRIOL did not. Study participants received 1 of 7 oral HRT regimens for a period of one year. The regimens included ESTRADIOL 2 milligrams (mg), ESTRADIOL 2 mg plus sequential medroxyprogesterone acetate (MPA) 5 mg for 10 to 16 days per cycle, ESTRADIOL 2 mg plus continuous MPA 2.5 mg, CEE 0.625 mg, CEE 0.625 mg plus sequential MPA 5 mg, ESTRIOL 2 mg, or tibolone 2.5 mg. Thirty age-matched postmenopausal women served as a control group. Increased mammographic density occurred in 27% to 67% of patients receiving ESTRADIOL or CEE. No patients receiving tibolone or ESTRIOL experienced increases (p less than 0.05 for both). Overall, 32% of patients receiving HRT (95% confidence interval (CI) 25.7%, 38.6%) experienced increases in mammographic density compared to 3% of the controls (95% CI 0%, 17.2%) (Valdivia & Ortega, 2000).

6) A reanalysis of data from 51 epidemiological studies of women with breast cancer (n=52,705) and without breast cancer (n=108,411) identified the risk of developing breast cancer is increased in women using hormone replacement therapy (HRT) and the risk increased with increasing duration of use, especially in women of lower body mass index (BMI). The relative risk (RR) of a breast cancer diagnosis in current users of HRT or in those who discontinued HRT 1 to 4 years earlier, increased by 1.023 (95% confidence interval (CI), 1.011 to 1.036) for each year of use. The RR for women who used HRT for 5 years or longer was 1.35 (95% CI, 1.21 to 1.49). The RR of breast cancer for women who never used HRT increases by 1.028 (95% CI, 1.021 to 1.034) for each year older at menopause. There was no significant increase in the incidence of breast cancer in women who had discontinued HRT for 5 or more years. Additionally, cancers were less advanced in women who ever used HRT compared to those who never used [152].

7) A 16-year cohort analysis of women enrolled in the Nurses' Health Study was conducted. Their results showed the risk of breast cancer to be significantly increased among women who were current users of estrogen alone (Relative Risk (RR) equal 1.32) or estrogen plus progestin (RR equal 1.41) compared with postmenopausal women who had never used hormones. The risk of breast cancer was increased in women taking postmenopausal hormone replacement therapy (HRT) for more than five years, and in women greater than 55 years of age (among women aged 60 to 64, RR equal 1.71. This study supports the conclusions of other research which shows that short term hormone replacement therapy (less than 5 years) seems to have no important effect on the risk for breast cancer. More importantly, the increased mortality related to breast cancer among a subgroup of current, long-term users (greater than 5 years) was offset by a trend toward decreased risk among former users. These findings support a hypothesis that current use of HRT promotes the growth of existing cancers rather than initiating new cancers. Analysis of this cohort a few years from now should provide more reliable data about the risks and benefits of long-term HRT [153].

8) A study of 537 women (aged 50 to 64 years) in the western United States was conducted to determine the risk for breast cancer from use of combined estrogen-progestin hormone replacement therapy (HRT). Compared with non-users of HRT, the relative odds (RO) of breast cancer in estrogen alone or estrogen-progestin users was 0.9. Long-term use of estrogen alone (greater than or equal to 20 years) and of combined estrogen-progestin (less than 8 years) did not contribute to increased risk for breast cancer. The risk of breast cancer was not substantially affected by the type, dose, or regimen of estrogen or progestin, nor by family history of breast cancer, previous benign breast disease, parity, alcohol use, or oral contraceptive use [154].

b) Risk Among Breast Cancer Survivors

1) The HABITS (hormonal replacement therapy after breast cancer - is it safe?) trial was discontinued early after safety results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events. The open-label trial randomized 434 women with previous breast cancer to hormone replacement therapy (n=219) or best treatment without hormones (n=215). Of the 434 women, 345 had at least one follow-up report. After a median of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. Further analyses were completed by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis. In all subsets, relative hazards for risk of new breast cancer events was above unity, but the confidence intervals were wide due to the small number of events. When the risk was compared by specific type of HRT, method of administration (continuous or sequential), and other preparations to estrogens only, the differences were small and not statistically significant. The authors acknowledge the results might change after the complete assessment of patients' original records, however, the steering committee for the trial judged the data mature enough to strongly indicate exposure to HRT is associated with an unacceptable risk. The women in the trial will be followed for at least 5 years after randomization [124].

2) Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors. Disease-free survivors (n=277) were prospectively given ERT and controls were matched for exact stage, a recurrence-free period similar to the period to ERT initiation in the ERT group, approximate age, and duration of follow-up. The mean time from breast cancer diagnosis to initiation of ERT was 3.6 years and the mean duration of ERT was 3.7 years. ERT was effective in relieving hot flashes in 92%, dyspareunia and vaginal dryness in 89%, and reactive depression, anxiety, and mood change in 88% of women. There were no statistical differences between the ERT and control groups for age, stage, pathology at diagnosis, progesterone receptor status, local therapy, breast at risk, prior chemotherapy, and duration of follow-up. In addition, there was no significant difference between the ERT and control groups in ipsilateral primary/recurrence (p=0.85), contralateral breast cancers (p=0.99), or systemic metastasis (p=0.13). Overall survival favored the ERT group (p=0.02) [125].

3) Hormone replacement therapy (HRT) after breast cancer was shown to have no adverse impact on recurrence and mortality in a cohort study comprised of 2755 women (aged 35 to 74 years) who were diagnosed with incident invasive breast cancer. Among the 2755 women, 174 users of HRT after diagnosis of breast cancer was identified. Each HRT user was matched to 4 randomly selected nonusers of HRT who were similar in respect to age, disease stage, and year of diagnosis. The women were free of recurrence at the time of HRT initiation or were equivalent in terms of time since diagnosis. The rate of recurrence was 17 per 1000 person-years in patients on HRT after diagnosis versus 30 per 1000 person-years in nonusers (relative risk (RR) 0.50; 95% confidence interval (CI) 0.30 to 0.85). Mortality rates from breast cancer were 5 per 1000 person- years and 15 per 1000 person-years for HRT users and nonusers, respectively (RR 0.34; 95% CI, 0.13 to 0.91). Total mortality rates were 16 per 1000 person-years for HRT users and 30 per 1000 person-years in nonusers (RR 0.48; 95% CI, 0.29 to 0.78). These results were similar for women using any type of HRT (oral, vaginal, oral plus vaginal) and lower relative risks were not associated with increased dosages (O'Meara et al, 2001).

4) In patients with breast cancer, estrogen replacement therapy did not increase recurrences or mortality rates. The addition of progestogens demonstrated a decrease in recurrence. This study involved 76 patients with breast cancer: 50 patients using estrogen replacement for up to 32 years; 8 patients using nonestrogenic hormone replacement for up to 6 years; and 18 patients using no hormone therapy for up to 10 years. Death occurred in 3 of 50 estrogens users, 1 of 8 nonestrogen users, and 6 of 18 no hormone users. The authors suggest patients with early breast cancer be offered hormone replacement therapy after a full discussion of benefits and risks [155].

Diabetes mellitus

a) Estrogen therapy may cause an exacerbation of diabetes mellitus [170].

Galactorrhea

a) Galactorrhea has been reported with the use of estrogen and/or progestin therapy [170].

b) Three prepubertal boys presented with gynecomastia and elevated estradiol levels as a result from indirect exposure to a custom-compounded preparation of estrogen cream being used by each child's mother [110]. The indirect exposure also resulted in rapid changes in growth and advanced bone age. It is recommended that women requiring estrogen therapy use an alternate form of estrogen delivery (transdermal or oral) if they are in frequent contact with children.

Hypercalcemia

a) Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases [170].

Hypertriglyceridemia

a) Summary

1) Estrogens generally cause an increase in HDL cholesterol and a decrease in LDL cholesterol, as well as an increase in serum triglycerides. The overall effect of these lipid changes is probably to reduce the risk of atherosclerosis. However, simultaneous use of progestins may prevent these benefits, and result in additional increases in LDL cholesterol. In addition, postmenopausal women with coronary disease who have the estrogen receptor alpha IVS1-401 C/C genotype or other closely related genotype have an augmented response of HDL cholesterol to hormone replacement therapy [156].

b) Estrogen therapy in patients with pre-existing hypertriglyceridemia may cause elevations of plasma triglycerides which may lead to pancreatitis and other complications [170].

c) Lower doses of both conjugated equine estrogens (CEE) alone and CEE plus medroxyprogesterone (MPA) were associated with favorable changes in lipids and lipid proteins compared to higher doses and placebo. Postmenopausal women (n=749) were randomized to CEE 0.3 to 0.625 milligrams (mg) daily or the combined regimen of CEE (range 0.3 to 0.625 mg) with MPA (range 1.5 to 2.5 mg) daily. After one year, all of the regimens were associated with an increase in high-density lipoprotein cholesterol, with similar increases between CEE 0.45 mg with MPA 1.5 mg and CEE 0.625 mg with MPA 2.5 mg. Low-density lipoprotein cholesterol was reduced in all treatment groups with the exception of CEE 0.3 mg with MPA 1.5 mg at cycle 13. Triglyceride levels increased in all groups as did apolipoprotein A-1 levels. Apolipoprotein B levels decreased in all groups [111].

d) The Lipid Research Clinics Program found a statistically insignificant trend towards increased LDL-cholesterol in 30 women under 45 years treated with estrogens (compared to 74 controls). This trend was not seen in older women receiving estrogen preparations, in whom a significant decrease in LDL-cholesterol was seen [157]. A statistically significant decrease in total serum cholesterol was seen in older women treated with estrogens, while the younger group showed a significant increase. Both HDL-cholesterol and triglycerides were increased in both old and young treatment groups, with a significant increase in VLDL-cholesterol seen only in the younger women (a statistically insignificant increase was noted in the older women). The treatment and control groups were comparable in terms of obesity, smoking, and alcohol usage. The reason for the differences between younger and older women with respect to LDL is not clear, though the authors speculate that the younger group may not all have been estrogen deficient, particularly as compared to the postmenopausal group.

Hypocalcemia

a) Hypocalcemia has been reported with the use of estrogen and/or progestin therapy [170].

Syndrome of carbohydrate intolerance

a) Reduced carbohydrate tolerance has been reported with the use of estrogen and/or progestin therapy [170].

Weight gain

a) Increases or decreases in weight has been reported with the use of estrogen and/or progestin therapy [170].

Estradiol Cypionate

Body fluid retention

a) Estrogens may cause some degree of fluid retention and may exacerbate conditions affected by fluid retention, such as cardiac or renal dysfunction [55].

Breast cancer

a) Risk Among Healthy Women

1) The overall results of studies are mixed, however, the more recent large-scale and long-term studies identify an increased risk of developing breast cancer with the use of hormone replacement therapy. Estrogen and progestin regimens appear to increase the risk of breast cancer (hazard ratio 1.26, 95% confidence interval 1.00 to 1.59). The risk associated with unopposed estrogen therapy is increased among long-term users (10 years or more) [143][144][145][123].

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10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

When analyses were stratified by body mass index (BMI), the risk of invasive breast cancer appeared to be greater in leaner women, however, the difference did not reach statistical significance (p=0.1). The RR for current estrogen use of 20 years or longer in women with a BMI of less than 25 was 1.77 (95% CI, 1.26 to 2.48) while the RR for current estrogen use of 20 years or longer in women with a BMI of 25 or greater was 1.25 (95% CI, 0.91 to 1.71). Additionally, the risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers was increased among current users of estrogen after 15 years of use (RR, 1.48; 95% CI, 1.05 to 2.07). Overall, there did not seem to be a strong dose-response relationship among estrogen use and risk of breast cancer [123].

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3) Results of the Women's Health Initiative substudy involving 16,608 postmenopausal women who received conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily demonstrated an increased risk of invasive breast cancer in women receiving hormone therapy relative to placebo. After an average follow-up of 5.2 years, the relative risk of invasive breast cancer was 1.26 (95% confidence interval, 1.00 to 1.59) [55].

4) Data from a retrospective cohort study of 46,355 postmenopausal women suggests the risk of developing breast cancer is less with estrogen alone than with estrogen-progestin combined. The data were derived from follow-up (mean=10.2 years) to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. During follow-up, 2082 cases of breast cancer were identified. Relative risks (RR) were adjusted for age, age at menopause, education, body mass index (BMI), and mammographic screening. The RR for current and recent use (previous 4 years) of estrogen only was 1.2 (95% confidence interval (CI), 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin. The RR increase by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users. The RR associated with ever using estrogen or estrogen-progestin was 1.1 (95% CI, 1.0-1.3) and 1.3 (95% CI, 1.0-

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b) Risk Among Breast Cancer Survivors

1) The HABITS (hormonal replacement therapy after breast cancer - is it safe?) trial was discontinued early after safety results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events. The open-label trial randomized 434 women with previous breast cancer to hormone replacement therapy (n=219) or best treatment without hormones (n=215). Of the 434 women, 345 had at least one follow-up report. After a median of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. Further analyses were completed by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis. In all subsets, relative hazards for risk of new breast cancer events was above unity, but the confidence intervals were wide due to the small number of events. When the risk was compared by specific type of HRT, method of administration (continuous or sequential), and other preparations to estrogens

only, the differences were small and not statistically significant. The authors acknowledge the results might change after the complete assessment of patients' original records, however, the steering committee for the trial judged the data mature enough to strongly indicate exposure to HRT is associated with an unacceptable risk. The women in the trial will be followed for at least 5 years after randomization [124].

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Galactorrhea

a) Galactorrhea has been reported with the use of estrogen and/or progestin therapy [55].

b) Three prepubertal boys presented with gynecomastia and elevated estradiol levels as a result from indirect exposure to a custom-compounded preparation of estrogen cream being used by each child's mother [110]. The indirect exposure also resulted in rapid changes in growth and advanced bone age. It is recommended that women requiring estrogen therapy use an alternate form of estrogen delivery (transdermal or oral) if they are in frequent contact with children.

Hypercalcemia

a) Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases [55].

Hypertriglyceridemia

a) Summary

1) Estrogens generally cause an increase in HDL cholesterol and a decrease in LDL cholesterol, as well as an increase in serum triglycerides. The overall effect of these lipid changes is probably to reduce the risk of atherosclerosis. However, simultaneous use of progestins may prevent these benefits, and result in additional increases in LDL cholesterol. In addition, postmenopausal women with coronary disease who have the estrogen receptor alpha IVS1-401 C/C genotype or other closely related genotype have an augmented response of HDL cholesterol to hormone replacement therapy [156].

b) Estrogen therapy in patients with pre-existing hypertriglyceridemia may cause elevations of plasma triglycerides which may lead to pancreatitis and other complications [55].
c) Lower doses of both conjugated equine estrogens (CEE) alone and CEE plus medroxyprogesterone (MPA) were associated with favorable changes in lipids and lipid proteins compared to higher doses and placebo. Postmenopausal women (n=749) were randomized to CEE 0.3 to 0.625 milligrams (mg) daily or the combined regimen of CEE (range 0.3 to 0.625 mg) with MPA (range 1.5 to 2.5 mg) daily. After one year, all of the regimens were associated with an increase in high-density lipoprotein cholesterol, with similar increases between CEE 0.45 mg with MPA 1.5 mg and CEE 0.625 mg with MPA 2.5 mg. Low-density lipoprotein cholesterol was reduced in all treatment groups with the exception of CEE 0.3 mg with MPA 1.5 mg at cycle 13. Triglyceride levels increased in all groups as did apolipoprotein A-1 levels. Apolipoprotein B levels decreased in all groups [111].
d) The Lipid Research Clinics Program found a statistically insignificant trend towards increased LDL-cholesterol in 30 women under 45 years treated with estrogens (compared to 74 controls). This trend was not seen in older women receiving estrogen preparations, in whom a significant decrease in LDL-cholesterol was seen [157]. A statistically significant decrease in total serum cholesterol was seen in older women treated with estrogens, while the younger group showed a significant increase. Both HDL-cholesterol and triglycerides were increased in both old and young treatment groups, with a significant increase in VLDL-cholesterol seen only in the younger women (a statistically insignificant increase was noted in the older women). The treatment and control groups were comparable in terms of obesity, smoking, and alcohol usage. The reason for the differences between younger and older women with respect to LDL is not clear, though the authors speculate that the younger group may not all have been estrogen deficient, particularly as compared to the postmenopausal group.

Hypocalcemia

a) Hypocalcemia has been reported with the use of estrogen and/or progestin therapy [55].

Syndrome of carbohydrate intolerance

a) Reduced carbohydrate tolerance has been reported with the use of estrogen and/or progestin therapy [55].

Weight gain

a) Increases or decreases in weight has been reported with the use of estrogen and/or progestin therapy [55].

Estradiol Valerate

Body fluid retention

a) Estrogens may cause some degree of fluid retention and may exacerbate conditions affected by fluid retention, such as cardiac or renal dysfunction [57].

Breast cancer

a) Risk Among Healthy Women

1) The overall results of studies are mixed, however, the more recent large-scale and long-term studies identify an increased risk of developing breast cancer with the use of hormone replacement therapy. Estrogen and progestin regimens appear to increase the risk of breast cancer (hazard ratio 1.26, 95% confidence interval 1.00 to 1.59). The risk associated with unopposed estrogen therapy is increased among long-term users (10 years or more) [143][144][145][123].

Final results from the Nurses' Health Study (NHS) reported an increased risk of invasive breast cancer in postmenopausal women without a uterus who had received unopposed estrogen for 10 years or longer. The NHS was an observational, prospective cohort study initially involving a total of 11,508 postmenopausal women who had a hysterectomy and reported information on estrogen use at baseline. With the expansion of the study population every 2 years to include subsequent postmenopausal women without a uterus, the final follow-up period included 28,835 women. Biennial questionnaires were used to assess estrogen use. The primary outcome was invasive breast cancer. During 335,296 person-years of follow-up, 934 invasive breast cancers were diagnosed, which included 226 among women who never used hormones and 708 among current estrogen users. The relative risk (RR) and 95 confidence intervals (95% CI) based on length of use is reported in the following table:

Length of Estrogen Use	RR	95% CI (p for trend less than 0.001)
less than 5 years	0.96	0.75 to 1.22
5 to 9.9 years	0.90	0.73 to 1.12
10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

When analyses were stratified by body mass index (BMI), the risk of invasive breast cancer appeared to be greater in leaner women, however, the difference did not reach statistical significance (p=0.1). The RR for current estrogen use of 20 years or longer in women with a BMI of less than 25 was 1.77 (95% CI, 1.26

to 2.48) while the RR for current estrogen use of 20 years or longer in women with a BMI of 25 or greater was 1.25 (95% CI, 0.91 to 1.71). Additionally, the risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers was increased among current users of estrogen after 15 years of use (RR, 1.48; 95% CI, 1.05 to 2.07). Overall, there did not seem to be a strong dose-response relationship among estrogen use and risk of breast cancer [123].

2) Results from the Women's Health Initiative (WHI) Estrogen-Alone trial indicate treatment with conjugated equine estrogens (CEE) does not increase breast cancer incidence in postmenopausal women without a uterus, however, it was associated with an increased frequency of mammography screening that required short interval follow-up. Women (n=10,739) with similar baseline breast cancer risk were randomized in a double-blind trial to CEE 0.625 milligrams (mg) or placebo daily. After a mean follow-up of 7.1 years, nonsignificant reductions for invasive breast cancer and total breast cancer were observed in women receiving CEE (hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.62 to 1.04; p=0.09 and HR, 0.82; 95% CI, 0.65 to 1.04; p=0.1, respectively) compared with placebo. No effect on in situ disease was evident. Breast cancers with localized disease were diagnosed less frequently in women receiving CEE compared with women receiving placebo (HR, 0.69; 95% CI, 0.51 to 0.95). Advanced stage cancer incidence was comparable between the 2 groups. Compared with placebo, ductal carcinomas were decreased in women receiving CEE (HR, 0.71; 95% CI, 0.52 to 0.99), but the test for interaction by tumor type (ductal versus lobular) was not significant (p=0.054). The interactions between treatment assignment and estimated 5-year breast cancer risk, history of benign breast disease, and number of first-degree relatives with breast cancer were significant (p=0.01, p=0.005, and p=0.01, respectively). The percentage of mammographies requiring follow-up after the first year was significantly higher in the CEE group compared with the placebo group (9.2% versus 5.5%, respectively; p less than 0.001). In addition, the cumulative number of mammograms over the course of the trial that required follow-up each year thereafter was significantly higher in the CEE group compared with the placebo group (36.2% versus 28.1%; p less than 0.001) [149].

3) Results of the Women's Health Initiative substudy involving 16,608 postmenopausal women who received conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily demonstrated an increased risk of invasive breast cancer in women receiving hormone therapy relative to placebo. After an average follow-up of 5.2 years, the relative risk of invasive breast cancer was 1.26 (95% confidence interval, 1.00 to 1.59) [57].

4) Data from a retrospective cohort study of 46,355 postmenopausal women suggests the risk of developing breast cancer is less with estrogen alone than with estrogen-progestin combined. The data were derived from follow-up (mean=10.2 years) to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. During follow-up, 2082 cases of breast cancer were identified. Relative risks (RR) were adjusted for age, age at menopause, education, body mass index (BMI), and mammographic screening. The RR for current and recent use (previous 4 years) of estrogen only was 1.2 (95% confidence interval (CI), 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin. The RR increase by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users. The RR associated with ever using estrogen or estrogen-progestin was 1.1 (95% CI, 1.0-1.3) and 1.3 (95% CI, 1.0-1.6), respectively. Increases in RR with each year of estrogen-only use and estrogen-progestin-only use among recent users with a BMI of 24.4 kilogram (kg) per meter squared or less were 0.03 (95% CI, 0.01-0.06) and 0.12 (95% CI, 0.02-0.25), respectively. Risk in heavier women did not increase in relation to use of either regimen. A limitation of the study includes retrospective collection and problems of recall in the reporting of hormone use, which does not make it a true prospective cohort study [150][151].

5) Results reported from a prospective, longitudinal study involving 210 postmenopausal women with normal baseline mammograms concluded hormone replacement therapy (HRT) with varying regimens of ESTRADIOL or CONJUGATED EQUINE ESTROGENS (CEE) increased mammographic density while tibolone and ESTRIOL did not. Study participants received 1 of 7 oral HRT regimens for a period of one year. The regimens included ESTRADIOL 2 milligrams (mg), ESTRADIOL 2 mg plus sequential medroxyprogesterone acetate (MPA) 5 mg for 10 to 16 days per cycle, ESTRADIOL 2 mg plus continuous MPA 2.5 mg, CEE 0.625 mg, CEE 0.625 mg plus sequential MPA 5 mg, ESTRIOL 2 mg, or tibolone 2.5 mg. Thirty age-matched postmenopausal women served as a control group. Increased mammographic density occurred in 27% to 67% of patients receiving ESTRADIOL or CEE. No patients receiving tibolone or ESTRIOL experienced increases (p less than 0.05 for both). Overall, 32% of patients receiving HRT (95% confidence interval (CI) 25.7%, 38.6%) experienced increases in mammographic density compared to 3% of the controls (95% CI 0%, 17.2%) (Valdivia & Ortega, 2000).

6) A reanalysis of data from 51 epidemiological studies of women with breast cancer (n=52,705) and without breast cancer (n=108,411) identified the risk of

developing breast cancer is increased in women using hormone replacement therapy (HRT) and the risk increased with increasing duration of use, especially in women of lower body mass index (BMI). The relative risk (RR) of a breast cancer diagnosis in current users of HRT or in those who discontinued HRT 1 to 4 years earlier, increased by 1.023 (95% confidence interval (CI), 1.011 to 1.036) for each year of use. The RR for women who used HRT for 5 years or longer was 1.35 (95% CI, 1.21 to 1.49). The RR of breast cancer for women who never used HRT increases by 1.028 (95% CI, 1.021 to 1.034) for each year older at menopause. There was no significant increase in the incidence of breast cancer in women who had discontinued HRT for 5 or more years. Additionally, cancers were less advanced in women who ever used HRT compared to those who never used [152].

7) A 16-year cohort analysis of women enrolled in the Nurses' Health Study was conducted. Their results showed the risk of breast cancer to be significantly increased among women who were current users of estrogen alone (Relative Risk (RR) equal 1.32) or estrogen plus progestin (RR equal 1.41) compared with postmenopausal women who had never used hormones. The risk of breast cancer was increased in women taking postmenopausal hormone replacement therapy (HRT) for more than five years, and in women greater than 55 years of age (among women aged 60 to 64, RR equal 1.71. This study supports the conclusions of other research which shows that short term hormone replacement therapy (less than 5 years) seems to have no important effect on the risk for breast cancer. More importantly, the increased mortality related to breast cancer among a subgroup of current, long-term users (greater than 5 years) was offset by a trend toward decreased risk among former users. These findings support a hypothesis that current use of HRT promotes the growth of existing cancers rather than initiating new cancers. Analysis of this cohort a few years from now should provide more reliable data about the risks and benefits of long-term HRT [153].

8) A study of 537 women (aged 50 to 64 years) in the western United States was conducted to determine the risk for breast cancer from use of combined estrogen-progestin hormone replacement therapy (HRT). Compared with non-users of HRT, the relative odds (RO) of breast cancer in estrogen alone or estrogen-progestin users was 0.9. Long-term use of estrogen alone (greater than or equal to 20 years) and of combined estrogen-progestin (less than 8 years) did not contribute to increased risk for breast cancer. The risk of breast cancer was not substantially affected by the type, dose, or regimen of estrogen or progestin, nor by family history of breast cancer, previous benign breast disease, parity, alcohol use, or oral contraceptive use [154].

b) Risk Among Breast Cancer Survivors

1) The HABITS (hormonal replacement therapy after breast cancer - is it safe?) trial was discontinued early after safety results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events. The open-label trial randomized 434 women with previous breast cancer to hormone replacement therapy (n=219) or best treatment without hormones (n=215). Of the 434 women, 345 had at least one follow-up report. After a median of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. Further analyses were completed by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis. In all subsets, relative hazards for risk of new breast cancer events was above unity, but the confidence intervals were wide due to the small number of events. When the risk was compared by specific type of HRT, method of administration (continuous or sequential), and other preparations to estrogens only, the differences were small and not statistically significant. The authors acknowledge the results might change after the complete assessment of patients' original records, however, the steering committee for the trial judged the data mature enough to strongly indicate exposure to HRT is associated with an unacceptable risk. The women in the trial will be followed for at least 5 years after randomization [124].

2) Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors. Disease-free survivors (n=277) were prospectively given ERT and controls were matched for exact stage, a recurrence-free period similar to the period to ERT initiation in the ERT group, approximate age, and duration of follow-up. The mean time from breast cancer diagnosis to initiation of ERT was 3.6 years and the mean duration of ERT was 3.7 years. ERT was effective in relieving hot flashes in 92%, dyspareunia and vaginal dryness in 89%, and reactive depression, anxiety, and mood change in 88% of women. There were no statistical differences between the ERT and control groups for age, stage, pathology at diagnosis, progesterone receptor status, local therapy, breast at risk, prior chemotherapy, and duration of follow-up. In addition, there was no significant difference between the ERT and control groups in ipsilateral primary/recurrence (p=0.85), contralateral breast cancers (p=0.99), or systemic metastasis (p=0.13). Overall survival favored the ERT group (p=0.02) [125].

3) Hormone replacement therapy (HRT) after breast cancer was shown to have no adverse impact on recurrence and mortality in a cohort study comprised of 2755

women (aged 35 to 74 years) who were diagnosed with incident invasive breast cancer. Among the 2755 women, 174 users of HRT after diagnosis of breast cancer was identified. Each HRT user was matched to 4 randomly selected nonusers of HRT who were similar in respect to age, disease stage, and year of diagnosis. The women were free of recurrence at the time of HRT initiation or were equivalent in terms of time since diagnosis. The rate of recurrence was 17 per 1000 person-years in patients on HRT after diagnosis versus 30 per 1000 person-years in nonusers (relative risk (RR) 0.50; 95% confidence interval (CI) 0.30 to 0.85). Mortality rates from breast cancer were 5 per 1000 person- years and 15 per 1000 person-years for HRT users and nonusers, respectively (RR 0.34; 95% CI, 0.13 to 0.91). Total mortality rates were 16 per 1000 person-years for HRT users and 30 per 1000 person-years in nonusers (RR 0.48; 95% CI, 0.29 to 0.78). These results were similar for women using any type of HRT (oral, vaginal, oral plus vaginal) and lower relative risks were not associated with increased dosages (O'Meara et al, 2001).

4) In patients with breast cancer, estrogen replacement therapy did not increase recurrences or mortality rates. The addition of progestogens demonstrated a decrease in recurrence. This study involved 76 patients with breast cancer: 50 patients using estrogen replacement for up to 32 years; 8 patients using nonestrogenic hormone replacement for up to 6 years; and 18 patients using no hormone therapy for up to 10 years. Death occurred in 3 of 50 estrogens users, 1 of 8 nonestrogen users, and 6 of 18 no hormone users. The authors suggest patients with early breast cancer be offered hormone replacement therapy after a full discussion of benefits and risks [155].

Diabetes mellitus

a) Estrogen therapy may cause an exacerbation of diabetes mellitus [57].

Galactorrhea

a) Galactorrhea has been reported with the use of estrogen and/or progestin therapy [57].

b) Three prepubertal boys presented with gynecomastia and elevated estradiol levels as a result from indirect exposure to a custom-compounded preparation of estrogen cream being used by each child's mother [110]. The indirect exposure also resulted in rapid changes in growth and advanced bone age. It is recommended that women requiring estrogen therapy use an alternate form of estrogen delivery (transdermal or oral) if they are in frequent contact with children.

Hypercalcemia

a) Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases [57].

Hypertriglyceridemia

a) Summary

1) Estrogens generally cause an increase in HDL cholesterol and a decrease in LDL cholesterol, as well as an increase in serum triglycerides. The overall effect of these lipid changes is probably to reduce the risk of atherosclerosis. However, simultaneous use of progestins may prevent these benefits, and result in additional increases in LDL cholesterol. In addition, postmenopausal women with coronary disease who have the estrogen receptor alpha IVS1-401 C/C genotype or other closely related genotype have an augmented response of HDL cholesterol to hormone replacement therapy [156].

b) Estrogen therapy in patients with pre-existing hypertriglyceridemia may cause elevations of plasma triglycerides which may lead to pancreatitis and other complications [57].

c) A case of severe hypertriglyceridemia and pancreatitis was reported in a 30-year-old woman being treated with estradiol valerate for endometrial preparation for cryopreserved embryo transfer. Four days after the patient's third injection of intramuscular estradiol valerate 6 milligrams biweekly, the patient presented with lower abdominal pain, nausea, vomiting, fever and diffuse right quadrant tenderness. Blood work revealed a significantly elevated triglyceride level (8062 milligrams/deciliter (mg/dL)) and a total cholesterol level of 1186 mg/dL. Estrogen therapy was discontinued and the patient was admitted for supportive care. The patient was discharged on day 4 with complete resolution of clinical symptoms and a total cholesterol and triglyceride level of 300 mg/dL and 780 mg/dL, respectively. After 2 months on a low-fat diet and gemfibrozil therapy, the patient was able to maintain a normal cholesterol level under 200 mg/dL and triglyceride levels of 300 to 500 mg/dL. The use of oral estradiol during subsequent cryothaw pregnancies did not produce the same degree of hyperlipidemia as did treatment with injectable estradiol [168].

d) Lower doses of both conjugated equine estrogens (CEE) alone and CEE plus medroxyprogesterone (MPA) were associated with favorable changes in lipids and lipid proteins compared to higher doses and placebo. Postmenopausal women (n=749) were randomized to CEE 0.3 to 0.625 milligrams (mg) daily or the combined regimen of CEE (range 0.3 to 0.625 mg) with MPA (range 1.5 to 2.5 mg) daily. After one year, all of the regimens were associated with an increase in high-density lipoprotein cholesterol, with similar increases between CEE 0.45 mg with MPA 1.5 mg and CEE 0.625 mg with MPA 2.5 mg. Low-density lipoprotein

cholesterol was reduced in all treatment groups with the exception of CEE 0.3 mg with MPA 1.5 mg at cycle 13. Triglyceride levels increased in all groups as did apolipoprotein A-1 levels. Apolipoprotein B levels decreased in all groups [111].
e) The Lipid Research Clinics Program found a statistically insignificant trend towards increased LDL-cholesterol in 30 women under 45 years treated with estrogens (compared to 74 controls). This trend was not seen in older women receiving estrogen preparations, in whom a significant decrease in LDL-cholesterol was seen [157]. A statistically significant decrease in total serum cholesterol was seen in older women treated with estrogens, while the younger group showed a significant increase. Both HDL-cholesterol and triglycerides were increased in both old and young treatment groups, with a significant increase in VLDL-cholesterol seen only in the younger women (a statistically insignificant increase was noted in the older women). The treatment and control groups were comparable in terms of obesity, smoking, and alcohol usage. The reason for the differences between younger and older women with respect to LDL is not clear, though the authors speculate that the younger group may not all have been estrogen deficient, particularly as compared to the postmenopausal group.

Hypocalcemia

a) Hypocalcemia has been reported with the use of estrogen and/or progestin therapy [57].

Syndrome of carbohydrate intolerance

a) Reduced carbohydrate tolerance has been reported with the use of estrogen and/or progestin therapy [57].

Weight gain

a) Increases or decreases in weight has been reported with the use of estrogen and/or progestin therapy [57].

Gastrointestinal Effects

Estradiol

Abdominal pain

a) Incidence: Topical gel, 7.7% [13]; transdermal system, up to 16% [19]; vaginal cream, 2% [15]; vaginal ring, 4% [15]; vaginal tablets, 7% [94]
b) General Information

1) Abdominal cramps have been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15][94].

c) Adult Clinical Trials

1) Estrogen replacement (vaginal route): 4% with estradiol vaginal ring vs 2% with estradiol vaginal cream [15]; 7% with estradiol vaginal tablets vs 4% with placebo [94]

2) Estrogen replacement (transdermal route): 0% to 16% vs 8% with placebo [19]

Bloating symptom

a) General Information

1) Bloating has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

Diarrhea

a) Incidence: Topical gel, 4.2% [13]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 4.2% vs 0% with placebo [13]

c) Postmarketing

1) Has been reported [29]

Disorder of gallbladder

a) General Information

1) A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported [29][74][76][7][38][35][8][19][11][12][36][14][15][94]

Flatulence

a) Incidence: Topical gel, 5.4% [74]; transdermal system, 1% to 7% [19]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 5.4% with estradiol vs 4.1% with placebo [74]

2) Estrogen replacement (transdermal route): 1% to 7% vs 1% with placebo [19]

Nausea

a) Incidence: Transdermal system, up to 6.2% [29][19]
b) General Information

1) Can be minimized by administration with meals; often disappears with continued administration [114].

c) Estrogen replacement (transdermal route): 0% to 6.2% vs 3.2% with placebo [29]

d) Estrogen replacement (transdermal route): 1% to 6% vs 3% with placebo [19]

Vomiting

a) General Information

1) Vomiting has been reported with estrogen and/or progestin therapy [76][7][38] [35][8][19][11][12][36][14][15]

Estradiol Acetate

Bloating symptom

a) Incidence: 2.7% to 7.1% [60]

b) Bloating has been reported with the use of estrogens and/or progestin therapy [170].

c) The incidences of abdominal distension reported with the use of estradiol acetate vaginal ring 0.05 milligrams/day and 0.10 milligrams/day were 2.7% and 7.1%, respectively [60].

Bowel obstruction

a) Bowel obstruction has been reported in post-marketing surveillance during vaginal ring use [173].

Disorder of gallbladder

a) A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported [170].

b) Estrogen use in postmenopausal women can produce greater cholesterol saturation in the bile due to changes in hepatic excretory function, thus predisposing patients to gallstone formation. However, results of studies have been mixed with regard to replacement therapy and the risk of gallbladder disease, specifically cholelithiasis [158]. One report described that the risk of surgically confirmed gallbladder disease was increased 2.5 times during conjugated estrogen therapy [159]. Another report indicated that estrogen replacement therapy increased the risk of cholesterol cholelithiasis, as did obesity [160]. However, another report indicated that the occurrence of gallbladder disease was significantly lower in estrogen users as compared to a control group [100]. A higher, although insignificant, incidence of cholelithiasis in patients receiving estrogen and progestin therapy has been reported [161].

Nausea

a) Incidence: 2.1% to 2.3% [170]

b) Nausea has been reported with the use of estrogens and/or progestin therapy [170].

Pancreatitis

a) A case of recurrent acute pancreatitis occurring in conjunction with intermittently used estrogen therapy over 7 years has been reported. The patient presented to the emergency room on 4 separate occasions complaining of sudden epigastric or upper abdominal pain. Alcohol use was denied on all occasions and severe dyslipidemia was not present. Medications included oral estrogen for menopausal symptoms and propranolol for migraines. The patient was managed with conservative care during all episodes and was discharged 4 to 10 days after presenting. Estrogen was discontinued and restarted after the third episode 5 years later and pancreatitis recurred after 6 weeks. Again, after conservative therapy, the patient was discharged and estrogens were permanently discontinued [162].

Stomach cramps

a) Abdominal cramps have been reported with the use of estrogens and/or progestin therapy [170].

Vomiting

a) Vomiting has been reported with the use of estrogens and/or progestin therapy [170].

Estradiol Cypionate

Bloating symptom

a) Bloating has been reported with the use of estrogens and/or progestin therapy [55].

Disorder of gallbladder

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Vomiting

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Estradiol Valerate

Bloating symptom

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Disorder of gallbladder

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Vomiting

a) Vomiting has been reported with the use of estrogens and/or progestin therapy [57].

Hematologic Effects

Estradiol

Blood coagulation pathway finding

a) General Information

1) Procoagulant effects of oral estrogen may be more pronounced during initial treatment period [78] and with higher doses [79][80][81]

b) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Procoagulant effects have been described [82][83][84][78]

2) Hormone replacement therapy (transdermal route): No effect on coagulation markers [82][83][84]

Deep venous thrombosis

a) General Information

1) Increased risk with estrogen monotherapy and with estrogen and progestin combination therapy [29][69][74]

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

b) Prevention and Management

1) Appropriately manage risk factors for VTE (eg, personal or family history, obesity, systemic lupus erythematosus) [29][69][74][19][76]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69][74]

3) Discontinue (when possible) 4 to 6 weeks before periods of prolonged immobilization or surgeries that increase thromboembolic risk [29][69][74][76]

4) Discontinue immediately if event occurs or is suspected [29][69][74][19][76]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): 47% higher risk with conjugated estrogens compared with placebo [29][69][74][76]

2) Hormone replacement therapy (oral route): 95% higher risk with conjugated estrogens plus medroxyprogesterone acetate compared with placebo [29][69][74][76]

Porphyria

a) General Information

1) Estrogen therapy may exacerbate porphyria [29][74][76][7][38][35][19][92][11][12][36][14][15]

Thrombocytopenic purpura

a) Adult Case Reports

1) Thrombotic thrombocytopenic purpura has been reported in 2 cases with the use of transdermal estradiol. Transdermal estradiol was used for 5 years and 6 months, respectively, prior to the diagnosis [85].

Venous thromboembolism

a) General Information

1) Increased risk of VTE (DVT and pulmonary embolism) with estrogen monotherapy and with combination estrogen and progestin therapy [29][74]

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

b) Prevention and Management

1) Appropriately manage risk factors for VTE (eg, personal or family history, obesity, systemic lupus erythematosus) [29][69][76][19]

2) Factor V Leiden significantly enhances hormone-associated risk of thrombosis [87].

3) Transdermal estrogen appears not to increase the risk of thromboembolism among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy [37]

4) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69][74]

5) Discontinue (if possible) 4 to 6 weeks before periods of prolonged immobilization or surgeries that increase thromboembolism risk [29][69]

6) Discontinue immediately if occurs or is suspected [29][69][76][19]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Though risk of pulmonary embolism among women (mean age, 63) treated with conjugated estrogens 0.625 mg/day monotherapy for a mean 7.1 years was not significantly greater than placebo, risk of DVT was 47% higher with conjugated estrogen monotherapy versus placebo. Increased VTE risk occurred during the first 2 years of therapy [69]

2) Hormone replacement therapy (oral route): Risk of DVT and pulmonary embolism were significantly greater than placebo in women (mean age, 63) treated with daily conjugated estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg for a mean 5.6 years [29][69]

3) Hormone replacement therapy (oral and transdermal route): Risk of VTE was 4.2-fold higher with oral estrogen therapy compared with placebo, while users of transdermal estrogen showed no significant difference. Additionally, risk of VTE was nearly 4-fold higher among users of norpregnane derivatives (nomegestrol acetate or promegestone) but showed no difference with use of micronized progesterone or pregnane derivatives (including medroxyprogesterone acetate) compared with placebo [37]

4) Hormone replacement therapy (oral route): Increased risk of DVT and VTE associated with conjugated estrogen monotherapy was 2- to nearly 3-fold higher compared with placebo during the first 2 years of therapy over 7.1 years of followup. Age, body mass index or other risk factors for VTE did not appear to influence risk. However, risk compared with placebo was lower with estrogen monotherapy (34% higher) versus with estrogen plus progestin combination therapy (more than 2-fold higher) [88].

5) Hormone replacement therapy (oral route): Risk of venous thromboembolism (VT) significantly increased with age and weight. Risk increased from about 2-fold higher with hormone replacement therapy (HRT) than with placebo among women aged 50 to 59 years and 60 to 69 years to more than 4-fold higher with HRT therapy than with placebo among women aged 70 to 79 years. VT risk rose from more than 2-fold higher with HRT than with placebo among women with a BMI between 25 and 30 to nearly 3-fold higher with HRT than with placebo among women with a BMI greater than 30. In addition, Factor V Leiden enhanced the hormone-associated risk of thrombosis with a nearly 7-fold higher risk than placebo in patients without the mutation [87].

6) Hormone replacement therapy (oral route): In more than 7 years of followup, women treated continuously with conjugated equine estrogen (CEE) showed a 65% greater risk of venous thromboembolism (VT) than placebo-treated women. No increased risk of VT compared with placebo was seen in women treated with esterified estrogen. Among estrogen users, women treated with CEE had a significant 78% higher risk of VT than women treated with esterified estrogen with continuous use [89].

7) Hormone replacement therapy (oral and transdermal routes): Estimated risk for venous thromboembolism was a significant 4-fold higher among current users of oral estrogen replacement therapy (ERT) compared with transdermal ERT users [90].

8) Hormone replacement therapy (oral route): In the Heart and Estrogen-progestin Replacement Study (HERS), women with coronary heart disease treated with conjugated estrogens and progestin showed a nearly 3-fold higher risk of venous thromboembolism than with placebo . Risk decreased with aspirin or statin use [91].

Venous thromboembolism, Recurrent

a) Adult Clinical Studies

1) Hormone replacement therapy (oral route): 6.4-fold higher risk of recurrent VTE in postmenopausal women [77]

2) Hormone replacement therapy (transdermal route): No increased risk of recurrent VTE in postmenopausal women[77]

Estradiol Acetate

Blood coagulation pathway finding

a) Estrogens can increase the concentrations of certain clotting factors. This effect is more obvious at higher dosages (greater than 1.25 mg/day conjugated estrogen equivalent). The dose-response relationship is not well-defined, and published studies on this problem in postmenopausal women are not definitive [79][80][81]. However, data suggests no overall increased risk of thromboembolic complications associated with lower replacement doses of estrogens (although certain subgroups

may be at increased risk).

b) It has been reported that long-term therapy with various estrogens did not affect clotting factors (thrombin time, prothrombin time, kaolin partial thromboplastin time) in 390 postmenopausal women. Many of these patients were on cyclic therapy or combination estrogen plus progestin therapy in varying doses and combinations. One patient in the treatment group developed deep venous thrombophlebitis and another had a myocardial infarction. No vascular complications occurred in the 110 patients who did not receive hormone therapy [79].

Porphyria

a) Estrogen therapy may cause an exacerbation of porphyria [170].

Venous thromboembolism

a) Summary

1) Results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicate estrogen plus progestin therapy leads to significant increases in the risk of venous thromboembolism in postmenopausal women with a uterus and health risks exceeded benefits [87]. Results from the WHI Estrogen Alone trial involving postmenopausal women without a uterus indicate the risk of venous thromboembolism was increased for women receiving estrogen (hazard ratio 1.32, 95% confidence interval 0.99 to 1.75) compared with placebo but to a lesser degree than compared to the risk associated with estrogen plus progestin [88]. Transdermal estrogen appears not to increase the risk of thromboembolism among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy [37].

b) Results from the Estrogen and Thromboembolism Risk (ESTHER) study indicate that transdermal estrogen use is not associated with an increased risk of venous thromboembolism (VTE) among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy. The multicenter, case-control study enrolled 271 consecutive cases of first documented episodes of idiopathic VTE and 610 matched community and hospital controls. The majority of current users of estrogen received 17-beta-estradiol. After adjusting for confounding factors, the odds ratios (OR) of VTE in current users of oral estrogen was 4.2 (95% confidence interval (CI), 1.5 to 11.6) compared with nonusers. The OR in current users of transdermal estrogen was 0.9 (95% CI, 0.4 to 2.1) compared with nonusers. Additionally, there was no significant association of VTE with the use of micronized progesterone or pregnane derivatives (including medroxyprogesterone acetate) while there was a 4-fold increase in OR of VTE (OR 3.9; 95% CI, 1.5 to 10.0) among users of norpregnane derivatives (nomegestrol acetate or promegestone). Stratification by dose and duration of estrogen therapy revealed similar results. There was no association between past estrogen use and VTE risk (OR, 1.1; 95% CI, 0.6 to 1.7) [37].

c) Final adjudicated results from the Women's Health Initiative (WHI) Estrogen Alone trial concluded there is an increased risk of venous thromboembolism (VT) in women receiving estrogen, particularly within the first 2 years, but the risk increase is less than the risk associated with the combination of estrogen plus progestin. Postmenopausal women without a uterus (n=10,739) were randomized in a double-blind trial to receive 0.625 milligrams (mg) of CEE or placebo. After a mean follow-up of 7.1 years, 111 women receiving CEE developed VT compared with 86 women receiving placebo (hazard ratio (HR), 1.32; 95% confidence interval (CI), 0.99 to 1.75). Deep vein thrombosis (DVT) occurred in 85 women receiving CEE compared with 59 women receiving placebo (HR, 1.47; 95% CI, 1.06 to 2.06). The HR for pulmonary embolism (PE) was similar between the two groups (1.37; 95% CI, 0.90 to 2.07). The increased risk of DVT, PE, and VT associated with CEE compared with placebo appeared to be greater within the first 2 years of therapy (HR, 2.79, 95% CI 1.24 to 6.27; HR, 2.21, 95% CI, 0.77 to 6.36; HR, 2.22, 95% CI, 1.12 to 4.39, respectively). Age, body mass index or other VT risk factors did not appear to have a significant effect on the interaction between estrogen use and risk of VT. Comparison of results from the WHI Estrogen Alone trial and the WHI Estrogen Plus Progestin trial indicates the HR for CEE is significantly lower than the HR for estrogen plus progestin (1.34, 95% CI, 1.01 to 1.77 versus 2.09, 95% CI 1.59 to 2.74) [88].

d) Final results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicate estrogen plus progestin therapy leads to a doubling in the rates of venous thromboembolism (VT) in postmenopausal women with a uterus. The WHI was a double-blind, controlled trial of 16,608 postmenopausal women who were randomized to oral conjugated equine estrogen (CEE) 0.625 milligrams (mg) daily plus oral medroxyprogesterone acetate (MPA) 2.5 mg daily or placebo. In a nested case-control study, baseline gene variants related to thrombosis risk were measured in the first 147 women who developed thrombosis and in 513 controls who were matched for age, randomization date, presence of baseline vascular disease, and time to follow-up. With a mean follow-up of 5.6 years, VT occurred in 167 women taking estrogen plus progestin and in 76 women taking placebo (3.5 per 1000 person-years and 1.7 per 1000 person-years, respectively; hazard ratio (HR), 2.06, 95% confidence interval (CI), 1.57 to 2.7). The risk of VT associated with hormone replacement therapy (HRT) was higher when compared to placebo and as age increased. The HR for women aged 50 to 59 receiving HRT was 2.27

(95% CI, 1.19 to 4.33) with an annualized rate per 1000 person years of 0.8 for placebo and 1.9 for HRT. Women aged 60 to 69 had an annualized rate of 1.9 and 3.5 per 1000 person-years when receiving placebo and HRT, respectively. The associated HR was 4.28 (95% CI, 2.38 to 7.72) for HRT and 2.31 (95% CI, 1.23 to 4.35) for placebo. Women aged 70 to 79 had an annualized rate per 1000-person years of 2.7 if receiving placebo and 6.2 if receiving HRT, with a HR of 3.37 (95% CI, 1.72 to 6.6) for placebo and 7.46 (95% CI, 4.32 to 14.38) for HRT. As weight increased, the incidence of VT also increased. The annual incidence of VT per 1000 person-years was 1.5 (when receiving placebo) and 3.5 (when receiving HRT) for women with a body mass index (BMI) between 25 and 30. A HR of 1.63 (95% CI, 0.83 to 3.2) for placebo and 3.8 (95% CI, 2.08 to 6.94) for HRT was reported. When BMI was greater than 30, the annual incidence per 1000 person-years increased to 2.5 (when receiving placebo) and 5.1 (when receiving HRT) with a corresponding HR of 2.87 (95% CI, 1.52 to 5.4) for placebo and 5.61 (95% CI, 3.12 to 10.11) for HRT. In addition, Factor V Leiden (n=17) enhanced the hormone-associated risk of thrombosis with a 6.69-fold increased risk compared with women in the placebo group (n=35) without the mutation (95% CI, 3.09 to 14.49) [87].

e) Results from a population-based, case-control, observational study indicate that conjugated equine estrogen (CEE) but not esterified estrogen is associated with an increased risk of venous thrombosis (VT). Cases (n=586) were perimenopausal and postmenopausal women aged 30 to 89 years who sustained a first deep vein venous thrombosis (DVT) or pulmonary embolism (PE) and controls (n=2268) were matched on age (within the decade), hypertension status, and calendar year of VT first episode. Pharmacy claims data and hospital records were reviewed for all patients. Continual estrogen use was defined as consecutive prescription refills with no more than a 90 day lapse. The study period was 7 years. Of the 586 women who experienced a first VT, 426 (73%) had DVT alone, 68 (12%) had DVT and PE, and 92 (16%) had PE, of which 33 were fatal. Compared with women not currently using hormones, current users of esterified estrogen had no increase in VT risk (odds ratio (OR), 0.92; 95% confidence interval (CI), 0.69 to 1.22). However, women currently taking CEE (121 cases and 289 controls) had an elevated risk (OR, 1.65; 95% CI, 1.24 to 2.19). Current users of CEE also had a higher risk compared to current users of esterified estrogen when the analyses were limited to estrogen users only (OR, 1.78; 95% CI, 1.11 to 2.84). Additionally, concomitant progestin use was associated with increased risk of VT compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13 to 2.26) [89].

f) When oral and transdermal estrogen replacement therapy (ERT) were compared in a multicenter, hospital-based, case-control study of postmenopausal women, oral ERT was associated with a risk of venous thromboembolism (VTE). Consecutive cases with a first documented episode of idiopathic VTE were recruited (n=155). During this same period, 381 controls matched for age and center were recruited. Overall, 22% and 7% of cases and controls, respectively, were current users of oral ERT while 19% and 24% of cases and controls, respectively, were current users of transdermal ERT. After adjustment for potential confounding variables (body mass index, family history of VTE, history of varicose veins, and education level), the odds ratio of VTE in current users of oral and transdermal ERT compared with non-users was 3.2 (95% confidence interval (CI) 1.8 to 6.8) and 0.9 (0.5 to 1.6), respectively. Estimated risk for VTE in current users of oral ERT compared with transdermal ERT users was 4.0 (95% CI 1.9 to 8.3) [90].

g) Data analyzed from the Heart and Estrogen-progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) with conjugated estrogens and progestin is associated with an increased risk for venous thromboembolism in women with coronary heart disease. With a mean follow-up of 4.1 years, 34 of 1380 women receiving HRT developed venous thromboembolic events compared to 13 of 1383 women receiving placebo (relative hazard (RH) 2.7; 95% confidence interval (CI) 1.4 to 5.0). The risk was increased among women with lower- extremity fractures, cancer and for 90 days after inpatient surgery or nonsurgical hospitalization. Decreased risk was associated with aspirin or statin use [91].

h) Estrogen replacement in hospitalized postmenopausal women was not an associated risk factor for venous thrombosis in a case-control study which included women with prior thrombotic risk factors [81]. This retrospective study included 121 thromboembolic cases and 236 controls which were matched for age, year of admission, admitting service, and socioeconomic status. The sample was of sufficient size to have a 95% probability of detecting a two-fold or greater increase in the proportion of estrogen users. Thus, a smaller but still significant increase in risk for estrogen use could have gone undetected.

Estradiol Cypionate

Blood coagulation pathway finding

a) Estrogens can increase the concentrations of certain clotting factors. This effect is more obvious at higher dosages (greater than 1.25 mg/day conjugated estrogen equivalent). The dose-response relationship is not well-defined, and published studies on this problem in postmenopausal women are not definitive [79][80][81]. However, data suggests no overall increased risk of thromboembolic complications associated with lower replacement doses of estrogens (although certain subgroups may be at increased risk).

b) It has been reported that long-term therapy with various estrogens did not affect clotting factors (thrombin time, prothrombin time, kaolin partial thromboplastin time) in 390 postmenopausal women. Many of these patients were on cyclic therapy or combination estrogen plus progestin therapy in varying doses and combinations. One patient in the treatment group developed deep venous thrombophlebitis and another had a myocardial infarction. No vascular complications occurred in the 110 patients who did not receive hormone therapy [79].

Porphyria

a) Estrogen therapy may cause an exacerbation of porphyria [55].

Venous thromboembolism

a) General Information

1) Results from the Estrogen and Thromboembolism Risk (ESTHER) study indicate that transdermal estrogen use is not associated with an increased risk of venous thromboembolism (VTE) among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy. The multicenter, case-control study enrolled 271 consecutive cases of first documented episodes of idiopathic VTE and 610 matched community and hospital controls. The majority of current users of estrogen received 17-beta-estradiol. After adjusting for confounding factors, the odds ratios (OR) of VTE in current users of oral estrogen was 4.2 (95% confidence interval (CI), 1.5 to 11.6) compared with nonusers. The OR in current users of transdermal estrogen was 0.9 (95% CI, 0.4 to 2.1) compared with nonusers. Additionally, there was no significant association of VTE with the use of micronized progesterone or pregnane derivatives (including medroxyprogesterone acetate) while there was a 4-fold increase in OR of VTE (OR 3.9; 95% CI, 1.5 to 10.0) among users of norpregnane derivatives (nomegestrol acetate or promegestone). Stratification by dose and duration of estrogen therapy revealed similar results. There was no association between past estrogen use and VTE risk (OR, 1.1; 95% CI, 0.6 to 1.7) [37].

2) Final adjudicated results from the Women's Health Initiative (WHI) Estrogen Alone trial concluded there is an increased risk of venous thromboembolism (VT) in women receiving estrogen, particularly within the first 2 years, but the risk increase is less than the risk associated with the combination of estrogen plus progestin. Postmenopausal women without a uterus (n=10,739) were randomized in a double-blind trial to receive 0.625 milligrams (mg) of CEE or placebo. After a mean follow-up of 7.1 years, 111 women receiving CEE developed VT compared with 86 women receiving placebo (hazard ratio (HR), 1.32; 95% confidence interval (CI), 0.99 to 1.75). Deep vein thrombosis (DVT) occurred in 85 women receiving CEE compared with 59 women receiving placebo (HR, 1.47; 95% CI, 1.06 to 2.06). The HR for pulmonary embolism (PE) was similar between the two groups (1.37; 95% CI, 0.90 to 2.07). The increased risk of DVT, PE, and VT associated with CEE compared with placebo appeared to be greater within the first 2 years of therapy (HR, 2.79, 95% CI 1.24 to 6.27; HR, 2.21, 95% CI, 0.77 to 6.36; HR, 2.22, 95% CI, 1.12 to 4.39, respectively). Age, body mass index or other VT risk factors did not appear to have a significant effect on the interaction between estrogen use and risk of VT. Comparison of results from the WHI Estrogen Alone trial and the WHI Estrogen Plus Progestin trial indicates the HR for CEE is significantly lower than the HR for estrogen plus progestin (1.34, 95% CI, 1.01 to 1.77 versus 2.09, 95% CI 1.59 to 2.74) [88].

3) Final results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicate estrogen plus progestin therapy leads to a doubling in the rates of venous thromboembolism (VT) in postmenopausal women with a uterus. The WHI was a double-blind, controlled trial of 16,608 postmenopausal women who were randomized to oral conjugated equine estrogen (CEE) 0.625 milligrams (mg) daily plus oral medroxyprogesterone acetate (MPA) 2.5 mg daily or placebo. In a nested case-control study, baseline gene variants related to thrombosis risk were measured in the first 147 women who developed thrombosis and in 513 controls who were matched for age, randomization date, presence of baseline vascular disease, and time to follow-up. With a mean follow-up of 5.6 years, VT occurred in 167 women taking estrogen plus progestin and in 76 women taking placebo (3.5 per 1000 person-years and 1.7 per 1000 person-years, respectively; hazard ratio (HR), 2.06, 95% confidence interval (CI), 1.57 to 2.7). The risk of VT associated with hormone replacement therapy (HRT) was higher when compared to placebo and as age increased. The HR for women aged 50 to 59 receiving HRT was 2.27 (95% CI, 1.19 to 4.33) with an annualized rate per 1000 person years of 0.8 for placebo and 1.9 for HRT. Women aged 60 to 69 had an annualized rate of 1.9 and 3.5 per 1000 person-years when receiving placebo and HRT, respectively. The associated HR was 4.28 (95% CI, 2.38 to 7.72) for HRT and 2.31 (95% CI, 1.23 to 4.35) for placebo. Women aged 70 to 79 had an annualized rate per 1000-person years of 2.7 if receiving placebo and 6.2 if receiving HRT, with a HR of 3.37 (95% CI, 1.72 to 6.6) for placebo and 7.46 (95% CI, 4.32 to 14.38) for HRT. As weight increased, the incidence of VT also increased. The annual incidence of VT per 1000 person-years was 1.5 (when receiving placebo) and 3.5 (when receiving HRT) for women with a body mass index (BMI) between 25 and 30. A HR of 1.63 (95% CI, 0.83 to 3.2) for placebo and 3.8 (95% CI, 2.08 to 6.94) for HRT was reported.

When BMI was greater than 30, the annual incidence per 1000 person-years increased to 2.5 (when receiving placebo) and 5.1 (when receiving HRT) with a corresponding HR of 2.87 (95% CI, 1.52 to 5.4) for placebo and 5.61 (95% CI, 3.12 to 10.11) for HRT. In addition, Factor V Leiden (n=17) enhanced the hormone-associated risk of thrombosis with a 6.69-fold increased risk compared with women in the placebo group (n=35) without the mutation (95% CI, 3.09 to 14.49) [87].

4) Results from a population-based, case-control, observational study indicate that conjugated equine estrogen (CEE) but not esterified estrogen is associated with an increased risk of venous thrombosis (VT). Cases (n=586) were perimenopausal and postmenopausal women aged 30 to 89 years who sustained a first deep vein venous thrombosis (DVT) or pulmonary embolism (PE) and controls (n=2268) were matched on age (within the decade), hypertension status, and calendar year of VT first episode. Pharmacy claims data and hospital records were reviewed for all patients. Continual estrogen use was defined as consecutive prescription refills with no more than a 90 day lapse. The study period was 7 years. Of the 586 women who experienced a first VT, 426 (73%) had DVT alone, 68 (12%) had DVT and PE, and 92 (16%) had PE, of which 33 were fatal. Compared with women not currently using hormones, current users of esterified estrogen had no increase in VT risk (odds ratio (OR), 0.92; 95% confidence interval (CI), 0.69 to 1.22). However, women currently taking CEE (121 cases and 289 controls) had an elevated risk (OR, 1.65; 95% CI, 1.24 to 2.19). Current users of CEE also had a higher risk compared to current users of esterified estrogen when the analyses were limited to estrogen users only (OR, 1.78; 95% CI, 1.11 to 2.84). Additionally, concomitant progestin use was associated with increased risk of VT compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13 to 2.26) [89].

5) When oral and transdermal estrogen replacement therapy (ERT) were compared in a multicenter, hospital-based, case-control study of postmenopausal women, oral ERT was associated with a risk of venous thromboembolism (VTE). Consecutive cases with a first documented episode of idiopathic VTE were recruited (n=155). During this same period, 381 controls matched for age and center were recruited. Overall, 22% and 7% of cases and controls, respectively, were current users of oral ERT while 19% and 24% of cases and controls, respectively, were current users of transdermal ERT. After adjustment for potential confounding variables (body mass index, family history of VTE, history of varicose veins, and education level), the odds ratio of VTE in current users of oral and transdermal ERT compared with non-users was 3.2 (95% confidence interval (CI) 1.8 to 6.8) and 0.9 (0.5 to 1.6), respectively. Estimated risk for VTE in current users of oral ERT compared with transdermal ERT users was 4.0 (95% CI 1.9 to 8.3) [90].

6) Data analyzed from the Heart and Estrogen-progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) with conjugated estrogens and progestin is associated with an increased risk for venous thromboembolism in women with coronary heart disease. With a mean follow-up of 4.1 years, 34 of 1380 women receiving HRT developed venous thromboembolic events compared to 13 of 1383 women receiving placebo (relative hazard (RH) 2.7; 95% confidence interval (CI) 1.4 to 5.0). The risk was increased among women with lower- extremity fractures, cancer and for 90 days after inpatient surgery or nonsurgical hospitalization. Decreased risk was associated with aspirin or statin use [91].

7) Estrogen replacement in hospitalized postmenopausal women was not an associated risk factor for venous thrombosis in a case-control study which included women with prior thrombotic risk factors. This retrospective study included 121 thromboembolic cases and 236 controls which were matched for age, year of admission, admitting service, and socioeconomic status. The sample was of sufficient size to have a 95% probability of detecting a two-fold or greater increase in the proportion of estrogen users. Thus, a smaller but still significant increase in risk for estrogen use could have gone undetected [81].

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or reference men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

Estradiol Valerate

Blood coagulation pathway finding

a) General Information

1) Estrogens can increase the concentrations of certain clotting factors. This effect is more obvious at higher dosages (greater than 1.25 mg/day conjugated estrogen equivalent). The dose-response relationship is not well-defined, and published

studies on this problem in postmenopausal women are not definitive [79][80][81]. However, data suggests no overall increased risk of thromboembolic complications associated with lower replacement doses of estrogens (although certain subgroups may be at increased risk).

2) It has been reported that long-term therapy with various estrogens did not affect clotting factors (thrombin time, prothrombin time, kaolin partial thromboplastin time) in 390 postmenopausal women. Many of these patients were on cyclic therapy or combination estrogen plus progestin therapy in varying doses and combinations. One patient in the treatment group developed deep venous thrombophlebitis and another had a myocardial infarction. No vascular complications occurred in the 110 patients who did not receive hormone therapy [79].

Porphyria

a) General Information

1) Estrogen therapy may cause an exacerbation of porphyria [57].

Venous thromboembolism

a) General Information

1) Results from the Estrogen and Thromboembolism Risk (ESTHER) study indicate that transdermal estrogen use is not associated with an increased risk of venous thromboembolism (VTE) among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy. The multicenter, case-control study enrolled 271 consecutive cases of first documented episodes of idiopathic VTE and 610 matched community and hospital controls. The majority of current users of estrogen received 17-beta-estradiol. After adjusting for confounding factors, the odds ratios (OR) of VTE in current users of oral estrogen was 4.2 (95% confidence interval (CI), 1.5 to 11.6) compared with nonusers. The OR in current users of transdermal estrogen was 0.9 (95% CI, 0.4 to 2.1) compared with nonusers. Additionally, there was no significant association of VTE with the use of micronized progesterone or pregnane derivatives (including medroxyprogesterone acetate) while there was a 4-fold increase in OR of VTE (OR 3.9; 95% CI, 1.5 to 10.0) among users of norpregnane derivatives (nomegestrol acetate or promegestone). Stratification by dose and duration of estrogen therapy revealed similar results. There was no association between past estrogen use and VTE risk (OR, 1.1; 95% CI, 0.6 to 1.7) [37].

2) Final adjudicated results from the Women's Health Initiative (WHI) Estrogen Alone trial concluded there is an increased risk of venous thromboembolism (VT) in women receiving estrogen, particularly within the first 2 years, but the risk increase is less than the risk associated with the combination of estrogen plus progestin. Postmenopausal women without a uterus (n=10,739) were randomized in a double-blind trial to receive 0.625 milligrams (mg) of CEE or placebo. After a mean follow-up of 7.1 years, 111 women receiving CEE developed VT compared with 86 women receiving placebo (hazard ratio (HR), 1.32; 95% confidence interval (CI), 0.99 to 1.75). Deep vein thrombosis (DVT) occurred in 85 women receiving CEE compared with 59 women receiving placebo (HR, 1.47; 95% CI, 1.06 to 2.06). The HR for pulmonary embolism (PE) was similar between the two groups (1.37; 95% CI, 0.90 to 2.07). The increased risk of DVT, PE, and VT associated with CEE compared with placebo appeared to be greater within the first 2 years of therapy (HR, 2.79, 95% CI 1.24 to 6.27; HR, 2.21, 95% CI, 0.77 to 6.36; HR, 2.22, 95% CI, 1.12 to 4.39, respectively). Age, body mass index or other VT risk factors did not appear to have a significant effect on the interaction between estrogen use and risk of VT. Comparison of results from the WHI Estrogen Alone trial and the WHI Estrogen Plus Progestin trial indicates the HR for CEE is significantly lower than the HR for estrogen plus progestin (1.34, 95% CI, 1.01 to 1.77 versus 2.09, 95% CI 1.59 to 2.74) [88].

3) Final results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicate estrogen plus progestin therapy leads to a doubling in the rates of venous thromboembolism (VT) in postmenopausal women with a uterus. The WHI was a double-blind, controlled trial of 16,608 postmenopausal women who were randomized to oral conjugated equine estrogen (CEE) 0.625 milligrams (mg) daily plus oral medroxyprogesterone acetate (MPA) 2.5 mg daily or placebo. In a nested case-control study, baseline gene variants related to thrombosis risk were measured in the first 147 women who developed thrombosis and in 513 controls who were matched for age, randomization date, presence of baseline vascular disease, and time to follow-up. With a mean follow-up of 5.6 years, VT occurred in 167 women taking estrogen plus progestin and in 76 women taking placebo (3.5 per 1000 person-years and 1.7 per 1000 person-years, respectively; hazard ratio (HR), 2.06, 95% confidence interval (CI), 1.57 to 2.7). The risk of VT associated with hormone replacement therapy (HRT) was higher when compared to placebo and as age increased. The HR for women aged 50 to 59 receiving HRT was 2.27 (95% CI, 1.19 to 4.33) with an annualized rate per 1000 person years of 0.8 for placebo and 1.9 for HRT. Women aged 60 to 69 had an annualized rate of 1.9 and 3.5 per 1000 person-years when receiving placebo and HRT, respectively. The associated HR was 4.28 (95% CI, 2.38 to 7.72) for HRT and 2.31 (95% CI, 1.23 to 4.35) for placebo. Women aged 70 to 79 had an annualized rate per 1000-person

years of 2.7 if receiving placebo and 6.2 if receiving HRT, with a HR of 3.37 (95% CI, 1.72 to 6.6) for placebo and 7.46 (95% CI, 4.32 to 14.38) for HRT. As weight increased, the incidence of VT also increased. The annual incidence of VT per 1000 person-years was 1.5 (when receiving placebo) and 3.5 (when receiving HRT) for women with a body mass index (BMI) between 25 and 30. A HR of 1.63 (95% CI, 0.83 to 3.2) for placebo and 3.8 (95% CI, 2.08 to 6.94) for HRT was reported. When BMI was greater than 30, the annual incidence per 1000 person-years increased to 2.5 (when receiving placebo) and 5.1 (when receiving HRT) with a corresponding HR of 2.87 (95% CI, 1.52 to 5.4) for placebo and 5.61 (95% CI, 3.12 to 10.11) for HRT. In addition, Factor V Leiden (n=17) enhanced the hormone-associated risk of thrombosis with a 6.69-fold increased risk compared with women in the placebo group (n=35) without the mutation (95% CI, 3.09 to 14.49) [87].

4) Results from a population-based, case-control, observational study indicate that conjugated equine estrogen (CEE) but not esterified estrogen is associated with an increased risk of venous thrombosis (VT). Cases (n=586) were perimenopausal and postmenopausal women aged 30 to 89 years who sustained a first deep vein venous thrombosis (DVT) or pulmonary embolism (PE) and controls (n=2268) were matched on age (within the decade), hypertension status, and calendar year of VT first episode. Pharmacy claims data and hospital records were reviewed for all patients. Continual estrogen use was defined as consecutive prescription refills with no more than a 90 day lapse. The study period was 7 years. Of the 586 women who experienced a first VT, 426 (73%) had DVT alone, 68 (12%) had DVT and PE, and 92 (16%) had PE, of which 33 were fatal. Compared with women not currently using hormones, current users of esterified estrogen had no increase in VT risk (odds ratio (OR), 0.92; 95% confidence interval (CI), 0.69 to 1.22). However, women currently taking CEE (121 cases and 289 controls) had an elevated risk (OR, 1.65; 95% CI, 1.24 to 2.19). Current users of CEE also had a higher risk compared to current users of esterified estrogen when the analyses were limited to estrogen users only (OR, 1.78; 95% CI, 1.11 to 2.84). Additionally, concomitant progestin use was associated with increased risk of VT compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13 to 2.26) [89].

5) When oral and transdermal estrogen replacement therapy (ERT) were compared in a multicenter, hospital-based, case-control study of postmenopausal women, oral ERT was associated with a risk of venous thromboembolism (VTE). Consecutive cases with a first documented episode of idiopathic VTE were recruited (n=155). During this same period, 381 controls matched for age and center were recruited. Overall, 22% and 7% of cases and controls, respectively, were current users of oral ERT while 19% and 24% of cases and controls, respectively, were current users of transdermal ERT. After adjustment for potential confounding variables (body mass index, family history of VTE, history of varicose veins, and education level), the odds ratio of VTE in current users of oral and transdermal ERT compared with non-users was 3.2 (95% confidence interval (CI) 1.8 to 6.8) and 0.9 (0.5 to 1.6), respectively. Estimated risk for VTE in current users of oral ERT compared with transdermal ERT users was 4.0 (95% CI 1.9 to 8.3) [90].

6) Data analyzed from the Heart and Estrogen-progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) with conjugated estrogens and progestin is associated with an increased risk for venous thromboembolism in women with coronary heart disease. With a mean follow-up of 4.1 years, 34 of 1380 women receiving HRT developed venous thromboembolic events compared to 13 of 1383 women receiving placebo (relative hazard (RH) 2.7; 95% confidence interval (CI) 1.4 to 5.0). The risk was increased among women with lower- extremity fractures, cancer and for 90 days after inpatient surgery or nonsurgical hospitalization. Decreased risk was associated with aspirin or statin use [91].

7) Estrogen replacement in hospitalized postmenopausal women was not an associated risk factor for venous thrombosis in a case-control study which included women with prior thrombotic risk factors [81]. This retrospective study included 121 thromboembolic cases and 236 controls which were matched for age, year of admission, admitting service, and socioeconomic status. The sample was of sufficient size to have a 95% probability of detecting a two-fold or greater increase in the proportion of estrogen users. Thus, a smaller but still significant increase in risk for estrogen use could have gone undetected.

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

Hepatic Effects

Estradiol

Cholestatic jaundice syndrome

a) General Information

1) Cholestatic jaundice has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15][94]

b) Prevention and Management

1) Discontinue if condition recurs [68][29][76][19]

Hemangioma of liver

a) General Information

1) Exacerbation of hepatic hemangiomas may occur [29]

b) Postmarketing

1) Enlargement of hepatic hemangiomas has been reported[76].

Hepatitis

a) Postmarketing

1) Acute hepatitis has been reported [74]

Estradiol Acetate

Cholestatic jaundice syndrome

a) Cholestatic jaundice has been reported during the use of estrogen and/or progestin therapy [170].

Hemangioma of liver

a) Estrogen therapy may cause an exacerbation or enlargement of hepatic hemangiomas and should be used with caution [170].

Estradiol Cypionate

Cholestatic jaundice syndrome

a) Cholestatic jaundice has been reported during the use of estrogen and/or progestin therapy [55].

Hemangioma of liver

a) Estrogen therapy may cause an exacerbation or enlargement of hepatic hemangiomas and should be used with caution [55].

Estradiol Valerate

Cholestatic jaundice syndrome

a) Cholestatic jaundice has been reported during the use of estrogen and/or progestin therapy [57].

Hemangioma of liver

a) Estrogen therapy may cause an exacerbation or enlargement of hepatic hemangiomas and should be used with caution [57].

Immunologic Effects

Estradiol

Anaphylaxis

a) General Information

1) May involve the skin, respiratory tract, and/or digestive tract [29]

b) Postmarketing

1) Anaphylactoid and/or anaphylactic reactions have been reported with the postmarketing use of estrogen and/or progestin therapy [29][66][19][76][7][38][35][8][11][36][14][15]

Systemic lupus erythematosus

a) General Information

1) May exacerbate systemic lupus erythematosus; use with caution [29][19][76][7][13][38][35][8][11][12][36][14][15]

b) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): 2.1-fold increased risk in postmenopausal estrogen ever users compared with never users; 1.8-fold increased risk in past users compared with never users [119].

Estradiol Acetate

Anaphylaxis

a) Anaphylactoid and/or anaphylactic reactions have been reported with the use of estrogen and/or progestin therapy [170].

Systemic lupus erythematosus

a) Estrogen therapy may cause an exacerbation of systemic lupus erythematosus and should be used with caution in these patients [170].
b) A cohort of 69,435 women was followed to examine the relationship between postmenopausal hormone use and development of systemic lupus erythematosus (SLE). Risk of SLE was determined by comparing ever-users of postmenopausal hormones to never-users. The age-adjusted relative risk (RR) for SLE was 2.1 for ever-users (RR equal 2.5 for current users, RR equal 1.8 for past users). There was a direct relationship between risk and duration of use of postmenopausal hormones [119].

Estradiol Cypionate

Anaphylaxis

a) Anaphylactoid and/or anaphylactic reactions have been reported with the use of estrogen and/or progestin therapy [55].

Systemic lupus erythematosus

a) Estrogen therapy may cause an exacerbation of systemic lupus erythematosus and should be used with caution in these patients [55].
b) A cohort of 69,435 women was followed to examine the relationship between postmenopausal hormone use and development of systemic lupus erythematosus (SLE). Risk of SLE was determined by comparing ever-users of postmenopausal hormones to never-users. The age-adjusted relative risk (RR) for SLE was 2.1 for ever-users (RR equal 2.5 for current users, RR equal 1.8 for past users). There was a direct relationship between risk and duration of use of postmenopausal hormones [119].

Estradiol Valerate

Anaphylaxis

a) Anaphylactoid and/or anaphylactic reactions have been reported with the use of estrogen and/or progestin therapy [57].

Systemic lupus erythematosus

a) Estrogen therapy may cause an exacerbation of systemic lupus erythematosus and should be used with caution in these patients [57].
b) A cohort of 69,435 women was followed to examine the relationship between postmenopausal hormone use and development of systemic lupus erythematosus (SLE). Risk of SLE was determined by comparing ever-users of postmenopausal hormones to never-users. The age-adjusted relative risk (RR) for SLE was 2.1 for ever-users (RR equal 2.5 for current users, RR equal 1.8 for past users). There was a direct relationship between risk and duration of use of postmenopausal hormones [119].

Musculoskeletal Effects

Estradiol

Arthralgia

a) Incidence: Transdermal system, 0% to 8.5% [29][19]
b) General Information

1) Joint pain has been reported with estrogen and/or progestin therapy [19][7] [38][35][8][11][12][36][14][15].

c) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 1% to 5% vs 3% with placebo [19]

2) Estrogen replacement (transdermal route): 0% to 8.5% vs 5.7% with placebo [29]

Backache

a) Incidence: 4% to 10.6% [29][19][15][15][94][94]
b) Adult Clinical Studies

1) Estrogen replacement (transdermal route): 4% to 10.6% vs 6% to 6.4% with placebo [29][19]

2) Estrogen replacement (vaginal route): 6% to 8% [15]

3) Estrogen replacement (oral route): 7% vs 6% with placebo [94]

Leg cramp

a) General Information

1) Leg cramps have been reported with estrogen and/or progestin therapy [76][7] [38][35][8][11][12][36][14][15]

Osteoarthritis

a) Incidence: 34.5% [118]
b) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): 34.5% in postmenopausal women using estrogen for at least 1 year vs 31% among nonusers [118].

Estradiol Acetate

Arthralgia

a) Joint pain has been reported during the use of estrogen and/or progestin therapy [170].

Backache

a) Incidence: 2.1% to 3.0% [170]
b) Back pain has been reported with the use of oral estradiol acetate at a dosage of 0.9 milligrams/day and 1.8 milligrams/day 2.1% to 3.0% [170].

Leg cramp

a) Leg cramps have been reported during the use of estrogen and/or progestin therapy [170].

Osteoarthritis

a) Postmenopausal estrogen use was associated with a higher incidence of osteoarthritis (OA). Women (n=638) in the study had used postmenopausal estrogen for at least 1 year (average duration of 14.6 years). The incidence of OA was 34.5% among women who had used estrogen for at least 1 year and 31% among women who did not use estrogen (age adjusted p=0.02). When adjusted for age, body mass index, smoking, exercise, and type of menopause, estrogen users were more likely to have hip OA and hand OA. Knee OA prevalence did not differ by estrogen use (p greater than 0.05) [118].

Estradiol Cypionate

Arthralgia

a) Joint pain has been reported during the use of estrogen and/or progestin therapy [55].

Leg cramp

a) Leg cramps have been reported during the use of estrogen and/or progestin therapy [55].

Osteoarthritis

a) Postmenopausal estrogen use was associated with a higher incidence of osteoarthritis (OA). Women (n=638) in the study had used postmenopausal estrogen for at least 1 year (average duration of 14.6 years). The incidence of OA was 34.5% among women who had used estrogen for at least 1 year and 31% among women who did not use estrogen (age adjusted p=0.02). When adjusted for age, body mass index, smoking, exercise, and type of menopause, estrogen users were more likely to have hip OA and hand OA. Knee OA prevalence did not differ by estrogen use (p greater than 0.05) [118].

Estradiol Valerate

Leg cramp

a) Leg cramps have been reported during the use of estrogen and/or progestin therapy [57].

Osteoarthritis

a) Postmenopausal estrogen use was associated with a higher incidence of osteoarthritis (OA). Women (n=638) in the study had used postmenopausal estrogen for at least 1 year (average duration of 14.6 years). The incidence of OA was 34.5% among women who had used estrogen for at least 1 year and 31% among women who did not use estrogen (age adjusted p=0.02). When adjusted for age, body mass index, smoking, exercise, and type of menopause, estrogen users were more likely to have hip OA and hand OA. Knee OA prevalence did not differ by estrogen use (p greater than 0.05) [118].

Neurologic Effects

Estradiol

Cerebrovascular accident

a) General Information

1) Increased risk with estrogen monotherapy or with estrogen and progestin combination therapy [29][69][74]

2) Increased risk of ischemic stroke was observed in users of oral estrogens in a dose-dependent fashion, and users of norpregnane derivatives in a retrospective case-control study [106].

3) No significant differences in distribution of stroke subtypes or severity, including fatal strokes, were seen in women treated with estrogen monotherapy compared with placebo [29][69].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-

up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

b) Prevention and Management

1) Appropriately manage risk factors for arterial vascular disease (eg, obesity, high cholesterol, tobacco use, diabetes, hypertension) [29][69][74]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69][74]

3) Do not use estrogen mono- or combination therapy to prevent stroke [29][69]

4) Discontinue immediately if event occurs or is suspected [29][69][74][76][19]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Overall adjusted risk of ischemic stroke was increased by 58% in a case (n=3144)-control (n=12158) study of French women aged 51 to 62 years [106]

2) Hormone replacement therapy (oral route): Overall stroke risk was 33% higher among women aged 50 to 79 years old treated with conjugated estrogens 0.625 mg/day for a mean of 7.1 years than among placebo-treated women, but there was no increased risk of stroke in women 50 to 59 years old [29][69][74]

3) Hormone replacement therapy (oral route): Ischemic stroke risk was 55% higher among women aged 50 to 79 years old treated with conjugated estrogens 0.625 mg/day for a mean of 7.1 years than among placebo-treated women, [29] [69]

4) Hormone replacement therapy (oral route): In a Women's Health Initiative substudy, overall stroke risk was 31% higher among women aged 50 to 79 years treated with conjugated estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day for a mean 5.6 years than among placebo-treated women [29] [69]

5) Hormone replacement therapy (oral route): Over a mean 7.1 years, overall stroke risk was 37% higher with conjugated equine estrogen therapy 0.625 mg compared with placebo. Risk of ischemic stroke was 55% higher and risk of hemorrhagic stroke was 64% higher than placebo [107]

6) Hormone replacement therapy (unspecified route): Decreased risk with noncontraceptive estrogen compared with women with no history of estrogen treatment, particularly in women under age 60; women treated with estrogen/progestin combination therapy also had a lower stroke risk [108]

Dementia

a) General Information

1) Increased risk with estrogen monotherapy or with estrogen and progestin combined therapy among postmenopausal women aged 65 or older [29][69][74]

2) Unknown if increased risk applies to younger postmenopausal women [29][69] [74]

b) Prevention and Management

1) Do not prescribe for dementia prophylaxis [29][69][74]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69][74]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): In the Women's Health Initiative Memory Study (WHIMS) of women aged 65 to 79 years, a nonsignificant increase in dementia risk occurred with a mean 5.2 years of conjugated estrogens 0.625 mg/day monotherapy compared with placebo. However, risk was more than 2-fold higher than placebo with a mean 4 years of daily conjugated estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg combination therapy. Pooled risk among both groups treated with hormone replacement therapy was a significant 76% higher than among placebo-treated women. It is unknown if these findings may be generalized to younger postmenopausal women [29][69][74][76] [7][38][35][8][19][11][12][14][15][47]

Headache

a) Incidence: Topical gel, 9.5% [74]transdermal spray, 9% to 12% [36]; transdermal system, 5% to 50% [29][19][11][12]; vaginal cream, 16% [15]; vaginal insert, 2.6% to 3.7% [5]; vaginal ring, 13% [15]; vaginal tablets, 9% to 10% [94]

b) Adult Clinical Trials

1) Dyspareunia (vaginal route): 3.7% with estradiol 4-mcg insert and 2.6% with estradiol 10-mcg insert vs 3.1% with placebo [5]

2) Estrogen replacement (vaginal route): 13% with estradiol ring vs 16% with estradiol cream [15]; 9% to 10% with estradiol tablets vs 6% with placebo [94]

3) Estrogen replacement (topical route): 9.5% with estradiol vs 2.7% with placebo [74]

4) Estrogen replacement (transdermal route): 9% to 12% with estradiol spray vs 5% to 9% with placebo [36]; 5% to 50% with estradiol patch vs 10% to 23.6% with placebo [29][19][11][12]

Impaired cognition

a) Adult Clinical Study

1) Hormone replacement therapy (route unknown): 47% increased risk of having a 10-unit decrease in Modified Mini-Mental State Examination (3MSE) score compared with placebo [105]

Meningioma

a) Postmarketing

1) Has been reported [74]

Migraine

a) General Information

1) Estrogen therapy can exacerbate preexisting migraine conditions [29]

b) Prevention and Management

1) Sudden onset of migraine may be associated with retinal vascular thrombosis; consider interruption of therapy pending evaluation [29]

c) Adult Clinical Studies

1) Perimenstrual headache (topical route): 40% rise in migraine attacks due to estradiol withdrawal within 5 days immediately following discontinuation of estradiol gel compared with placebo [50]

d) Postmarketing

1) Has been reported [29]

Estradiol Acetate

Cerebrovascular accident

a) Summary

1) A significant increase in the risk of stroke was reported during the Women's Health Initiative (WHI) Estrogen Plus Progestin trial involving estrogen and progestin (hazard ratio 1.41, 95% confidence interval 1.07 to 1.85) [171] and in the WHI Estrogen Alone trial that compared estrogen only to placebo (hazard ratio 1.37, 95% confidence interval 1.09 to 1.73) [143][144]. A secondary analysis of the WHI Estrogen Plus Progestin trial demonstrated the risk of stroke was increased with hormone therapy (HR, 1.32; 95% CI, 1.12 to 1.56) but the risk did not vary significantly by age or time since menopause [146]. In several other studies, the relative risk (RR) of stroke among HRT users varied from 0.23 to 1.46, with one study reporting a RR of 2.6. Initiation and continuation of HRT should be based on established noncoronary benefits and risks, possible coronary benefits and risks, and patient preference. Use should be based on factors other than stroke risk [172].

b) Final results from the Women's Health Initiative Estrogen Alone trial indicate that conjugated equine estrogen (CEE) therapy increases the risk of ischemic stroke in postmenopausal women who are generally healthy and the risk is not differentiated among patient subgroups. The WHI Estrogen Alone trial randomized 10,739 healthy postmenopausal women (aged 50 to 79 years) without a uterus to CEE 0.625 milligrams (mg) (n=5310) or placebo (n=5429) daily. After an average follow-up of 7.1 years, a total of 168 and 127 strokes occurred in the CEE and placebo groups, respectively. The intention-to-treat hazard ratio (HR) for all stroke subtypes (ischemic, hemorrhagic, and other strokes) for CEE versus placebo was 1.37, 95% confidence interval (CI) 1.09 to 1.73. The HR for ischemic stroke was 1.55 (95% CI 1.19 to 2.01) while the HR for hemorrhagic stroke was 0.64 (95% CI 0.35 to 1.18). Ischemic strokes attributed for 80% of all strokes and hemorrhagic strokes accounted for 15%. The HRs for ischemic stroke were consistent among patient subgroups based on age, race, years since menopause, prior cardiovascular disease, hypertension or diabetes mellitus status, body mass index, smoking, prior hormone use, or statin or aspirin use at baseline. This indicated excess risk existed in all subgroups of women examined [107].

c) Results of a population-based, case-control study indicated there was no difference in risk of myocardial infarction (MI) or stroke associated with the use of oral conjugated equine estrogen (CEE) or esterified estrogens (EE) but there was a suggested higher risk of ischemic stroke associated with CEE use alone and higher risk of MI associated with recent initiation of CEE. A total of 2724 postmenopausal women (mean age 67 to 70 years) with an incident MI (n=1644) or stroke (n=1080) were identified. The control group was comprised of a random sample of age-matched postmenopausal women without MI or stroke (n=4205). Compared with no use of hormone therapy, use of CEE or EE, with or without progestin, demonstrated little or no difference in risk of MI, ischemic stroke, or hemorrhagic stroke. When CEE and EE were compared, the use of CEE was not associated with any increased risk of MI (adjusted odds ratio (OR), 0.93; 95% confidence interval

(CI), 0.65 to 1.31) or ischemic stroke (adjusted OR, 1.31; 95% CI, 0.88 to 1.97). The additional adjustment for progestin use had little impact on OR for either therapy. When CEE and EE use (without progestin) were compared to each other, there was no difference in risk of MI, but there was a suggestion of higher risk of ischemic stroke associated with the use of CEE alone (OR, 1.57; 95% CI, 0.98 to 2.53; p=0.06). There was also a suggestion of higher risk of MI and ischemic stroke associated with CEE when high daily doses (greater than 0.625 milligrams) of CEE and EE were compared, however, the number of subjects was small and the CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

d) Analyzed data from the Heart and Estrogen-progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) with conjugated estrogens and progestin had no significant impact on the risk for stroke among postmenopausal women (n=2763) with coronary disease. The women were randomized to HRT or placebo. With a mean follow-up of 4.1 years, 149 women experienced 1 or more strokes (85% ischemic) which resulted in 26 deaths. The relative hazard (RH) for nonfatal stroke associated with HRT was 1.18; 95% confidence interval (CI) 0.83 to 1.66. The RH for fatal stroke was 1.61; 95% CI 0.73 to 3.55. More direct risks for stroke in this study were increased age, hypertension, diabetes, cigarette smoking, and atrial fibrillation [148].

e) A study in approximately 23,000 Swedish women was conducted to determine the relative risk of stroke in women who had been prescribed noncontraceptive estrogens. The cohort was followed for 6 years. The primary endpoint was the occurrence of a first stroke; secondary endpoints included the occurrence of subtypes of stroke such as subarachnoid hemorrhage (classified as acute stroke), intracerebral hemorrhage, cerebral infarction, cerebral embolism, and transient ischemic attack. For all endpoints, the risk of stroke was decreased in estrogen users compared to never users, particularly in those women under 60 years of age. This is the first study to show that women who were prescribed the progestin-estrogen regimen also had a lowered risk for stroke, which may indicate that progestins do not attenuate or eliminate the protective effects of estrogen alone [108]. The mechanisms of a possible protective effect of estrogen therapy against stroke is not known.

Dementia

a) Results of the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with conjugated estrogens (CE) 0.625 milligrams (mg) alone and during 4 years of treatment with CE 0.625 mg combined with medroxyprogesterone acetate (MPA) 2.5 mg, relative to placebo. Findings from the estrogen-alone WHIMS indicated that conjugated equine estrogen (CEE) therapy alone did not reduce dementia or mild cognitive impairment in postmenopausal patients but increased the risk for both endpoints combined. Women aged 65 to 79 years (n=2947) participated in the estrogen-alone WHIMS, which compared CEE 0.625 mg with placebo. During follow-up, the hazard ratio (HR) of probable dementia for women receiving CEE compared to placebo was 1.49 (95% Confidence Interval (CI), 0.83 to 2.66). This negative trend did not reach statistical significance (p=0.18) and it is unknown whether this finding applies to younger postmenopausal women. The HR for probable dementia in the CEE/MPA substudy group compared to placebo was 2.05 (95% CI, 1.21 to 3.48). When data were pooled for estrogen alone and estrogen plus progestin therapy, the overall HR for probable dementia was 1.76 (95% CI, 1.19 to 2.60; p=0.005) [170][47].

Epilepsy

a) Estrogen therapy may cause an exacerbation of epilepsy [170].

Headache

a) Incidence: 3 to 5% [170]

b) Headache has been reported with estrogen and/or progestin therapy [170].

Impaired cognition

a) Conjugated equine estrogen (CEE) therapy did not improve global cognitive function but actually had an adverse effect on cognition. Women aged 65 to 79 years who participated in the Women's Health Initiative Memory Study (WHIMS), which compared CEE with placebo, demonstrated a trend toward an increased risk of probable dementia and/or mild cognitive impairment. The relative risk of having a 10-unit decrease in Modified Mini-Mental State Examination (3MSE) scores for women assigned to CEE compared with placebo was estimated to be 1.47 (95% Confidence Interval, 1.04 to 2.07) [105].

Migraine

a) Estrogen therapy may cause an exacerbation of migraine headaches [170].

Estradiol Cypionate

Cerebrovascular accident

a) General Information

1) Final results from the Women's Health Initiative Estrogen Alone trial indicate that conjugated equine estrogen (CEE) therapy increases the risk of ischemic stroke in postmenopausal women who are generally healthy and the risk is not differentiated among patient subgroups. The WHI Estrogen Alone trial randomized 10,739 healthy postmenopausal women (aged 50 to 79 years) without a uterus to CEE 0.625 milligrams (mg) (n=5310) or placebo (n=5429) daily. After an average follow-up of 7.1 years, a total of 168 and 127 strokes occurred in the CEE and placebo groups, respectively. The intention-to-treat hazard ratio (HR) for all stroke subtypes (ischemic, hemorrhagic, and other strokes) for CEE versus placebo was 1.37, 95% confidence interval (CI) 1.09 to 1.73. The HR for ischemic stroke was 1.55 (95% CI 1.19 to 2.01) while the HR for hemorrhagic stroke was 0.64 (95% CI 0.35 to 1.18). Ischemic strokes attributed for 80% of all strokes and hemorrhagic strokes accounted for 15%. The HRs for ischemic stroke were consistent among patient subgroups based on age, race, years since menopause, prior cardiovascular disease, hypertension or diabetes mellitus status, body mass index, smoking, prior hormone use, or statin or aspirin use at baseline. This indicated excess risk existed in all subgroups of women examined [107].

2) Results of a population-based, case-control study indicated there was no difference in risk of myocardial infarction (MI) or stroke associated with the use of oral conjugated equine estrogen (CEE) or esterified estrogens (EE) but there was a suggested higher risk of ischemic stroke associated with CEE use alone and higher risk of MI associated with recent initiation of CEE. A total of 2724 postmenopausal women (mean age 67 to 70 years) with an incident MI (n=1644) or stroke (n=1080) were identified. The control group was comprised of a random sample of age-matched postmenopausal women without MI or stroke (n=4205). Compared with no use of hormone therapy, use of CEE or EE, with or without progestin, demonstrated little or no difference in risk of MI, ischemic stroke, or hemorrhagic stroke. When CEE and EE were compared, the use of CEE was not associated with any increased risk of MI (adjusted odds ratio (OR), 0.93; 95% confidence interval (CI), 0.65 to 1.31) or ischemic stroke (adjusted OR, 1.31; 95% CI, 0.88 to 1.97). The additional adjustment for progestin use had little impact on OR for either therapy. When CEE and EE use (without progestin) were compared to each other, there was no difference in risk of MI, but there was a suggestion of higher risk of ischemic stroke associated with the use of CEE alone (OR, 1.57; 95% CI, 0.98 to 2.53; p=0.06). There was also a suggestion of higher risk of MI and ischemic stroke associated with CEE when high daily doses (greater than 0.625 milligrams) of CEE and EE were compared, however, the number of subjects was small and the CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

3) Analyzed data from the Heart and Estrogen-progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) with conjugated estrogens and progestin had no significant impact on the risk for stroke among postmenopausal women (n=2763) with coronary disease. The women were randomized to HRT or placebo. With a mean follow-up of 4.1 years, 149 women experienced 1 or more strokes (85% ischemic) which resulted in 26 deaths. The relative hazard (RH) for nonfatal stroke associated with HRT was 1.18; 95% confidence interval (CI) 0.83 to 1.66. The RH for fatal stroke was 1.61; 95% CI 0.73 to 3.55. More direct risks for stroke in this study were increased age, hypertension, diabetes, cigarette smoking, and atrial fibrillation [148].

4) A study in approximately 23,000 Swedish women was conducted to determine the relative risk of stroke in women who had been prescribed noncontraceptive estrogens. The cohort was followed for 6 years. The primary endpoint was the occurrence of a first stroke; secondary endpoints included the occurrence of subtypes of stroke such as subarachnoid hemorrhage (classified as acute stroke), intracerebral hemorrhage, cerebral infarction, cerebral embolism, and transient ischemic attack. For all endpoints, the risk of stroke was decreased in estrogen users compared to never users, particularly in those women under 60 years of age. This is the first study to show that women who were prescribed the progestin-estrogen regimen also had a lowered risk for stroke, which may indicate that progestins do not attenuate or eliminate the protective effects of estrogen alone [108]. The mechanisms of a possible protective effect of estrogen therapy against stroke is not known.

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

Dementia

a) Results of the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with conjugated estrogens (CE) 0.625 milligrams (mg) alone and during 4 years of treatment with CE 0.625 mg combined with medroxyprogesterone acetate (MPA) 2.5 mg, relative to placebo. Findings from the estrogen-alone WHIMS indicated that conjugated equine estrogen (CEE) therapy alone did not reduce dementia or mild cognitive impairment in postmenopausal patients but increased the risk for both endpoints combined. Women aged 65 to 79 years (n=2947) participated in the estrogen-alone WHIMS, which compared CEE 0.625 mg with placebo. During follow-up, the hazard ratio (HR) of probable dementia for women receiving CEE compared to placebo was 1.49 (95% Confidence Interval (CI), 0.83 to 2.66). This negative trend did not reach statistical significance (p=0.18) and it is unknown whether this finding applies to younger postmenopausal women. The HR for probable dementia in the CEE/MPA substudy group compared to placebo was 2.05 (95% CI, 1.21 to 3.48). When data were pooled for estrogen alone and estrogen plus progestin therapy, the overall HR for probable dementia was 1.76 (95% CI, 1.19 to 2.60; p=0.005) [55][47].

Epilepsy

a) Estrogen therapy may cause an exacerbation of epilepsy [55].

Headache

a) Headache has been reported with estrogen and/or progestin therapy [55].

Impaired cognition

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Migraine

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Estradiol Valerate

Cerebrovascular accident

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CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

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Epilepsy

a) General Information

1) Estrogen therapy may cause an exacerbation of epilepsy [57].

Headache

a) General Information

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Impaired cognition

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Migraine

a) General Information

1) Estrogen therapy may cause an exacerbation of migraine headaches [57].

Ophthalmic Effects

Estradiol

Disorder of cornea associated with contact lens

a) Postmarketing

1) Intolerance to contact lenses has been reported during the postmarketing use of estrogen and/or progestin therapy [19][76][7][38][35][8][11][12][36][14][15]

Dry eye syndrome

a) Incidence: 9% [115]

b) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): 9% with estrogen alone; 6.7% with estrogen plus progestin; 5.9% with no hormone use [115]

Thrombosis of retinal vein

a) General information

1) Retinal vascular thrombosis has been reported in patients receiving estrogens [29][74][19][76][7][38][35][8][11][12][36][14][15][94]

b) Prevention and Management

1) Consider interruption of therapy and evaluation if sudden partial or complete loss of vision occurs, or with sudden onset of proptosis, diplopia, or migraine [29]

2) Permanently discontinue if exam reveals papilledema or retinal vascular lesions [68][29][19][76]

c) Postmarketing

1) Retinal vein occlusion has been reported [74]

Estradiol Acetate

Disorder of cornea associated with contact lens

a) Intolerance to contact lenses has been reported during the use of estrogen and/or progestin therapy [170].

Dry eye syndrome

a) Data from the Women's Health Study suggest hormone replacement therapy (HRT) is associated with the risk of developing dry eye syndrome and the risk appears to be greater with HRT using estrogen alone. Among data provided by 25,389 women, the prevalence for dry eye syndrome among women who used no HRT was 5.9%, compared to 9% for those who used estrogen alone and 6.7% for those who used estrogen and progestin combined therapy [115].

Eye / vision finding

a) Results of a cross-sectional study of women suggest that estrogen rather than age is the primary predictive factor for changes in vascular resistance distal to the ophthalmic artery. Three groups of women were identified for the study. Group 1 (n=20) consisted of young women (20- to 26-years-old); group 2 (n=16) was comprised of postmenopausal women at least 50-years-old who had never used estrogen replacement therapy (ERT); and group 3 had 16 postmenopausal women who were receiving ERT. Color Doppler imaging analysis of flow velocities in the ophthalmic, central retinal, and nasal and temporal posterior ciliary arteries revealed that young women and postmenopausal women on estrogen had reduced resistance indexes compared to postmenopausal women not receiving estrogen (p less than 0.001). Flow velocities in the central retinal artery were similar among the 3 groups while young women demonstrated greater peak systolic and end- diastolic velocities at similar resistance index (p less 0.05) in the posterior ciliary arteries [163].

Thrombosis of retinal vein

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Estradiol Cypionate

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Thrombosis of retinal vein

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Psychiatric Effects

Estradiol

Anxiety

a) Incidence: Topical gel, 1.8% [13]; transdermal system, 0% to 10% [29][8]
b) Estrogen replacement (topical route): 1.8% vs 0% with placebo [13]
c) Estrogen replacement (transdermal route): 0% to 10% vs 2.5% to 3.4% with placebo [29][8]

Depression

a) Incidence: Transdermal system, 0% to 10.6% [29][19]
b) General Information

1) Depression has been reported with estrogen and/or progestin therapy [19][76][7][38][35][8][11][12][36][14][15]

c) Adult Clinical Studies

1) Estrogen replacement (transdermal route): 0% to 10.6% vs 0% to 3.8% with placebo [29][19].

Disturbance in mood

a) Postmarketing

1) Mood disturbances have been reported with the postmarketing use of estrogen

and/or progestin therapy [29][19][76][7][13][38][35][8][11][12][36][14][15].

Estradiol Acetate

Depression

a) Depression has been reported with the use of estrogen and/or progestin therapy [170].

Disturbance in mood

a) Mood disturbances have been reported with the use of estrogen and/or progestin therapy [170].

Estradiol Cypionate

Depression

a) Depression has been reported with the use of estrogen and/or progestin therapy [55].

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Depression

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Disturbance in mood

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Renal Effects

Estradiol Acetate

Device adherence, To bladder wall

a) General Information

1) May make vaginal ring removal difficult [174].

2) Bladder wall ulceration or erosion have been reported [174].

b) Management

1) Evaluate for bladder wall ulceration or erosion [174].

2) Consider not replacing ring until healing is complete [174].

c) Postmarketing Reports

1) Cases of ring adherence to the bladder wall have been reported [174].

Reproductive Effects

Estradiol

Abnormal cervical smear

a) Incidence: 5.4% [13]

b) Adult Clinical Trials

1) Estrogen replacement (topical route): 5.4% vs 2.7% with placebo [13]

Abrasion of vagina

a) General Information

1) May manifest as vaginal irritation, erythema, abrasion, or spotting [142]

b) Prevention and Management

1) Carefully evaluate if occurs; consider leaving ring out and not replacing it until healing is complete to prevent adherence of ring to the healing tissue [142].

c) Postmarketing

1) Vaginal erosion has been reported [142].

Breast cancer

a) General Information

1) Increased risk with conjugated estrogen monotherapy or with estrogen and progestin combined therapy [29][69][74], though no significant increased risk with estradiol monotherapy was reported in a systematic review/meta-analysis [120]

2) Tumors were larger, more advanced, and more likely node-positive with combination conjugated estrogen/progestin therapy than with placebo treatment [29][69][74]

3) Risk increases with duration of use [29][69][74]

4) Risk may occur earlier when given with progestins [29][69][74]

5) More abnormal mammograms may occur [29][69][74]

b) Prevention and Management

1) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69][74].

c) Adult Clinical Studies

1) Risk Among Healthy Women

a) Estrogen replacement, estrogen monotherapy (oral or transdermal route): Significantly increased risk in current estrogen users (except vaginal estrogens) vs nonusers (RR, 1.37; 95% CI, 1.33 to 1.41) in a meta-analysis of worldwide epidemiological data (24 prospective studies and 61,383 cases of breast cancer; randomized studies did not have sufficient breast cancer cases for inclusion); 1 through 4 years of use (RR, 1.17; 95% CI 1.1 to 1.26); 5 through 14 years of estrogen use (RR, 1.33; 95% CI, 1.28 to 1.37). Starting at age 50 years, the absolute 20-year breast cancer incidence rates were 7.4% with 10 years of estrogen use and 6.8% with 5 years use versus 6.3% with no MHT use. There was no difference in risk between equine estrogen and estradiol or between oral and transdermal administration. In past users, excess duration-dependent risks continued for more than 10 years after MHT discontinuation [121]

b) Estrogen replacement, estradiol monotherapy (oral or transdermal route): No significant difference in the odds of developing breast cancer between users of estradiol-only hormone replacement therapy (HRT) compared with non-use of estradiol HRT, according to a systematic review and meta-analysis or 12 studies. The odds of breast cancer were increased with estradiol/progestogen combinations based on the type of progestogen [120].

c) Estrogen replacement, conjugated estrogen monotherapy (oral route): A non-significant decrease in invasive breast cancer was seen in women (mean age, 63) treated with conjugated estrogens 0.625 mg/day monotherapy for a mean of 7.1 years compared with placebo-treated women. However, the risk was 24% higher than among placebo-treated patients in women (mean age, 63) treated with daily conjugated estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg for a mean 5.6 years. Compared with placebo, the risk was 86% higher with a history of hormone replacement therapy (HRT) and 9% higher with no prior history of HRT [69][74][76].

d) Estrogen replacement, estrogen monotherapy: Risk was 38% to 42% higher with estrogen monotherapy than with no history of estrogen use [122][123]; when stratified by duration of estrogen use, however, women treated with estrogen monotherapy for 10 years or more had the greatest increase in risk (6% to 42%) [123].

e) Estrogen replacement, combination therapy: Risk was 96% higher with current use of estrogen and progestin vs 38% higher with current use of estrogen monotherapy than among women who had never used hormone therapy (HT). Risk remained 8% higher among former HT users for up to 4 years vs 68% higher with current HT use [122].

2) Risk Among Breast Cancer Survivors

a) Estrogen replacement: One trial was discontinued early after results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events [124].

b) Estrogen replacement, estrogen monotherapy: Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors [125].

c) Estrogen replacement (oral and intravaginal routes): Rate of recurrence was 50% lower and breast cancer mortality 34% lower with use of hormone replacement therapy (HRT) than with non-use (O'Meara et al, 2001).

Breast tenderness

a) Incidence: Topical gel, 2.5% to 8.8% [76][38]; transdermal spray, 5% to 7% [36]; transdermal system, 6.5% to 17.0% [29][11]

b) General Information

1) Breast tenderness and pain have been reported with estrogen and/or progestin therapy [76][7][38][35][8][19][11][12][36][14][15]

c) Adult Clinical Trials

1) Estrogen replacement (topical route): 2.5% to 8.8% vs 1.6% to 3.6% with placebo [76][38].

2) Estrogen replacement (transdermal route): 5% to 7% vs 0% to 5% with placebo [36]

3) Estrogen replacement (transdermal route): 6.5% to 17% vs 0% with placebo [29][11][12]

Candida vaginitis

a) Incidence: Topical gel, 0.8% to 6.4% [38]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 0.8% to 6.4% vs 3.2% with placebo [38]

Candidiasis

a) Incidence: Vaginal cream, 7% [15]; vaginal ring, 6% [15]; vaginal tablets, 5% [94]
b) Adult Clinical Trials

1) Estrogen replacement (vaginal route); genital moniliasis, 6% with vaginal ring, 7% with vaginal cream [15], 5% with vaginal tablet vs 2% with placebo [94]

Disorder of menstruation

a) General Information

1) Breakthrough bleeding, spotting, and dysmenorrhea have been reported with estrogen and/or progestin therapy [66][76][7][38][35][8][19][11][12][36][14][15]

Endometrial cancer

a) General Information

1) Increased risk in women with intact uteri who use estrogens alone [69][74]

2) Malignancy in residual endometrial implants have been reported in women treated with estrogen monotherapy following hysterectomy [29][69]

3) Risk appears to be 2- to 12-fold greater with unopposed estrogen use compared with non-users [29][69][74][19][7][38][35][8][11][12][14][15][94]

4) Risk is linked to estrogen dose and duration of use [29][69][74][19][76][7][38][35][8][11][12][14][15][94]

5) Prolonged use (ie, 5 to 10 years) is associated with a 15- to 24-fold increased risk compared with estrogen non-users, which persists for 8 to 15 years after treatment discontinuation [29][69]

6) Most studies indicated no significant increased risk when estrogens are used for less than 1 year [29][69][74][19][76][7][38][35][8][11][12][14][15][94].

7) Periodic bleeding may occur with estrogen and progestin combination therapy [98]

b) Prevention and Management

1) Estrogen therapy with concomitant progestin has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor [29][69][74][130][131][132][133][134][135][136][137]

2) Consider adding medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle to reduce the risk of hyperplasia and carcinoma [69][138].

3) Assess persistent or recurring abnormal genital bleeding in postmenopausal women with directed or random endometrial sampling when indicated to exclude malignancy [29][69][74][76][19]

4) In women with vaginal atrophy, consider low-dose vaginal estrogen formulations instead of oral forms for endometrial hyperplasia prophylaxis [139]

5) Consider long-term gynecologic monitoring in women with intact uteri and a history of 1 or more years of estrogen use, regardless of when treatment was received [140]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Nonsignificant decrease in endometrial cancer risk compared with placebo among women (mean age, 63) treated with daily conjugated estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg for a mean 5.6 years [29][69]

2) Estrogen replacement (oral, transdermal, vaginal routes): Endometrial cancer recurrence rate: 1% with estrogen replacement vs 14% without estrogen. About half of estrogen-treated patients also received progestin. The disease-free interval was significantly longer among estrogen-treated patients vs untreated patients [141]

3) Estrogen replacement (oral, transdermal, vaginal routes): Risk of endometrial cancer was strongly related to daily, long-term estrogen use, with women using higher estrogen doses experiencing an 8-fold increased risk with 5 or more years of use and a 4-fold increased risk with low-dose therapies compared to no hormonal therapy [139].

4) Multiple indications (breast conditions, endometriosis, estrogen replacement, menstrual problems or irregularities, sexual difficulties): 31% with noncontraceptive estrogens vs 15% among controls. Women who received 1 or more years of estrogen therapy were at increased risk for endometrial carcinoma for at least 10 years after estrogen treatment discontinuation [140].

Endometrial disorder

a) Incidence: Topical emulsion, 15% [35]
b) Adult Clinical Trials

1) Estrogen replacement (topical route, emulsion); 15% vs 8% with placebo [35].

Endometrial hyperplasia

a) Prevention and Management

1) Consider adding progestin to the treatment regimen [29]

b) Postmarketing

1) Has been reported [76].

Endometriosis

a) General Information

1) May exacerbate preexisting endometriosis; malignant transformation of residual endometrial implants have been reported in women who have been treated with estrogen-alone therapy after hysterectomy [29][74][76][7][38][35][8][92][11][12][36][14][15]

b) Prevention and Management

1) Consider adding progestin to the treatment regimen [29][74][76][7][38][35][8][92][11][12][36][14][15]

Erectile dysfunction

a) Adult Case Studies

1) Gynecomastia and impotence have been reported in 2 men after regular use of an estrogen-containing hair lotion (50 mg estradiol/100 mL alcoholic solution). Although 1 patient had return of libido and regression of the gynecomastia 4 weeks after discontinuing the hair lotion, the other patient had no regression of his gynecomastia. This patients underwent bilateral mastectomy 6 months after discontinuation of the hair product [109].

Fibrocystic breast changes

a) Postmarketing

1) Have been reported [76].

Intermenstrual bleeding - irregular

a) Incidence: Topical gel, 4.1% to 9.6% [76][38]; transdermal system, 0% to 10.6% [29]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 4.1% to 9.6% vs 1.6% to 2.2% with placebo [76][38]

2) Estrogen replacement (transdermal route): 0% to 10.6% vs 4.5% with placebo [29]

Leukorrhea

a) Incidence: Transdermal system, 1% to 7% [19]
b) General Information

1) Leukorrhea has been reported with estrogen and/or progestin therapy [19][7][13][38][35][8][11][12][36][14][15].

c) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 1% to 7% vs 1% with placebo [19]

Normal libido, Change in

a) General Information

1) Changes in libido have been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

Ovarian cancer

a) General Information

1) Risk increases with longer duration of use in current users; no significantly increased risk with 0 to 5 years of use, 24% increased risk with 5 to 9 years of use, 31% increased risk with 10 or more years of use [126].

2) No difference in risk with route of administration or preparation used [126]

3) Mean time to diagnosis in current users is after 9.2 years of estrogen only use, and after 6.9 years of estrogen/progestin combination therapy [126].

4) Mean time to diagnosis in past users is 5.6 years after discontinuation [126].

5) Approximately 95% of cancers were epithelial; greater risk for serous tumors versus mucinous, endometrioid, or clear cell tumors [126]

b) Adult Clinical Studies

1) Hormone replacement therapy (unknown route): Increased risk for ovarian cancer, relative risk with current use was 1.41 (95% CI, 1.32 to 1.50); relative risk with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI, 1.27 to 1.48). The elevated risk was significant for both estrogen-alone and estrogen plus progestin products according to meta-analysis (17 prospective studies; 12,110 cancer cases) [127][128]

a) UK Million Women Study

1% increased risk with ever use; 20% increased risk with current use; no significant increase in risk with past use [126]

Ovarian cancer incidence rate per 1000 over 5 years: 2.6 for current users vs 2.2 for never users [126]

1 extra ovarian cancer case per 2500 users [126]

Ovarian cancer mortality rate per 1000 over 5 years: 1.6 for current users vs 1.3 for never users [126]

1 extra ovarian cancer death per 3300 users [126]

b) Women's Health Initiative Study

No significant increase in risk for invasive ovarian cancer after 5.6 years of treatment with estrogen/progestin combination therapy [127][128][129][7][13][38][35][8][11][12][36][14][15]

Cases per 10,000 women: 4.2 with estrogen/progestin combination therapy vs 2.7 with placebo [129][7][13][38][35][8][11][12][36][14][15]

Pain of breast

a) Incidence: Topical emulsion, 10% [35]; topical gel, 10.7% [74]; transdermal system, 5% to 34.8% [8][19]; vaginal cream, 7% [15]; vaginal ring, 1% [15]
b) Adult Clinical Studies

1) Estrogen replacement (vaginal route): 1% with estradiol vaginal ring vs 7% with estradiol vaginal cream [15]

2) Estrogen replacement (topical route): 10.7% with estradiol vs 8.2% with placebo [74]; 10% with estradiol emulsion vs 3% with placebo [35]

3) Estrogen replacement (transdermal route): 5% to 34.8% with estradiol patch vs 4% to 8% with placebo [19][8]

Pruritus of genital organs

a) Incidence: Vaginal tablets, 6% [94]
b) Adult Clinical Trials

1) Estrogen replacement (vaginal route): 6% [94]

Sore nipple

a) Incidence: Transdermal spray, 1% to 7% [36]
b) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 1% to 7% vs 0% with placebo [36]

Swelling of breast

a) General Information

1) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [19][76][7][13][38][35][8][11][12][36][14][15].

b) Postmarketing

1) Breast enlargement has been reported [29]

Vaginal bleeding

a) Incidence: Transdermal, 8.7% to 33.3% [8]
b) Estrogen replacement (transdermal route): 8.7% to 33.3% vs 12.9% with placebo [8]

Vaginal discomfort

a) Incidence: Vaginal cream and ring, 5% [15][15]
b) General Information

1) Vaginal discomfort or pain commonly contributed to the discontinuation of treatment with estradiol vaginal ring during clinical studies [15].

c) Adult Clinical Studies

1) Estrogen replacement (vaginal route): 5% [15]

Vaginal ulcer

a) General Information

1) May manifest as vaginal irritation, erythema, abrasion, or spotting [142]

b) Prevention and Management

1) Carefully evaluate if occurs; consider leaving ring out and not replacing it until healing is complete to prevent adherence of ring to healing tissue [142].

c) Postmarketing

1) Has been reported [142]

Vaginal wall finding

a) Prevention and Management

1) If vaginal ulceration or erosion occurs; consider leaving ring out and not replacing it until healing is complete to prevent adherence of ring to the healing tissue [142].

b) Postmarketing

1) Adherence of ring to vaginal wall, making ring removal difficult, has been reported; in some cases, surgery was necessary [142].

Vaginitis

a) Postmarketing

1) Vaginitis, including vaginal candidiasis, has been reported in postmarketing surveillance [76]

Withdrawal bleeding

a) General Information

1) Changes in vaginal bleeding patterns and abnormal withdrawal bleeding or flow have been reported with estrogen and/or progestin therapy [66][76][7][38][35][8][19][11][36][14][15]

Estradiol Acetate

Abnormal vaginal bleeding

a) General Information

1) Changes in vaginal bleeding patterns and abnormal withdrawal bleeding or flow have been reported with estrogen and/or progestin therapy [59].

b) Prevention and Management

1) Patients should inform their healthcare provider of abnormal vaginal bleeding immediately [59].

Breast tenderness

a) Incidence: oral, 0.8% to 6.3%; vaginal, 6.2% to 10.7% [173]
b) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy. The incidence is higher for the vaginal ring preparation (6.2% to 10.7%) than for the oral preparation (0.8% to 6.3%) [170][173].

Candida vaginitis

a) Incidence: 6.2% to 10.7% [173]
b) The incidences of vaginal candidiasis reported with the use of estradiol acetate vaginal ring 0.05 milligrams/day and 0.10 milligrams/day were 6.2% and 10.7%, respectively [173].

Device adherence, To vaginal wall

a) General Information

1) May make vaginal ring removal difficult [174].

2) Vaginal wall ulceration or erosion have been reported [174].

b) Management

1) Evaluate for vaginal wall ulceration or erosion [174].

2) Consider not replacing ring until healing is complete [174].

c) Postmarketing Reports

1) Cases of ring adherence to the vaginal wall have been reported [174].

Disorder of menstruation

a) Incidence: oral, 2.0% to 3.2%; vaginal, 8.0% to 9.8% [170][173]
b) Breakthrough bleeding, spotting, and dysmenorrhea have been reported with estrogen and/or progestin therapy. The incidence is higher for the vaginal ring preparation (8.0% to 9.8%) than for the oral preparation (2.0% to 3.2%) [170][173].

Endometrial cancer

a) Summary

1) Estrogen replacement therapy increases the risk of endometrial carcinoma in postmenopausal women but does not appear to increase the rate of recurrence and death among endometrial cancer survivors [141]. Unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer; the risk is approximately 2- to 12-fold greater in these women when compared with non-users. The risk appears to be dependent on duration of use and on estrogen dose. Most studies indicated no significant increased risk when estrogens are used for less than one year. The risk increased 15- to 24-fold when therapy continued for five to ten years or more and the risk persisted for at least 8 to 15 years after discontinuation of estrogen therapy. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [170].

b) General Information

1) The rate of recurrence and death among endometrial cancer survivors (n=249) did not increase with estrogen replacement therapy with or without the addition of progestins. After receiving similar primary cancer treatment, 130 of the 249 women began estrogen replacement (oral, transdermal, or vaginal), with 49% electing to add medroxyprogesterone 2.5 milligrams to their daily regimen. The study included 75 matched endometrial cancer patients not treated with estrogen. After a mean follow-up of 83 months for estrogen users (n=75) and 69 months for nonusers (n=75), the rate of recurrence was 1% (95% confidence interval (CI) 71.0 to 91.4) and 14% (95% CI 59.1 to 87.7), respectively. The disease-free interval was significantly longer for those receiving estrogen compared to those who did not (p=0.006). The addition of medroxyprogesterone to the regimen did not appear to make a difference in the risk of recurrence or death rate [141].

2) In a large, population-based, case-control study, treatment with estradiol or conjugated estrogens and continuous progestins decreased the relative risk below levels seen in unexposed women. Information was collected from 709 case patients using hormone replacement and 3368 control subjects. Treatment was classified as 1) medium-potency estrogens (conjugated estrogens, estradiol, and other synthetic estrogens) without added progestins; 2) medium-potency estrogens with progestin cyclically combined or added continuously; 3) low-potency estrogens (oral estradiol or vaginal dienoestrol, estriol, or estradiol); or 4) progestins without estrogen. Relative risk for endometrial cancer was strongly related to the daily dose of estrogens. With 5 or more years of use, women using low-dose therapies had a fourfold increased relative risk, and women using higher doses had an eightfold increase [139]. In the same study, the authors recommend vaginal, rather than oral, formulations of low-potency estrogens for women with atrophy as the only indication for treatment. Oral treatment with low-potency estrogen formulations increased the relative risk of endometrial neoplasia [165].

3) Results from the 3-year Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated that for endometrial protection from hyperplastic changes in postmenopausal women with a uterus, estrogen and progestin (cyclically or continuously) should be administered concomitantly (n=596). Patients were given a 28-day cycle of 1) placebo; 2) conjugated estrogens (0.625 milligram per day); 3) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (10 milligrams per day) for the first 12 days 4) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (2.5 milligrams per day) for the first 12 days; 5) conjugated estrogens (0.625 milligram per day) plus micronized progesterone (200 milligrams per day) for the first 12 days. If women receive conjugated estrogens only, an annual endometrial evaluation should be done with discontinuation of therapy following the diagnosis of endometrial hyperplasia. In these patients hyperplasia usually returns to normal with progestin therapy [166].

4) The addition of a progestin to the estrogen regimen seems to provide a protective effect against endometrial cancer, by assuring more complete sloughing of the endometrium, which in turn prevents the continued proliferation that may result in hyperplastic neoplasia secondary to unopposed estrogen treatment [130] [131][132][133][134][135][136][137]. However, combination therapy can result in periodic vaginal bleeding which may be unacceptable to some postmenopausal patients. Recommended therapy in women who have a uterus is the addition of medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle. This reduces the risk of hyperplasia and endometrial carcinoma [138]. Estrogen replacement therapy exerts stimulatory effects on the postmenopausal endometrium, comparable to premenopausal specimens taken in the proliferative phase [167].

5) A large case-control study has suggested that long-term use of estrogens can increase the risk of both localized and widespread endometrial cancer [140]. Women are at an increased risk of developing endometrial carcinoma for at least 10 years after discontinuing estrogens if they had taken estrogen for 1 or more years. It is suggested that all women who have not had hysterectomies and who have used estrogens for 1 year or more should be considered for long-term gynecologic monitoring regardless of when they received estrogens. Endometrial carcinoma was not associated with estrogen use for a period of less than 1 year. In this study, 31% of 425 women with endometrial carcinoma reported having used estrogens, compared to 15% of 792 controls. Histories were obtained in these patients with regard to noncontraceptive estrogens, and whether patients had used estrogens for numerous indications and not just postmenopausal symptoms (regulation of periods, menstrual problems, infertility, breast conditions, endometriosis or sexual difficulties).

c) Prevention and Management

1) Postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding should be tested to rule out malignancy [59]

Endometriosis

a) Administration of estrogen therapy may exacerbate pre-existing endometriosis. Malignant transformation of residual endometrial implants have been reported in

women who have been treated with estrogen-alone therapy after a hysterectomy. The addition of a progestin should be considered [170].

Leukorrhea

a) Leukorrhea has been reported with estrogen and/or progestin therapy [170].

Libido - finding

a) Changes in libido have been reported with the use of estrogen and/or progestin therapy [170].

Ovarian cancer

a) The use of hormone replacement therapy (HRT) among postmenopausal women was associated with increased risk of fatal and incident ovarian cancer. In a large cohort UK Million Women Study (n=948,576), postmenopausal women who did not have previous cancer or bilateral oophorectomy (ovariotomy) were followed for an average of 5.3 years (over 5 million woman-years) for ovarian cancer incidence, and an average of 6.9 years (6.5 million woman-years) for death. The mean age was 57.2 +/- 4.6 years at baseline; and at the time of last contact, 50% participants had ever used HRT while 30% were current users. Ever users of HRT experienced an increased risk of ovarian cancer compared with never users (relative risk (RR) 1.11, 95% confidence interval (CI), 1.02 to 1.21; p=0.02). Unlike past users (RR 0.98, 95% CI, 0.88 to 1.11; p=0.7), current users of HRT exhibited significantly higher ovarian cancer risk relative to never users (RR 1.2, 95% CI, 1.09 to 1.32; p=0.0002); and the difference between the current- and past-users were significant (p=0.01 for heterogeneity). It was estimated that current users developed ovarian cancer after 7.7 years of HRT use overall (9.2 years for estrogen-only and 6.9 years for estrogen-progestagen therapy). Past users, on the other hand, were diagnosed with ovarian cancer 5.6 +/- 4.3 years after discontinuing HRT. The relative risk of ovarian cancer also increased with longer duration of HRT among current users (p=0.04 for trend): 1.05 (95% CI, 0.9 to 1.23) for fewer than 5 years of use, 1.24 (95% CI, 1.09 to 1.41) for 5 to 9 years of use, and 1.31 (95% CI, 1.12 to 1.53) for 10 years or more of use; but did not differ significantly by type of preparation used, constituents, or route of administration. While 95% of the malignant ovarian cancers were epithelial, HRT was greater for serous (RR 1.53, 95% CI, 1.31 to 1.79) than for mucinous (RR 0.72, 95% CI, 0.52 to 1), endometroid (RR 1.05, 95% CI, 0.77 to 1.43), or clear cell tumors (RR 0.77, 95% CI, 0.48 to 1.23). Current users of HRT also exhibited higher mortality risk than never users (RR 1.23, 95% CI, 1.09 to 1.38; p=0.0006), but past users did not (RR 0.97, 95% CI, 0.84 to 1.11). Over 5 years, the standardized incidence and mortality rates for ovarian cancer for never users were 2.2 (2.1 to 2.3) and 1.3 (1.2 to 1.4) per 1000, respectively, and 2.6 (2.4 to 2.9) and 1.6 (1.4 to 1.8) per 1000, respectively, for current users; resulting in a projected 1 extra ovarian cancer case in every 2500 users, and 1 extra death from the malignancy in every 3300 users [126].

b) Results of the Women's Health Initiative (WHI) randomized, double-blind, placebo-controlled trial indicate continuous combined estrogen and progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. Postmenopausal women with a uterus (n=16,608) were randomized to treatment with conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone 2.5 mg or placebo. After 5.6 years follow-up, the hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval (CI) 0.77 to 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years [129][170].

c) Results from a cohort study of former participants in the Breast Cancer Detection Demonstration Project indicate short-term estrogen-progestin use did not increase the risk for ovarian cancer but further study is warranted. Of 44,241 women, 329 developed ovarian cancer during follow-up. After adjustment for age, menopause type, and oral contraceptive use, the results were:

TYPE OF HORMONE REPLACEMENT	RATE RATIO (RR) and 95% CONFIDENCE INTERVAL (CI)
Ever use of estrogen	RR=1.6; 95% CI, 1.2 to 2.0
Estrogen only for 10 to 19 years	RR=1.8; 95% CI, 1.1 to 3.0*
Estrogen only for 20 or more years	RR=3.2; 95% CI, 1.7 to 5.7*
Estrogen-progestin use after estrogen	RR=1.5; 95% CI, 0.91 to 2.4
Estrogen-progestin use only	RR=1.1; 95% CI, 0.64 to 1.7
Estrogen-progestin use only, less than 2 yrs	RR=1.6; 95% CI, 0.78 to 3.3**
Estrogen-progestin use only, 2 or more yrs	RR=0.8; 95% CI, 0.35 to 1.8**

* p value for trend less than 0.001

** p value for trend equal to 0.30

d) A 7% increase in rate ratio (RR) per year of estrogen-only use was observed (95% confidence interval, 2% to 13%). Also observed were significantly elevated RRs with increasing duration of estrogen-only use across all degrees of other ovarian cancer risk factors [164].

Pain of breast

a) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [170].

Pain of uterus

a) Incidence: 1.8% to 4.5% [173]
b) The incidences of uterine pain reported with the use of estradiol acetate vaginal ring 0.05 milligrams/day and 0.10 milligrams/day were 1.8% and 4.5%, respectively [173].

Swelling of breast

a) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [170].

Estradiol Cypionate

Breast tenderness

a) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [55].

Disorder of menstruation

a) Breakthrough bleeding, spotting, and dysmenorrhea have been reported with estrogen and/or progestin therapy [55].

Endometrial cancer

a) Summary

1) Estrogen replacement therapy increases the risk of endometrial carcinoma in postmenopausal women but does not appear to increase the rate of recurrence and death among endometrial cancer survivors [141]. Unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer; the risk is approximately 2- to 12-fold greater in these women when compared with non-users. The risk appears to be dependent on duration of use and on estrogen dose. Most studies indicated no significant increased risk when estrogens are used for less than one year. The risk increased 15- to 24-fold when therapy continued for five to ten years or more and the risk persisted for at least 8 to 15 years after discontinuation of estrogen therapy. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [55].

b) The rate of recurrence and death among endometrial cancer survivors (n=249) did not increase with estrogen replacement therapy with or without the addition of progestins. After receiving similar primary cancer treatment, 130 of the 249 women began estrogen replacement (oral, transdermal, or vaginal), with 49% electing to add medroxyprogesterone 2.5 milligrams to their daily regimen. The study included 75 matched endometrial cancer patients not treated with estrogen. After a mean follow-up of 83 months for estrogen users (n=75) and 69 months for nonusers (n=75), the rate of recurrence was 1% (95% confidence interval (CI) 71.0 to 91.4) and 14% (95% CI 59.1 to 87.7), respectively. The disease-free interval was significantly longer for those receiving estrogen compared to those who did not (p=0.006). The addition of medroxyprogesterone to the regimen did not appear to make a difference in the risk of recurrence or death rate [141].

c) In a large, population-based, case-control study, treatment with estradiol or conjugated estrogens and continuous progestins decreased the relative risk below levels seen in unexposed women. Information was collected from 709 case patients using hormone replacement and 3368 control subjects. Treatment was classified as 1) medium-potency estrogens (conjugated estrogens, estradiol, and other synthetic estrogens) without added progestins; 2) medium-potency estrogens with progestin cyclically combined or added continuously; 3) low- potency estrogens (oral estradiol or vaginal dienoestrol, estriol, or estradiol); or 4) progestins without estrogen. Relative risk for endometrial cancer was strongly related to the daily dose of estrogens. With 5 or more years of use, women using low-dose therapies had a fourfold increased relative risk, and women using higher doses had an eightfold increase [139]. In the same study, the authors recommend vaginal, rather than oral, formulations of low-potency estrogens for women with atrophy as the only indication for treatment. Oral treatment with low-potency estrogen formulations increased the relative risk of endometrial neoplasia [165].

d) Results from the 3-year Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated that for endometrial protection from hyperplastic changes in postmenopausal women with a uterus, estrogen and progestin (cyclically or continuously) should be administered concomitantly (n=596). Patients were given a 28-day cycle of 1) placebo; 2) conjugated estrogens (0.625 milligram per day); 3) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (10 milligrams per day) for the first 12 days 4) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (2.5 milligrams per day) for the first 12 days; 5) conjugated estrogens (0.625 milligram per day) plus micronized progesterone (200 milligrams per day) for the first 12 days. If women

receive conjugated estrogens only, an annual endometrial evaluation should be done with discontinuation of therapy following the diagnosis of endometrial hyperplasia. In these patients hyperplasia usually returns to normal with progestin therapy [166].

e) The addition of a progestin to the estrogen regimen seems to provide a protective effect against endometrial cancer, by assuring more complete sloughing of the endometrium, which in turn prevents the continued proliferation that may result in hyperplastic neoplasia secondary to unopposed estrogen treatment [130] [131][132][133][134][135][136][137]. However, combination therapy can result in periodic vaginal bleeding which may be unacceptable to some postmenopausal patients. Recommended therapy in women who have a uterus is the addition of medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle. This reduces the risk of hyperplasia and endometrial carcinoma [138]. Estrogen replacement therapy exerts stimulatory effects on the postmenopausal endometrium, comparable to premenopausal specimens taken in the proliferative phase [167].

f) A large case-control study has suggested that long-term use of estrogens can increase the risk of both localized and widespread endometrial cancer [140]. Women are at an increased risk of developing endometrial carcinoma for at least 10 years after discontinuing estrogens if they had taken estrogen for 1 or more years. It is suggested that all women who have not had hysterectomies and who have used estrogens for 1 year or more should be considered for long-term gynecologic monitoring regardless of when they received estrogens. Endometrial carcinoma was not associated with estrogen use for a period of less than 1 year. In this study, 31% of 425 women with endometrial carcinoma reported having used estrogens, compared to 15% of 792 controls. Histories were obtained in these patients with regard to noncontraceptive estrogens, and whether patients had used estrogens for numerous indications and not just postmenopausal symptoms (regulation of periods, menstrual problems, infertility, breast conditions, endometriosis or sexual difficulties).

g) Summary

1) Estrogen replacement therapy increases the risk of endometrial carcinoma in postmenopausal women but does not appear to increase the rate of recurrence and death among endometrial cancer survivors [141]. Unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer; the risk is approximately 2- to 12-fold greater in these women when compared with non-users. The risk appears to be dependent on duration of use and on estrogen dose. Most studies indicated no significant increased risk when estrogens are used for less than one year. The risk increased 15- to 24-fold when therapy continued for five to ten years or more and the risk persisted for at least 8 to 15 years after discontinuation of estrogen therapy. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [55].

h) The rate of recurrence and death among endometrial cancer survivors (n=249) did not increase with estrogen replacement therapy with or without the addition of progestins. After receiving similar primary cancer treatment, 130 of the 249 women began estrogen replacement (oral, transdermal, or vaginal), with 49% electing to add medroxyprogesterone 2.5 milligrams to their daily regimen. The study included 75 matched endometrial cancer patients not treated with estrogen. After a mean follow-up of 83 months for estrogen users (n=75) and 69 months for nonusers (n=75), the rate of recurrence was 1% (95% confidence interval (CI) 71.0 to 91.4) and 14% (95% CI 59.1 to 87.7), respectively. The disease-free interval was significantly longer for those receiving estrogen compared to those who did not (p=0.006). The addition of medroxyprogesterone to the regimen did not appear to make a difference in the risk of recurrence or death rate [141].

i) In a large, population-based, case-control study, treatment with estradiol or conjugated estrogens and continuous progestins decreased the relative risk below levels seen in unexposed women. Information was collected from 709 case patients using hormone replacement and 3368 control subjects. Treatment was classified as 1) medium-potency estrogens (conjugated estrogens, estradiol, and other synthetic estrogens) without added progestins; 2) medium-potency estrogens with progestin cyclically combined or added continuously; 3) low- potency estrogens (oral estradiol or vaginal dienoestrol, estriol, or estradiol); or 4) progestins without estrogen. Relative risk for endometrial cancer was strongly related to the daily dose of estrogens. With 5 or more years of use, women using low-dose therapies had a fourfold increased relative risk, and women using higher doses had an eightfold increase [139]. In the same study, the authors recommend vaginal, rather than oral, formulations of low-potency estrogens for women with atrophy as the only indication for treatment. Oral treatment with low-potency estrogen formulations increased the relative risk of endometrial neoplasia [165].

j) Results from the 3-year Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated that for endometrial protection from hyperplastic changes in postmenopausal women with a uterus, estrogen and progestin (cyclically or continuously) should be administered concomitantly (n=596). Patients were given a 28-day cycle of 1) placebo; 2) conjugated estrogens (0.625 milligram per day); 3) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (10

milligrams per day) for the first 12 days 4) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (2.5 milligrams per day) for the first 12 days; 5) conjugated estrogens (0.625 milligram per day) plus micronized progesterone (200 milligrams per day) for the first 12 days. If women receive conjugated estrogens only, an annual endometrial evaluation should be done with discontinuation of therapy following the diagnosis of endometrial hyperplasia. In these patients hyperplasia usually returns to normal with progestin therapy [166].
k) The addition of a progestin to the estrogen regimen seems to provide a protective effect against endometrial cancer, by assuring more complete sloughing of the endometrium, which in turn prevents the continued proliferation that may result in hyperplastic neoplasia secondary to unopposed estrogen treatment [130] [131][132][133][134][135][136][137]. However, combination therapy can result in periodic vaginal bleeding which may be unacceptable to some postmenopausal patients. Recommended therapy in women who have a uterus is the addition of medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle. This reduces the risk of hyperplasia and endometrial carcinoma [138]. Estrogen replacement therapy exerts stimulatory effects on the postmenopausal endometrium, comparable to premenopausal specimens taken in the proliferative phase [167].
l) A large case-control study has suggested that long-term use of estrogens can increase the risk of both localized and widespread endometrial cancer [140]. Women are at an increased risk of developing endometrial carcinoma for at least 10 years after discontinuing estrogens if they had taken estrogen for 1 or more years. It is suggested that all women who have not had hysterectomies and who have used estrogens for 1 year or more should be considered for long-term gynecologic monitoring regardless of when they received estrogens. Endometrial carcinoma was not associated with estrogen use for a period of less than 1 year. In this study, 31% of 425 women with endometrial carcinoma reported having used estrogens, compared to 15% of 792 controls. Histories were obtained in these patients with regard to noncontraceptive estrogens, and whether patients had used estrogens for numerous indications and not just postmenopausal symptoms (regulation of periods, menstrual problems, infertility, breast conditions, endometriosis or sexual difficulties).

Endometriosis

a) Administration of estrogen therapy may exacerbate pre-existing endometriosis. Malignant transformation of residual endometrial implants have been reported in women who have been treated with estrogen-alone therapy after a hysterectomy. The addition of a progestin should be considered [55].

Leukorrhea

a) Leukorrhea has been reported with estrogen and/or progestin therapy [55].

Libido - finding

a) Changes in libido have been reported with the use of estrogen and/or progestin therapy [55].

Ovarian cancer

a) The use of hormone replacement therapy (HRT) among postmenopausal women was associated with increased risk of fatal and incident ovarian cancer. In a large cohort UK Million Women Study (n=948,576), postmenopausal women who did not have previous cancer or bilateral oophorectomy (ovariotomy) were followed for an average of 5.3 years (over 5 million woman-years) for ovarian cancer incidence, and an average of 6.9 years (6.5 million woman-years) for death. The mean age was 57.2 +/- 4.6 years at baseline; and at the time of last contact, 50% participants had ever used HRT while 30% were current users. Ever users of HRT experienced an increased risk of ovarian cancer compared with never users (relative risk (RR) 1.11, 95% confidence interval (CI), 1.02 to 1.21; p=0.02). Unlike past users (RR 0.98, 95% CI, 0.88 to 1.11; p=0.7), current users of HRT exhibited significantly higher ovarian cancer risk relative to never users (RR 1.2, 95% CI, 1.09 to 1.32; p=0.0002); and the difference between the current- and past-users were significant (p=0.01 for heterogeneity). It was estimated that current users developed ovarian cancer after 7.7 years of HRT use overall (9.2 years for estrogen-only and 6.9 years for estrogen-progestagen therapy). Past users, on the other hand, were diagnosed with ovarian cancer 5.6 +/- 4.3 years after discontinuing HRT. The relative risk of ovarian cancer also increased with longer duration of HRT among current users (p=0.04 for trend): 1.05 (95% CI, 0.9 to 1.23) for fewer than 5 years of use, 1.24 (95% CI, 1.09 to 1.41) for 5 to 9 years of use, and 1.31 (95% CI, 1.12 to 1.53) for 10 years or more of use; but did not differ significantly by type of preparation used, constituents, or route of administration. While 95% of the malignant ovarian cancers were epithelial, HRT was greater for serous (RR 1.53, 95% CI, 1.31 to 1.79) than for mucinous (RR 0.72, 95% CI, 0.52 to 1), endometroid (RR 1.05, 95% CI, 0.77 to 1.43), or clear cell tumors (RR 0.77, 95% CI, 0.48 to 1.23). Current users of HRT also exhibited higher mortality risk than never users (RR 1.23, 95% CI, 1.09 to 1.38; p=0.0006), but past users did not (RR 0.97, 95% CI, 0.84 to 1.11). Over 5 years, the standardized incidence and mortality rates for ovarian cancer for never users were 2.2 (2.1 to 2.3) and 1.3 (1.2 to 1.4) per 1000, respectively, and 2.6 (2.4 to 2.9) and 1.6 (1.4 to 1.8) per 1000,

respectively, for current users; resulting in a projected 1 extra ovarian cancer case in every 2500 users, and 1 extra death from the malignancy in every 3300 users [126].

b) Results of the Women's Health Initiative (WHI) randomized, double-blind, placebo-controlled trial indicate continuous combined estrogen and progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. Postmenopausal women with a uterus (n=16,608) were randomized to treatment with conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone 2.5 mg or placebo. After 5.6 years follow-up, the hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval (CI) 0.77 to 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years [129][55].

c) Results from a cohort study of former participants in the Breast Cancer Detection Demonstration Project indicate short-term estrogen-progestin use did not increase the risk for ovarian cancer but further study is warranted. Of 44,241 women, 329 developed ovarian cancer during follow-up. After adjustment for age, menopause type, and oral contraceptive use, the results were:

TYPE OF HORMONE REPLACEMENT	RATE RATIO (RR) and 95% CONFIDENCE INTERVAL (CI)
Ever use of estrogen	RR=1.6; 95% CI, 1.2 to 2.0
Estrogen only for 10 to 19 years	RR=1.8; 95% CI, 1.1 to 3.0*
Estrogen only for 20 or more years	RR=3.2; 95% CI, 1.7 to 5.7*
Estrogen-progestin use after estrogen	RR=1.5; 95% CI, 0.91 to 2.4
Estrogen-progestin use only	RR=1.1; 95% CI, 0.64 to 1.7
Estrogen-progestin use only, less than 2 yrs	RR=1.6; 95% CI, 0.78 to 3.3**
Estrogen-progestin use only, 2 or more yrs	RR=0.8; 95% CI, 0.35 to 1.8**

* p value for trend less than 0.001

** p value for trend equal to 0.30

d) A 7% increase in rate ratio (RR) per year of estrogen-only use was observed (95% confidence interval, 2% to 13%). Also observed were significantly elevated RRs with increasing duration of estrogen-only use across all degrees of other ovarian cancer risk factors [164].

Pain of breast

a) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [55].

Swelling of breast

a) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [55].

Withdrawal bleeding

a) Changes in vaginal bleeding patterns and abnormal withdrawal bleeding or flow have been reported with estrogen and/or progestin therapy [55].

Estradiol Valerate

Breast cancer

a) General Information

1) Increased risk with estrogen monotherapy or with estrogen and progestin combined therapy [169]

2) Increased risk of invasive breast cancer in postmenopausal women without an uterus who had received unopposed estrogen for 10 years or longer [123].

3) Tumors were larger, more advanced, and more likely node-positive with combination estrogen/progestin therapy than with placebo treatment [169]

4) Risk increases with duration of use [169]

5) Risk may occur earlier when given with progestins [169]

6) Risk returns to baseline 5 years after therapy discontinuation [169]

7) More abnormal mammograms may occur [169]

b) Prevention and Management

1) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [169]

c) Adult Clinical Studies

1) Risk Among Healthy Women

a) Hormone replacement therapy (route unknown): Increases in mammographic density, 32% with estrogen or conjugated equine estrogen (95% CI, 25.7%, 38.6%) vs 3% with controls (95% CI, 0%, 17.2%) (Valdivia & Ortega, 2000)

b) Hormone replacement therapy (unknown route, 50 to 64 years of age): Relative odds (RO) of breast cancer in estrogen alone or estrogen-progestin users, 0.9 [154]

1) Women's Health Initiative

a) Conjugated Estrogens Plus Medroxyprogesterone

1) Hormone replacement therapy (oral route): Relative risk of invasive breast cancer was 1.26 (95% confidence interval, 1.00 to 1.59) with conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily after an average follow-up of 5.2 years [169]

2) Hormone replacement therapy (oral route): 8 more invasive breast cancer cases per 10,000 women years with conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily [169]

b) Estrogen Monotherapy

1) A non-significant decrease in invasive breast cancer, hazard ratio 0.80 (95% CI, 0.62 to 1.04; p=0.09) with conjugated estrogens 0.625 mg/day monotherapy for a mean of 7.1 years compared with 0.82 (95% CI, 0.65 to 1.04; p=0.1) with placebo-treated women [149]

2) Breast cancers with localized disease, hazard ratio 0.69 (95% CI, 0.51 to 0.95) with conjugated equine estrogens [149]

3) Decreased ductal carcinomas, hazard ratio 0.71 with conjugated equine estrogens (95% CI, 0.52 to 0.99); test for interaction by tumor type (ductal versus lobular) was not significant (p=0.054) [149]

4) Mammographies requiring follow-up after the first year was significantly higher, 9.2% with conjugated equine estrogen group compared with 5.5% with placebo group [149]

5) Cumulative number of mammograms over the course of the trial that required follow-up each year thereafter was significantly higher, 36.2% with conjugated equine estrogen group compared with 28.1% the placebo group [149]

2) Nurses' Health Study

a) Hormone replacement therapy (unknown route): 32% increased risk with current users of estrogen alone compared with never use, 41% increased risk with estrogen plus progestin compared with postmenopausal women who had never used hormones [153]

b) Hormone replacement therapy (unknown route): 934 invasive breast cancers diagnosed; 226 who never used hormones and 708 current estrogen users (335,296 person-years of follow-up) [123]

c) Hormone replacement therapy (unknown route): Relative risk, current estrogen use 20 years or longer and BMI of less than 25, 1.77 (95% CI, 1.26 to 2.48); current estrogen use 20 years or longer and BMI 25 or greater 1.25 (95% CI, 0.91 to 1.71) [123]

d) Hormone replacement therapy (unknown route): Relative risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers increased with current users of estrogen after 15 years of use, 1.48 (95% CI, 1.05 to 2.07) [123]

e) The relative risk (RR) and 95% CI based on length of use is reported in the following table:

Length of Estrogen Use	RR	95% CI
less than 5 years	0.96	0.75 to 1.22
5 to 9.9 years	0.90	0.73 to 1.12
10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

3) Breast Cancer Detection Demonstration Project

a) Cases of breast cancer identified, 2082 (Study N=46,355) [150][151]

b) Hormone replacement therapy (unknown route): Relative risk, 1.2 current and recent use (previous 4 years) of estrogen only (95% CI, 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin [150][151]

c) Hormone replacement therapy (unknown route): Relative risk increase by 0.01 with estrogen-only use per year vs 0.08 with estrogen-progestin-only use

per year [150][151]

d) Hormone replacement therapy (unknown route): Relative risk, 1.1 with ever using estrogen (95% CI, 1.0-1.3) vs 1.3 with estrogen-progestin (95% CI, 1.0-1.6); increases in relative risk with a BMI of 24.4 kg/m(2) or less, 0.03 with estrogen-only use per year (95% CI, 0.01-0.06) and 0.12 with estrogen-progestin-only use per year (95% CI, 0.02-0.25) [150][151]

2) Risk Among Breast Cancer Survivors

a) Estrogen replacement: The HABITS trial was discontinued early after results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events [124].

b) Estrogen replacement, estrogen monotherapy: Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors [125].

c) Estrogen replacement (oral and intravaginal routes): Rate of recurrence was 50% lower and breast cancer mortality 34% lower with use of hormone replacement therapy (HRT) than with non-use (O'Meara et al, 2001).

d) Estrogen replacement therapy (unknown route) No increase in recurrences or mortality rates; estrogen plus progestogens demonstrated a decrease in recurrence. Death occurred in 3 of 50 estrogens users, 1 of 8 nonestrogen users, and 6 of 18 no hormone users [155].

Breast tenderness

a) General Information

1) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [57].

Disorder of menstruation

a) General Information

1) Breakthrough bleeding, spotting, and dysmenorrhea have been reported with estrogen and/or progestin therapy [57].

Endometrial cancer

a) General Information

1) Increased risk in women with intact uteri who use estrogens alone [169]

2) Malignancy in residual endometrial implants have been reported in women treated with estrogen monotherapy following hysterectomy [169].

3) Risk appears to be 2- to 12-fold greater with unopposed estrogen use compared with non-users [169]

4) Risk is linked to estrogen dose and duration of use [169]

5) Prolonged use (ie, 5 to 10 years) is associated with a 15- to 24-fold increased risk compared with estrogen non-users, which persists for 8 to 15 years after treatment discontinuation [169]

6) Most studies indicated no significant increased risk when estrogens are used for less than 1 year [169].

b) Prevention and Management

1) Estrogen therapy with concomitant progestin has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor [169].

2) Consider adding medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle to reduce the risk of hyperplasia and carcinoma [169][138].

3) Assess persistent or recurring abnormal genital bleeding in postmenopausal women with directed or random endometrial sampling when indicated to exclude malignancy [169]

4) In women with vaginal atrophy, consider low-dose vaginal estrogen formulations instead of oral forms [139]

5) Consider long-term gynecologic monitoring in women with intact uteri and a history of 1 or more years of estrogen use, regardless of when treatment was received [140]

c) Adult Clinical Studies

1) Estrogen replacement (oral, transdermal, vaginal routes): Endometrial cancer recurrence rate: 1% with estrogen replacement vs 14% without estrogen. About half of estrogen-treated patients also received progestin. The disease-free interval was significantly longer among estrogen-treated patients vs untreated patients [141].

2) Estrogen replacement (oral, transdermal, vaginal routes): Risk of endometrial cancer, higher estrogen doses were associated with an 8-fold increased risk with 5

or more years of use compared with no estrogen use; lower estrogen doses were associated with a 4-fold increased risk [139].

Endometriosis

a) General Information

1) Administration of estrogen therapy may exacerbate pre-existing endometriosis. Malignant transformation of residual endometrial implants have been reported in women who have been treated with estrogen-alone therapy after a hysterectomy [57].

b) Prevention

1) The addition of a progestin should be considered [57].

Libido - finding

a) General Information

1) Changes in libido have been reported with the use of estrogen and/or progestin therapy [57].

Ovarian cancer

a) General Information

1) Risk increases with longer duration of use in current users; no significantly increased risk with 0 to 5 years of use, 24% increased risk with 5 to 9 years of use, 31% increased risk with 10 or more years of use [126].

2) No difference in risk with route of administration or preparation used [126]

3) Mean time to diagnosis in current users is after 9.2 years of estrogen only use, and after 6.9 years of estrogen/progestin combination therapy [126].

4) Mean time to diagnosis in past users is 5.6 years after discontinuation [126].

5) Approximately 95% of cancers were epithelial; greater risk for serous tumors vs mucinous, endometrioid, or clear cell tumors [126]

b) Adult Clinical Studies

1) Hormone replacement therapy (unknown route): Increased risk for ovarian cancer, relative risk with current use was 1.41 (95% CI, 1.2 to 150); relative risk with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI, 1.27 to 1.48). The elevated risk was significant for both estrogen-alone and estrogen plus progestin products according to meta-analysis (17 prospective studies; 12,110 cancer cases) [169]

a) UK Million Women Study

1) 11% increased risk with ever use compared with never use; 20% increased risk with current use compared with never use [126]

2) Ovarian cancer incidence rate per 1000 over 5 years: 2.6 for current users vs 2.2 for never users [126]

3) 1 extra ovarian cancer case per 2500 users [126]

4) Ovarian cancer mortality rate per 1000 patients over 5 years: 1.6 for current users vs 1.3 for never users [126]

5) 1 extra ovarian cancer death per 3300 users [126]

b) Women's Health Initiative Study

1) No significant increase in risk for invasive ovarian cancer after 5.6 years of treatment with estrogen/progestin combination therapy [129]

2) Cases per 10,000 women: 4.2 with estrogen/progestin combination therapy vs 2.7 with placebo [129]

c) Breast Cancer Detection Demonstration Project

1) Short-term estrogen-progestin use did not increase the risk for ovarian cancer [164].

2) Of 44,241 women, 329 developed ovarian cancer during follow-up [164].

3) After adjustment for age, menopause type, and oral contraceptive use, the results were:

Type of Hormone Replacement	Rate Ratio and 95% Confidence Interval (CI)
Ever use of estrogen	1.6; 95% CI, 1.2 to 2.0
Estrogen only for 10 to 19 years	1.8; 95% CI, 1.1 to 3.0*
Estrogen only for 20 or more years	3.2; 95% CI, 1.7 to 5.7*
Estrogen-progestin use after estrogen	1.5; 95% CI, 0.91 to 2.4
Estrogen-progestin use only	1.1; 95% CI, 0.64 to 1.7
Estrogen-progestin use only, less than 2 yrs	1.6; 95% CI, 0.78 to 3.3**

Type of Hormone Replacement	Rate Ratio and 95% Confidence Interval (CI)
Estrogen-progestin use only, 2 or more yrs	0.8; 95% CI, 0.35 to 1.8**

* p value for trend less than 0.001

** p value for trend equal to 0.30

4) A 7% increase in rate ratio (RR) per year of estrogen-only use was observed (95% CI, 2% to 13%). Also observed were significantly elevated RRs with increasing duration of estrogen-only use across all degrees of other ovarian cancer risk factors [164].

Pain of breast

a) General Information

1) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [57].

Swelling of breast

a) General Information

1) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [57].

Withdrawal bleeding

a) General Information

1) Changes in vaginal bleeding patterns and abnormal withdrawal bleeding or flow have been reported with estrogen and/or progestin therapy [57].

Respiratory Effects

Estradiol

Asthma

a) General Information

1) Exacerbation of asthma may occur [29]

b) Adult Clinical Trials

1) Hormone replacement therapy (route unknown): 2.29-fold increase in rate of asthma with estrogen alone compared with never use [116]

Multiple leiomyoma of lung

a) Adult Case Study

1) Pulmonary leiomyomatosis manifesting as recurrent pneumothorax has been associated in a single patient with combination hormone replacement therapy consisting of conjugated estrogens 0.625 mg and medroxyprogesterone 10 mg given sequentially. Although the time course of events was somewhat unclear, it appeared that the pulmonary symptoms began with the addition of the progestin, while estrogen monotherapy for an extended period of time prior to this had not produced these effects. The condition resolved gradually over 3 months after discontinuing hormone replacement [117].

Nasopharyngitis

a) Incidence: Topical gel, 4.1% to 10.3% [76][38]; transdermal system, 6.4% to 19.6% [29]

b) Adult Clinical Trials

1) Estrogen replacement (topical route): 4.1% to 10.3% vs 4% to 7.3% with placebo [76][38]

2) Estrogen replacement (transdermal route): 6.4% to 19.6% vs 15.3% with placebo [29]

Pharyngitis

a) Incidence: Transdermal system, 0.5% to 7% [19]

b) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 0.5% to 7% vs 3% with placebo [19]

Pulmonary embolism

a) General Information

1) Increased risk with estrogen monotherapy and with combination estrogen and progestin therapy [29][69][74]

b) Prevention and Management

1) Appropriately manage risk factors for venous thromboembolism (eg, personal or family history, obesity, systemic lupus erythematosus) [29][69][74][76][19]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69]

3) Discontinue (if possible) 4 to 6 weeks before periods of prolonged immobilization or surgeries that increase thromboembolism risk [29][69][74][76]

4) Discontinue immediately if occurs or is suspected [29][69][74][76][19]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Risk of DVT was 47% higher with conjugated estrogen monotherapy versus placebo in a Women's Health Initiative substudy. Increased venous thromboembolism risk occurred during the first 2 years of therapy [69][74][19][76][7][13][38][35][8][11][12][14][15][88]

2) Hormone replacement therapy (oral route): Risk of DVT and pulmonary embolism was 95% and more than 2-fold higher, respectively, compared with placebo among women (mean age, 63) treated with daily conjugated estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg for a mean 5.6 years [29][69][74][19][76][7][13][38][35][8][11][12][14][15][88]

d) Postmarketing

1) Has been reported [66].

Rhinitis

a) Incidence: Transdermal system, 2% to 6% [19]
b) Estrogen replacement (transdermal route): 2% to 6% vs 1% with placebo [19]

Sinusitis

a) Incidence: Topical gel, 3.6% [13]; transdermal system, 4% to 13.1% [29][19]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 3.6% vs 1.4% with placebo [13]

2) Estrogen replacement (transdermal route): 4% to 5% vs 3% with placebo [19]

3) Estrogen replacement (transdermal route): 5.3% to 13.1% vs 10.2% with placebo [29]

Upper respiratory infection

a) Incidence: Topical gel, 1.6% to 5.9% [76][38]; transdermal system, 4.5% to 17% [29][19]; vaginal cream, 6% [15]; vaginal ring, 5% [15]; vaginal tablets, 5% [94]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 1.6% to 5.9% vs 1.6% to 3.6% with placebo [76][38]

2) Estrogen replacement (transdermal route): 4.5% to 10.7% vs 5.7% with placebo [29]

3) Estrogen replacement (transdermal route): 6% to 17% vs 8% with placebo [19]

4) Estrogen replacement (transvaginal route): 5% vaginal ring; 6% with vaginal cream [15]

5) Estrogen replacement (oral route): 5% vs 4% with placebo [94]

Estradiol Acetate

Asthma, acute

a) Estrogen therapy may cause an exacerbation of asthma and should be used with caution in patients with asthma [170].
b) Results from a prospective cohort study indicate postmenopausal treatment with estrogen alone or estrogen plus progestin is associated with an increased rate of newly diagnosed asthma but not chronic obstructive pulmonary disease (COPD). During 546,259 person-years of follow-up, current use of estrogen alone was associated with an increased rate of asthma (multivariate adjusted rate ratio, 2.29; 95% confidence interval (CI), 1.59 to 3.29) compared with those who never used hormones. Women who used estrogen plus progestin had a similarly increased rate of a new diagnosis of definite asthma (multivariate rate ratio, 2.03; 95% CI, 1.42 to 2.90). Rates of newly diagnosed COPD were the same among hormone users and nonusers (multivariate rate ratio, 1.05; 95% CI, 0.80 to 1.37) [116].

Pulmonary embolism

a) The estrogen-plus-progestin substudy of the Women's Health Initiative (WHI) reported an increased risk of pulmonary emboli in postmenopausal women aged 50 to 79 years during 5.6 years of treatment with oral conjugated estrogens 0.625 milligrams (mg) combined with oral medroxyprogesterone acetate 2.5 mg per day relative to placebo. The relative risk of pulmonary embolism in the estrogen-alone substudy of WHI after an average follow-up of 7.1 years was 1.37 (95% confidence interval 0.90 to 2.07) compared with 2.13 (95% confidence interval 1.45 to 3.11) seen in the estrogen-plus-progestin substudy of WHI [88].
b) Results from a population-based, case-control, observational study indicate that conjugated equine estrogen (CEE) but not esterified estrogen is associated with an increased risk of venous thrombosis (VT). Cases (n=586) were perimenopausal and

postmenopausal women aged 30 to 89 years who sustained a first deep vein venous thrombosis (DVT) or pulmonary embolism (PE) and controls (n=2268) were matched on age (within the decade), hypertension status, and calendar year of VT first episode. Pharmacy claims data and hospital records were reviewed for all patients. Continual estrogen use was defined as consecutive prescription refills with no more than a 90 day lapse. The study period was 7 years. Of the 586 women who experienced a first VT, 426 (73%) had DVT alone, 68 (12%) had DVT and PE, and 92 (16%) had PE, of which 33 were fatal. Compared with women not currently using hormones, current users of esterified estrogen had no increase in VT risk (odds ratio (OR), 0.92; 95% confidence interval (CI), 0.69 to 1.22). However, women currently taking CEE (121 cases and 289 controls) had an elevated risk (OR, 1.65; 95% CI, 1.24 to 2.19). Current users of CEE also had a higher risk compared to current users of esterified estrogen when the analyses were limited to estrogen users only (OR, 1.78; 95% CI, 1.11 to 2.84). Additionally, concomitant progestin use was associated with increased risk of VT compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13 to 2.26) [89].

Estradiol Cypionate

Asthma, acute

a) Estrogen therapy may cause an exacerbation of asthma and should be used with caution in patients with asthma [55].
b) Results from a prospective cohort study indicate postmenopausal treatment with estrogen alone or estrogen plus progestin is associated with an increased rate of newly diagnosed asthma but not chronic obstructive pulmonary disease (COPD). During 546,259 person-years of follow-up, current use of estrogen alone was associated with an increased rate of asthma (multivariate adjusted rate ratio, 2.29; 95% confidence interval (CI), 1.59 to 3.29) compared with those who never used hormones. Women who used estrogen plus progestin had a similarly increased rate of a new diagnosis of definite asthma (multivariate rate ratio, 2.03; 95% CI, 1.42 to 2.90). Rates of newly diagnosed COPD were the same among hormone users and nonusers (multivariate rate ratio, 1.05; 95% CI, 0.80 to 1.37) [116].

Pulmonary embolism

a) The estrogen-plus-progestin substudy of the Women's Health Initiative (WHI) reported an increased risk of pulmonary emboli in postmenopausal women aged 50 to 79 years during 5.6 years of treatment with oral conjugated estrogens 0.625 milligrams (mg) combined with oral medroxyprogesterone acetate 2.5 mg per day relative to placebo. The relative risk of pulmonary embolism in the estrogen-alone substudy of WHI after an average follow-up of 7.1 years was 1.37 (95% confidence interval 0.90 to 2.07) compared with 2.13 (95% confidence interval 1.45 to 3.11) seen in the estrogen-plus-progestin substudy of WHI [88].
b) Results from a population-based, case-control, observational study indicate that conjugated equine estrogen (CEE) but not esterified estrogen is associated with an increased risk of venous thrombosis (VT). Cases (n=586) were perimenopausal and postmenopausal women aged 30 to 89 years who sustained a first deep vein venous thrombosis (DVT) or pulmonary embolism (PE) and controls (n=2268) were matched on age (within the decade), hypertension status, and calendar year of VT first episode. Pharmacy claims data and hospital records were reviewed for all patients. Continual estrogen use was defined as consecutive prescription refills with no more than a 90 day lapse. The study period was 7 years. Of the 586 women who experienced a first VT, 426 (73%) had DVT alone, 68 (12%) had DVT and PE, and 92 (16%) had PE, of which 33 were fatal. Compared with women not currently using hormones, current users of esterified estrogen had no increase in VT risk (odds ratio (OR), 0.92; 95% confidence interval (CI), 0.69 to 1.22). However, women currently taking CEE (121 cases and 289 controls) had an elevated risk (OR, 1.65; 95% CI, 1.24 to 2.19). Current users of CEE also had a higher risk compared to current users of esterified estrogen when the analyses were limited to estrogen users only (OR, 1.78; 95% CI, 1.11 to 2.84). Additionally, concomitant progestin use was associated with increased risk of VT compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13 to 2.26) [89].

Estradiol Valerate

Asthma, acute

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Other

Estradiol

Angioedema

a) General Information

1) May lead to airway obstruction [29]

b) Prevention and Management

1) Do not reuse if patient develops angioedema at anytime during course of treatment [29]

c) Postmarketing

1) Has been reported [29][76].

Death, Overall Mortality

a) General Information

1) Among current users, protective effect is greater for younger patients; age not a risk modifier among former users [104]

b) Adult Clinical Studies

1) Overall mortality rate: 6.9% for current users of estrogen with or without progestin, 17.9% for former users, and 18.3% for never users [104]

Hereditary angioedema, Exacerbation

a) General Information

1) Estrogen therapy may exacerbate symptoms of hereditary angioedema [29][69][74].

Infectious disease

a) Incidence: Topical emulsion, 12% [35]; topical gel, 17.3% [13]
b) General Information

1) Infections included upper respiratory tract infection, the common cold, and eye infection [13]

c) Adult Clinical Trials

1) Estrogen replacement (topical emulsion): 12% vs 7% with placebo [35].

2) Estrogen replacement (topical gel): 17.3% vs 6.8% with placebo [13]

Influenza-like illness

a) Incidence: up to 7.8% [29][13]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 5.4% vs 1.4% with placebo [13]

2) Estrogen replacement (transdermal route): 0% to 7.8% vs 6.4% with placebo [29]

Mesenchymoma (clinical), Malignant

a) Postmarketing

1) Malignant mesenchymoma has been reported [74]

Pain

a) Incidence: Transdermal system, 0% to 11% [29][19]
b) Estrogen replacement (transdermal route): 0% to 6.2% vs 4.5% with placebo [29]
c) Estrogen replacement (transdermal route): 1% to 11% vs 7% with placebo [19]

Estradiol Acetate

Angioedema

a) General Information

1) Estrogen therapy can exacerbate symptoms of angioedema in women with hereditary angioedema [59].

Breast cancer

a) Risk Among Healthy Women

1) The overall results of studies are mixed, however, the more recent large-scale and long-term studies identify an increased risk of developing breast cancer with the use of hormone replacement therapy. Estrogen and progestin regimens appear to increase the risk of breast cancer (hazard ratio 1.26, 95% confidence interval 1.00 to 1.59). The risk associated with unopposed estrogen therapy is increased among long-term users (10 years or more) [143][144][145][123].

Final results from the Nurses' Health Study (NHS) reported an increased risk of invasive breast cancer in postmenopausal women without a uterus who had received unopposed estrogen for 10 years or longer. The NHS was an observational, prospective cohort study initially involving a total of 11,508 postmenopausal women who had a hysterectomy and reported information on estrogen use at baseline. With the expansion of the study population every 2 years to include subsequent postmenopausal women without a uterus, the final follow-up period included 28,835 women. Biennial questionnaires were used to assess estrogen use. The primary outcome was invasive breast cancer. During 335,296 person-years of follow-up, 934 invasive breast cancers were diagnosed, which included 226 among women who never used hormones and 708 among current estrogen users. The relative risk (RR) and 95 confidence intervals (95% CI) based on length of use is reported in the following table:

Length of Estrogen Use	RR	95% CI (p for trend less than 0.001)
less than 5 years	0.96	0.75 to 1.22
5 to 9.9 years	0.90	0.73 to 1.12
10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

When analyses were stratified by body mass index (BMI), the risk of invasive breast cancer appeared to be greater in leaner women, however, the difference did not reach statistical significance (p=0.1). The RR for current estrogen use of 20 years or longer in women with a BMI of less than 25 was 1.77 (95% CI, 1.26 to 2.48) while the RR for current estrogen use of 20 years or longer in women with a BMI of 25 or greater was 1.25 (95% CI, 0.91 to 1.71). Additionally, the risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers was increased among current users of estrogen after 15 years of use (RR, 1.48; 95% CI, 1.05 to 2.07). Overall, there did not seem to be a strong dose-response relationship among estrogen use and risk of breast cancer [123].

2) Results from the Women's Health Initiative (WHI) Estrogen-Alone trial indicate treatment with conjugated equine estrogens (CEE) does not increase breast cancer incidence in postmenopausal women without a uterus, however, it was associated with an increased frequency of mammography screening that required short interval follow-up. Women (n=10,739) with similar baseline breast cancer risk were randomized in a double-blind trial to CEE 0.625 milligrams (mg) or placebo daily. After a mean follow-up of 7.1 years, nonsignificant reductions for invasive breast cancer and total breast cancer were observed in women receiving CEE (hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.62 to 1.04; p=0.09 and HR, 0.82; 95% CI, 0.65 to 1.04; p=0.1, respectively) compared with placebo. No effect on in situ disease was evident. Breast cancers with localized disease were diagnosed less frequently in women receiving CEE compared with women receiving placebo (HR, 0.69; 95% CI, 0.51 to 0.95). Advanced stage cancer incidence was comparable between the 2 groups. Compared with placebo, ductal carcinomas were decreased in women receiving CEE (HR, 0.71; 95% CI, 0.52 to 0.99), but the test for interaction by tumor type (ductal versus lobular) was not significant (p=0.054). The interactions between treatment assignment and estimated 5-year breast cancer risk, history of benign breast disease, and number of first-degree relatives with breast cancer were significant (p=0.01, p=0.005, and p=0.01, respectively). The percentage of mammographies requiring follow-up after the first year was significantly higher in the CEE group compared with the placebo group (9.2% versus 5.5%, respectively; p less than 0.001). In addition, the cumulative number of mammograms over the course of the trial that required follow-up each year

thereafter was significantly higher in the CEE group compared with the placebo group (36.2% versus 28.1%; p less than 0.001) [149].

3) Results of the Women's Health Initiative substudy involving 16,608 postmenopausal women who received conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily demonstrated an increased risk of invasive breast cancer in women receiving hormone therapy relative to placebo. After an average follow-up of 5.2 years, the relative risk of invasive breast cancer was 1.26; 95% confidence interval, 1.00 to 1.59) [170].

4) Data from a retrospective cohort study of 46,355 postmenopausal women suggests the risk of developing breast cancer is less with estrogen alone than with estrogen-progestin combined. The data were derived from follow-up (mean=10.2 years) to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. During follow-up, 2082 cases of breast cancer were identified. Relative risks (RR) were adjusted for age, age at menopause, education, body mass index (BMI), and mammographic screening. The RR for current and recent use (previous 4 years) of estrogen only was 1.2 (95% confidence interval (CI), 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin. The RR increase by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users. The RR associated with ever using estrogen or estrogen-progestin was 1.1 (95% CI, 1.0-1.3) and 1.3 (95% CI, 1.0-1.6), respectively. Increases in RR with each year of estrogen-only use and estrogen-progestin-only use among recent users with a BMI of 24.4 kilogram (kg) per meter squared or less were 0.03 (95% CI, 0.01-0.06) and 0.12 (95% CI, 0.02-0.25), respectively. Risk in heavier women did not increase in relation to use of either regimen. A limitation of the study includes retrospective collection and problems of recall in the reporting of hormone use, which does not make it a true prospective cohort study [150][151].

5) Results reported from a prospective, longitudinal study involving 210 postmenopausal women with normal baseline mammograms concluded hormone replacement therapy (HRT) with varying regimens of estradiol or conjugated equine estrogens (CEE) increased mammographic density while tibolone and estriol did not. Study participants received 1 of 7 oral HRT regimens for a period of one year. The regimens included estradiol 2 milligrams (mg), estradiol 2 mg plus sequential medroxyprogesterone acetate (MPA) 5 mg for 10 to 16 days per cycle, estradiol 2 mg plus continuous MPA 2.5 mg, CEE 0.625 mg, CEE 0.625 mg plus sequential MPA 5 mg, estriol 2 mg, or tibolone 2.5 mg. Thirty age-matched postmenopausal women served as a control group. Increased mammographic density occurred in 27% to 67% of patients receiving estradiol or CEE. No patients receiving tibolone or estriol experienced increases (p less than 0.05 for both). Overall, 32% of patients receiving HRT (95% confidence interval (CI) 25.7%, 38.6%) experienced increases in mammographic density compared to 3% of the controls (95% CI 0%, 17.2%) (Valdivia & Ortega, 2000).

6) A reanalysis of data from 51 epidemiological studies of women with breast cancer (n=52,705) and without breast cancer (n=108,411) identified the risk of developing breast cancer is increased in women using hormone replacement therapy (HRT) and the risk increased with increasing duration of use, especially in women of lower body mass index (BMI). The relative risk (RR) of a breast cancer diagnosis in current users of HRT or in those who discontinued HRT 1 to 4 years earlier, increased by 1.023 (95% confidence interval (CI), 1.011 to 1.036) for each year of use. The RR for women who used HRT for 5 years or longer was 1.35 (95% CI, 1.21 to 1.49). The RR of breast cancer for women who never used HRT increases by 1.028 (95% CI, 1.021 to 1.034) for each year older at menopause. There was no significant increase in the incidence of breast cancer in women who had discontinued HRT for 5 or more years. Additionally, cancers were less advanced in women who ever used HRT compared to those who never used [152].

7) A 16-year cohort analysis of women enrolled in the Nurses' Health Study was conducted. Their results showed the risk of breast cancer to be significantly increased among women who were current users of estrogen alone (Relative Risk (RR) equal 1.32) or estrogen plus progestin (RR equal 1.41) compared with postmenopausal women who had never used hormones. The risk of breast cancer was increased in women taking postmenopausal hormone replacement therapy (HRT) for more than five years, and in women greater than 55 years of age (among women aged 60 to 64, RR equal 1.71. This study supports the conclusions of other research which shows that short term hormone replacement therapy (less than 5 years) seems to have no important effect on the risk for breast cancer. More importantly, the increased mortality related to breast cancer among a subgroup of current, long-term users (greater than 5 years) was offset by a trend toward decreased risk among former users. These findings support a hypothesis that current use of HRT promotes the growth of existing cancers rather than initiating new cancers. Analysis of this cohort a few years from now should provide more reliable data about the risks and benefits of long-term HRT [153].

8) A study of 537 women (aged 50 to 64 years) in the western United States was conducted to determine the risk for breast cancer from use of combined estrogen-

progestin hormone replacement therapy (HRT). Compared with non-users of HRT, the relative odds (RO) of breast cancer in estrogen alone or estrogen-progestin users was 0.9. Long-term use of estrogen alone (greater than or equal to 20 years) and of combined estrogen-progestin (less than 8 years) did not contribute to increased risk for breast cancer. The risk of breast cancer was not substantially affected by the type, dose, or regimen of estrogen or progestin, nor by family history of breast cancer, previous benign breast disease, parity, alcohol use, or oral contraceptive use [154].

b) Risk Among Breast Cancer Survivors

1) The HABITS (hormonal replacement therapy after breast cancer - is it safe?) trial was discontinued early after safety results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events. The open-label trial randomized 434 women with previous breast cancer to hormone replacement therapy (n=219) or best treatment without hormones (n=215). Of the 434 women, 345 had at least one follow-up report. After a median of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. Further analyses were completed by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis. In all subsets, relative hazards for risk of new breast cancer events was above unity, but the confidence intervals were wide due to the small number of events. When the risk was compared by specific type of HRT, method of administration (continuous or sequential), and other preparations to estrogens only, the differences were small and not statistically significant. The authors acknowledge the results might change after the complete assessment of patients' original records, however, the steering committee for the trial judged the data mature enough to strongly indicate exposure to HRT is associated with an unacceptable risk. The women in the trial will be followed for at least 5 years after randomization [124].

2) Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors. Disease-free survivors (n=277) were prospectively given ERT and controls were matched for exact stage, a recurrence-free period similar to the period to ERT initiation in the ERT group, approximate age, and duration of follow-up. The mean time from breast cancer diagnosis to initiation of ERT was 3.6 years and the mean duration of ERT was 3.7 years. ERT was effective in relieving hot flashes in 92%, dyspareunia and vaginal dryness in 89%, and reactive depression, anxiety, and mood change in 88% of women. There were no statistical differences between the ERT and control groups for age, stage, pathology at diagnosis, progesterone receptor status, local therapy, breast at risk, prior chemotherapy, and duration of follow-up. In addition, there was no significant difference between the ERT and control groups in ipsilateral primary/recurrence (p=0.85), contralateral breast cancers (p=0.99), or systemic metastasis (p=0.13). Overall survival favored the ERT group (p=0.02) [125].

3) Hormone replacement therapy (HRT) after breast cancer was shown to have no adverse impact on recurrence and mortality in a cohort study comprised of 2755 women (aged 35 to 74 years) who were diagnosed with incident invasive breast cancer. Among the 2755 women, 174 users of HRT after diagnosis of breast cancer was identified. Each HRT user was matched to 4 randomly selected nonusers of HRT who were similar in respect to age, disease stage, and year of diagnosis. The women were free of recurrence at the time of HRT initiation or were equivalent in terms of time since diagnosis. The rate of recurrence was 17 per 1000 person-years in patients on HRT after diagnosis versus 30 per 1000 person-years in nonusers (relative risk (RR) 0.50; 95% confidence interval (CI) 0.30 to 0.85). Mortality rates from breast cancer were 5 per 1000 person- years and 15 per 1000 person-years for HRT users and nonusers, respectively (RR 0.34; 95% CI, 0.13 to 0.91). Total mortality rates were 16 per 1000 person-years for HRT users and 30 per 1000 person-years in nonusers (RR 0.48; 95% CI, 0.29 to 0.78). These results were similar for women using any type of HRT (oral, vaginal, oral plus vaginal) and lower relative risks were not associated with increased dosages (O'Meara et al, 2001).

4) In patients with breast cancer, estrogen replacement therapy did not increase recurrences or mortality rates. The addition of progestogens demonstrated a decrease in recurrence. This study involved 76 patients with breast cancer: 50 patients using estrogen replacement for up to 32 years; 8 patients using nonestrogenic hormone replacement for up to 6 years; and 18 patients using no hormone therapy for up to 10 years. Death occurred in 3 of 50 estrogens users, 1 of 8 nonestrogen users, and 6 of 18 no hormone users. The authors suggest patients with early breast cancer be offered hormone replacement therapy after a full discussion of benefits and risks [155].

Endometrial cancer

a) Summary

1) Estrogen replacement therapy increases the risk of endometrial carcinoma in postmenopausal women but does not appear to increase the rate of recurrence

and death among endometrial cancer survivors [141]. Unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer; the risk is approximately 2- to 12-fold greater in these women when compared with non-users. The risk appears to be dependent on duration of use and on estrogen dose. Most studies indicated no significant increased risk when estrogens are used for less than one year. The risk increased 15- to 24-fold when therapy continued for five to ten years or more and the risk persisted for at least 8 to 15 years after discontinuation of estrogen therapy. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [170].

b) The rate of recurrence and death among endometrial cancer survivors (n=249) did not increase with estrogen replacement therapy with or without the addition of progestins. After receiving similar primary cancer treatment, 130 of the 249 women began estrogen replacement (oral, transdermal, or vaginal), with 49% electing to add medroxyprogesterone 2.5 milligrams to their daily regimen. The study included 75 matched endometrial cancer patients not treated with estrogen. After a mean follow-up of 83 months for estrogen users (n=75) and 69 months for nonusers (n=75), the rate of recurrence was 1% (95% confidence interval (CI) 71.0 to 91.4) and 14% (95% CI 59.1 to 87.7), respectively. The disease-free interval was significantly longer for those receiving estrogen compared to those who did not (p=0.006). The addition of medroxyprogesterone to the regimen did not appear to make a difference in the risk of recurrence or death rate [141].

c) In a large, population-based, case-control study, treatment with estradiol or conjugated estrogens and continuous progestins decreased the relative risk below levels seen in unexposed women. Information was collected from 709 case patients using hormone replacement and 3368 control subjects. Treatment was classified as 1) medium-potency estrogens (conjugated estrogens, estradiol, and other synthetic estrogens) without added progestins; 2) medium-potency estrogens with progestin cyclically combined or added continuously; 3) low- potency estrogens (oral estradiol or vaginal dienoestrol, estriol, or estradiol); or 4) progestins without estrogen. Relative risk for endometrial cancer was strongly related to the daily dose of estrogens. With 5 or more years of use, women using low-dose therapies had a fourfold increased relative risk, and women using higher doses had an eightfold increase [139]. In the same study, the authors recommend vaginal, rather than oral, formulations of low-potency estrogens for women with atrophy as the only indication for treatment. Oral treatment with low-potency estrogen formulations increased the relative risk of endometrial neoplasia [165].

d) Results from the 3-year Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated that for endometrial protection from hyperplastic changes in postmenopausal women with a uterus, estrogen and progestin (cyclically or continuously) should be administered concomitantly (n=596). Patients were given a 28-day cycle of 1) placebo; 2) conjugated estrogens (0.625 milligram per day); 3) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (10 milligrams per day) for the first 12 days 4) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (2.5 milligrams per day) for the first 12 days; 5) conjugated estrogens (0.625 milligram per day) plus micronized progesterone (200 milligrams per day) for the first 12 days. If women receive conjugated estrogens only, an annual endometrial evaluation should be done with discontinuation of therapy following the diagnosis of endometrial hyperplasia. In these patients hyperplasia usually returns to normal with progestin therapy [166].

e) The addition of a progestin to the estrogen regimen seems to provide a protective effect against endometrial cancer, by assuring more complete sloughing of the endometrium, which in turn prevents the continued proliferation that may result in hyperplastic neoplasia secondary to unopposed estrogen treatment [130] [131][132][133][134][135][136][137]. However, combination therapy can result in periodic vaginal bleeding which may be unacceptable to some postmenopausal patients. Recommended therapy in women who have a uterus is the addition of medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle. This reduces the risk of hyperplasia and endometrial carcinoma [138]. Estrogen replacement therapy exerts stimulatory effects on the postmenopausal endometrium, comparable to premenopausal specimens taken in the proliferative phase [167].

f) A large case-control study has suggested that long-term use of estrogens can increase the risk of both localized and widespread endometrial cancer [140]. Women are at an increased risk of developing endometrial carcinoma for at least 10 years after discontinuing estrogens if they had taken estrogen for 1 or more years. It is suggested that all women who have not had hysterectomies and who have used estrogens for 1 year or more should be considered for long-term gynecologic monitoring regardless of when they received estrogens. Endometrial carcinoma was not associated with estrogen use for a period of less than 1 year. In this study, 31% of 425 women with endometrial carcinoma reported having used estrogens, compared to 15% of 792 controls. Histories were obtained in these patients with regard to noncontraceptive estrogens, and whether patients had used estrogens for numerous indications and not just postmenopausal symptoms (regulation of

periods, menstrual problems, infertility, breast conditions, endometriosis or sexual difficulties).

Ovarian cancer

a) The use of hormone replacement therapy (HRT) among postmenopausal women was associated with increased risk of fatal and incident ovarian cancer. In a large cohort UK Million Women Study (n=948,576), postmenopausal women who did not have previous cancer or bilateral oophorectomy (ovariotomy) were followed for an average of 5.3 years (over 5 million woman-years) for ovarian cancer incidence, and an average of 6.9 years (6.5 million woman-years) for death. The mean age was 57.2 +/- 4.6 years at baseline; and at the time of last contact, 50% participants had ever used HRT while 30% were current users. Ever users of HRT experienced an increased risk of ovarian cancer compared with never users (relative risk (RR) 1.11, 95% confidence interval (CI), 1.02 to 1.21; p=0.02). Unlike past users (RR 0.98, 95% CI, 0.88 to 1.11; p=0.7), current users of HRT exhibited significantly higher ovarian cancer risk relative to never users (RR 1.2, 95% CI, 1.09 to 1.32; p=0.0002); and the difference between the current- and past-users were significant (p=0.01 for heterogeneity). It was estimated that current users developed ovarian cancer after 7.7 years of HRT use overall (9.2 years for estrogen-only and 6.9 years for estrogen-progestagen therapy). Past users, on the other hand, were diagnosed with ovarian cancer 5.6 +/- 4.3 years after discontinuing HRT. The relative risk of ovarian cancer also increased with longer duration of HRT among current users (p=0.04 for trend): 1.05 (95% CI, 0.9 to 1.23) for fewer than 5 years of use, 1.24 (95% CI, 1.09 to 1.41) for 5 to 9 years of use, and 1.31 (95% CI, 1.12 to 1.53) for 10 years or more of use; but did not differ significantly by type of preparation used, constituents, or route of administration. While 95% of the malignant ovarian cancers were epithelial, HRT was greater for serous (RR 1.53, 95% CI, 1.31 to 1.79) than for mucinous (RR 0.72, 95% CI, 0.52 to 1), endometroid (RR 1.05, 95% CI, 0.77 to 1.43), or clear cell tumors (RR 0.77, 95% CI, 0.48 to 1.23). Current users of HRT also exhibited higher mortality risk than never users (RR 1.23, 95% CI, 1.09 to 1.38; p=0.0006), but past users did not (RR 0.97, 95% CI, 0.84 to 1.11). Over 5 years, the standardized incidence and mortality rates for ovarian cancer for never users were 2.2 (2.1 to 2.3) and 1.3 (1.2 to 1.4) per 1000, respectively, and 2.6 (2.4 to 2.9) and 1.6 (1.4 to 1.8) per 1000, respectively, for current users; resulting in a projected 1 extra ovarian cancer case in every 2500 users, and 1 extra death from the malignancy in every 3300 users [126].

b) Results of the Women's Health Initiative (WHI) randomized, double-blind, placebo-controlled trial indicate continuous combined estrogen and progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. Postmenopausal women with a uterus (n=16,608) were randomized to treatment with conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone 2.5 mg or placebo. After 5.6 years follow-up, the hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval (CI) 0.77 to 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years [129][170].

c) Results from a cohort study of former participants in the Breast Cancer Detection Demonstration Project indicate short-term estrogen-progestin use did not increase the risk for ovarian cancer but further study is warranted. Of 44,241 women, 329 developed ovarian cancer during follow-up. After adjustment for age, menopause type, and oral contraceptive use, the results were:

TYPE OF HORMONE REPLACEMENT	RATE RATIO (RR) and 95% CONFIDENCE INTERVAL (CI)
Ever use of estrogen	RR=1.6; 95% CI, 1.2 to 2.0
Estrogen only for 10 to 19 years	RR=1.8; 95% CI, 1.1 to 3.0*
Estrogen only for 20 or more years	RR=3.2; 95% CI, 1.7 to 5.7*
Estrogen-progestin use after estrogen	RR=1.5; 95% CI, 0.91 to 2.4
Estrogen-progestin use only	RR=1.1; 95% CI, 0.64 to 1.7
Estrogen-progestin use only, less than 2 yrs	RR=1.6; 95% CI, 0.78 to 3.3**
Estrogen-progestin use only, 2 or more yrs	RR=0.8; 95% CI, 0.35 to 1.8**

* p value for trend less than 0.001

** p value for trend equal to 0.30

d) A 7% increase in rate ratio (RR) per year of estrogen-only use was observed (95% confidence interval, 2% to 13%). Also observed were significantly elevated RRs with increasing duration of estrogen-only use across all degrees of other ovarian cancer risk factors [164].

Toxic shock syndrome

a) Rarely, cases of toxic shock syndrome have been reported in women using vaginal rings during post-marketing experience [173].

Estradiol Cypionate

Breast cancer

a) Risk Among Healthy Women

1) The overall results of studies are mixed, however, the more recent large-scale and long-term studies identify an increased risk of developing breast cancer with the use of hormone replacement therapy. Estrogen and progestin regimens appear to increase the risk of breast cancer (hazard ratio 1.26, 95% confidence interval 1.00 to 1.59). The risk associated with unopposed estrogen therapy is increased among long-term users (10 years or more) [143][144][145][123].

Final results from the Nurses' Health Study (NHS) reported an increased risk of invasive breast cancer in postmenopausal women without a uterus who had received unopposed estrogen for 10 years or longer. The NHS was an observational, prospective cohort study initially involving a total of 11,508 postmenopausal women who had a hysterectomy and reported information on estrogen use at baseline. With the expansion of the study population every 2 years to include subsequent postmenopausal women without a uterus, the final follow-up period included 28,835 women. Biennial questionnaires were used to assess estrogen use. The primary outcome was invasive breast cancer. During 335,296 person-years of follow-up, 934 invasive breast cancers were diagnosed, which included 226 among women who never used hormones and 708 among current estrogen users. The relative risk (RR) and 95 confidence intervals (95% CI) based on length of use is reported in the following table:

Length of Estrogen Use	RR	95% CI (p for trend less than 0.001)
less than 5 years	0.96	0.75 to 1.22
5 to 9.9 years	0.90	0.73 to 1.12
10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

When analyses were stratified by body mass index (BMI), the risk of invasive breast cancer appeared to be greater in leaner women, however, the difference did not reach statistical significance (p=0.1). The RR for current estrogen use of 20 years or longer in women with a BMI of less than 25 was 1.77 (95% CI, 1.26 to 2.48) while the RR for current estrogen use of 20 years or longer in women with a BMI of 25 or greater was 1.25 (95% CI, 0.91 to 1.71). Additionally, the risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers was increased among current users of estrogen after 15 years of use (RR, 1.48; 95% CI, 1.05 to 2.07). Overall, there did not seem to be a strong dose-response relationship among estrogen use and risk of breast cancer [123].

2) Results from the Women's Health Initiative (WHI) Estrogen-Alone trial indicate treatment with conjugated equine estrogens (CEE) does not increase breast cancer incidence in postmenopausal women without a uterus, however, it was associated with an increased frequency of mammography screening that required short interval follow-up. Women (n=10,739) with similar baseline breast cancer risk were randomized in a double-blind trial to CEE 0.625 milligrams (mg) or placebo daily. After a mean follow-up of 7.1 years, nonsignificant reductions for invasive breast cancer and total breast cancer were observed in women receiving CEE (hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.62 to 1.04; p=0.09 and HR, 0.82; 95% CI, 0.65 to 1.04; p=0.1, respectively) compared with placebo. No effect on in situ disease was evident. Breast cancers with localized disease were diagnosed less frequently in women receiving CEE compared with women receiving placebo (HR, 0.69; 95% CI, 0.51 to 0.95). Advanced stage cancer incidence was comparable between the 2 groups. Compared with placebo, ductal carcinomas were decreased in women receiving CEE (HR, 0.71; 95% CI, 0.52 to 0.99), but the test for interaction by tumor type (ductal versus lobular) was not significant (p=0.054). The interactions between treatment assignment and estimated 5-year breast cancer risk, history of benign breast disease, and number of first-degree relatives with breast cancer were significant (p=0.01, p=0.005, and p=0.01, respectively). The percentage of mammographies requiring follow-up after the first year was significantly higher in the CEE group compared with the placebo group (9.2% versus 5.5%, respectively; p less than 0.001). In addition, the cumulative number of mammograms over the course of the trial that required follow-up each year thereafter was significantly higher in the CEE group compared with the placebo group (36.2% versus 28.1%; p less than 0.001) [149].

3) Results of the Women's Health Initiative substudy involving 16,608 postmenopausal women who received conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily demonstrated an increased risk of invasive breast cancer in women receiving hormone therapy relative to placebo. After an average follow-up of 5.2 years, the relative risk of invasive breast cancer was 1.26 (95% confidence interval, 1.00 to 1.59) [55].

4) Data from a retrospective cohort study of 46,355 postmenopausal women suggests the risk of developing breast cancer is less with estrogen alone than with estrogen-progestin combined. The data were derived from follow-up (mean=10.2 years) to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. During follow-up, 2082 cases of breast cancer were identified. Relative risks (RR) were adjusted for age, age at menopause, education, body mass index (BMI), and mammographic screening. The RR for current and recent use (previous 4 years) of estrogen only was 1.2 (95% confidence interval (CI), 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin. The RR increase by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users. The RR associated with ever using estrogen or estrogen-progestin was 1.1 (95% CI, 1.0-1.3) and 1.3 (95% CI, 1.0-1.6), respectively. Increases in RR with each year of estrogen-only use and estrogen-progestin-only use among recent users with a BMI of 24.4 kilogram (kg) per meter squared or less were 0.03 (95% CI, 0.01-0.06) and 0.12 (95% CI, 0.02-0.25), respectively. Risk in heavier women did not increase in relation to use of either regimen. A limitation of the study includes retrospective collection and problems of recall in the reporting of hormone use, which does not make it a true prospective cohort study [150][151].

5) Results reported from a prospective, longitudinal study involving 210 postmenopausal women with normal baseline mammograms concluded hormone replacement therapy (HRT) with varying regimens of ESTRADIOL or CONJUGATED EQUINE ESTROGENS (CEE) increased mammographic density while tibolone and ESTRIOL did not. Study participants received 1 of 7 oral HRT regimens for a period of one year. The regimens included ESTRADIOL 2 milligrams (mg), ESTRADIOL 2 mg plus sequential medroxyprogesterone acetate (MPA) 5 mg for 10 to 16 days per cycle, ESTRADIOL 2 mg plus continuous MPA 2.5 mg, CEE 0.625 mg, CEE 0.625 mg plus sequential MPA 5 mg, ESTRIOL 2 mg, or tibolone 2.5 mg. Thirty age-matched postmenopausal women served as a control group. Increased mammographic density occurred in 27% to 67% of patients receiving ESTRADIOL or CEE. No patients receiving tibolone or ESTRIOL experienced increases (p less than 0.05 for both). Overall, 32% of patients receiving HRT (95% confidence interval (CI) 25.7%, 38.6%) experienced increases in mammographic density compared to 3% of the controls (95% CI 0%, 17.2%) (Valdivia & Ortega, 2000).

6) A reanalysis of data from 51 epidemiological studies of women with breast cancer (n=52,705) and without breast cancer (n=108,411) identified the risk of developing breast cancer is increased in women using hormone replacement therapy (HRT) and the risk increased with increasing duration of use, especially in women of lower body mass index (BMI). The relative risk (RR) of a breast cancer diagnosis in current users of HRT or in those who discontinued HRT 1 to 4 years earlier, increased by 1.023 (95% confidence interval (CI), 1.011 to 1.036) for each year of use. The RR for women who used HRT for 5 years or longer was 1.35 (95% CI, 1.21 to 1.49). The RR of breast cancer for women who never used HRT increases by 1.028 (95% CI, 1.021 to 1.034) for each year older at menopause. There was no significant increase in the incidence of breast cancer in women who had discontinued HRT for 5 or more years. Additionally, cancers were less advanced in women who ever used HRT compared to those who never used [152].

7) A 16-year cohort analysis of women enrolled in the Nurses' Health Study was conducted. Their results showed the risk of breast cancer to be significantly increased among women who were current users of estrogen alone (Relative Risk (RR) equal 1.32) or estrogen plus progestin (RR equal 1.41) compared with postmenopausal women who had never used hormones. The risk of breast cancer was increased in women taking postmenopausal hormone replacement therapy (HRT) for more than five years, and in women greater than 55 years of age (among women aged 60 to 64, RR equal 1.71. This study supports the conclusions of other research which shows that short term hormone replacement therapy (less than 5 years) seems to have no important effect on the risk for breast cancer. More importantly, the increased mortality related to breast cancer among a subgroup of current, long-term users (greater than 5 years) was offset by a trend toward decreased risk among former users. These findings support a hypothesis that current use of HRT promotes the growth of existing cancers rather than initiating new cancers. Analysis of this cohort a few years from now should provide more reliable data about the risks and benefits of long-term HRT [153].

8) A study of 537 women (aged 50 to 64 years) in the western United States was conducted to determine the risk for breast cancer from use of combined estrogen-progestin hormone replacement therapy (HRT). Compared with non-users of HRT, the relative odds (RO) of breast cancer in estrogen alone or estrogen-progestin users was 0.9. Long-term use of estrogen alone (greater than or equal to 20 years) and of combined estrogen-progestin (less than 8 years) did not contribute to increased risk for breast cancer. The risk of breast cancer was not substantially affected by the type, dose, or regimen of estrogen or progestin, nor by family history of breast cancer, previous benign breast disease, parity, alcohol use, or oral contraceptive use [154].

b) Risk Among Breast Cancer Survivors

1) The HABITS (hormonal replacement therapy after breast cancer - is it safe?) trial was discontinued early after safety results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events. The open-label trial randomized 434 women with previous breast cancer to hormone replacement therapy (n=219) or best treatment without hormones (n=215). Of the 434 women, 345 had at least one follow-up report. After a median of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. Further analyses were completed by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis. In all subsets, relative hazards for risk of new breast cancer events was above unity, but the confidence intervals were wide due to the small number of events. When the risk was compared by specific type of HRT, method of administration (continuous or sequential), and other preparations to estrogens only, the differences were small and not statistically significant. The authors acknowledge the results might change after the complete assessment of patients' original records, however, the steering committee for the trial judged the data mature enough to strongly indicate exposure to HRT is associated with an unacceptable risk. The women in the trial will be followed for at least 5 years after randomization [124].

2) Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors. Disease-free survivors (n=277) were prospectively given ERT and controls were matched for exact stage, a recurrence-free period similar to the period to ERT initiation in the ERT group, approximate age, and duration of follow-up. The mean time from breast cancer diagnosis to initiation of ERT was 3.6 years and the mean duration of ERT was 3.7 years. ERT was effective in relieving hot flashes in 92%, dyspareunia and vaginal dryness in 89%, and reactive depression, anxiety, and mood change in 88% of women. There were no statistical differences between the ERT and control groups for age, stage, pathology at diagnosis, progesterone receptor status, local therapy, breast at risk, prior chemotherapy, and duration of follow-up. In addition, there was no significant difference between the ERT and control groups in ipsilateral primary/recurrence (p=0.85), contralateral breast cancers (p=0.99), or systemic metastasis (p=0.13). Overall survival favored the ERT group (p=0.02) [125].

3) Hormone replacement therapy (HRT) after breast cancer was shown to have no adverse impact on recurrence and mortality in a cohort study comprised of 2755 women (aged 35 to 74 years) who were diagnosed with incident invasive breast cancer. Among the 2755 women, 174 users of HRT after diagnosis of breast cancer was identified. Each HRT user was matched to 4 randomly selected nonusers of HRT who were similar in respect to age, disease stage, and year of diagnosis. The women were free of recurrence at the time of HRT initiation or were equivalent in terms of time since diagnosis. The rate of recurrence was 17 per 1000 person-years in patients on HRT after diagnosis versus 30 per 1000 person-years in nonusers (relative risk (RR) 0.50; 95% confidence interval (CI) 0.30 to 0.85). Mortality rates from breast cancer were 5 per 1000 person- years and 15 per 1000 person-years for HRT users and nonusers, respectively (RR 0.34; 95% CI, 0.13 to 0.91). Total mortality rates were 16 per 1000 person-years for HRT users and 30 per 1000 person-years in nonusers (RR 0.48; 95% CI, 0.29 to 0.78). These results were similar for women using any type of HRT (oral, vaginal, oral plus vaginal) and lower relative risks were not associated with increased dosages (O'Meara et al, 2001).

4) In patients with breast cancer, estrogen replacement therapy did not increase recurrences or mortality rates. The addition of progestogens demonstrated a decrease in recurrence. This study involved 76 patients with breast cancer: 50 patients using estrogen replacement for up to 32 years; 8 patients using nonestrogenic hormone replacement for up to 6 years; and 18 patients using no hormone therapy for up to 10 years. Death occurred in 3 of 50 estrogens users, 1 of 8 nonestrogen users, and 6 of 18 no hormone users. The authors suggest patients with early breast cancer be offered hormone replacement therapy after a full discussion of benefits and risks [155].

Endometrial cancer

a) Summary

1) Estrogen replacement therapy increases the risk of endometrial carcinoma in postmenopausal women but does not appear to increase the rate of recurrence and death among endometrial cancer survivors [141]. Unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer; the risk is approximately 2- to 12-fold greater in these women when compared with non-users. The risk appears to be dependent on duration of use and on estrogen dose. Most studies indicated no significant increased risk when estrogens are used for less than one year. The risk increased 15- to 24-fold when therapy continued for five to ten years or more and the risk persisted for at least 8 to 15 years after discontinuation of estrogen therapy. Adding a progestin to

postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [55].

b) The rate of recurrence and death among endometrial cancer survivors (n=249) did not increase with estrogen replacement therapy with or without the addition of progestins. After receiving similar primary cancer treatment, 130 of the 249 women began estrogen replacement (oral, transdermal, or vaginal), with 49% electing to add medroxyprogesterone 2.5 milligrams to their daily regimen. The study included 75 matched endometrial cancer patients not treated with estrogen. After a mean follow-up of 83 months for estrogen users (n=75) and 69 months for nonusers (n=75), the rate of recurrence was 1% (95% confidence interval (CI) 71.0 to 91.4) and 14% (95% CI 59.1 to 87.7), respectively. The disease-free interval was significantly longer for those receiving estrogen compared to those who did not (p=0.006). The addition of medroxyprogesterone to the regimen did not appear to make a difference in the risk of recurrence or death rate [141].

c) In a large, population-based, case-control study, treatment with estradiol or conjugated estrogens and continuous progestins decreased the relative risk below levels seen in unexposed women. Information was collected from 709 case patients using hormone replacement and 3368 control subjects. Treatment was classified as 1) medium-potency estrogens (conjugated estrogens, estradiol, and other synthetic estrogens) without added progestins; 2) medium-potency estrogens with progestin cyclically combined or added continuously; 3) low- potency estrogens (oral estradiol or vaginal dienoestrol, estriol, or estradiol); or 4) progestins without estrogen. Relative risk for endometrial cancer was strongly related to the daily dose of estrogens. With 5 or more years of use, women using low-dose therapies had a fourfold increased relative risk, and women using higher doses had an eightfold increase [139]. In the same study, the authors recommend vaginal, rather than oral, formulations of low-potency estrogens for women with atrophy as the only indication for treatment. Oral treatment with low-potency estrogen formulations increased the relative risk of endometrial neoplasia [165].

d) Results from the 3-year Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated that for endometrial protection from hyperplastic changes in postmenopausal women with a uterus, estrogen and progestin (cyclically or continuously) should be administered concomitantly (n=596). Patients were given a 28-day cycle of 1) placebo; 2) conjugated estrogens (0.625 milligram per day); 3) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (10 milligrams per day) for the first 12 days 4) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (2.5 milligrams per day) for the first 12 days; 5) conjugated estrogens (0.625 milligram per day) plus micronized progesterone (200 milligrams per day) for the first 12 days. If women receive conjugated estrogens only, an annual endometrial evaluation should be done with discontinuation of therapy following the diagnosis of endometrial hyperplasia. In these patients hyperplasia usually returns to normal with progestin therapy [166].

e) The addition of a progestin to the estrogen regimen seems to provide a protective effect against endometrial cancer, by assuring more complete sloughing of the endometrium, which in turn prevents the continued proliferation that may result in hyperplastic neoplasia secondary to unopposed estrogen treatment [130][131][132][133][134][135][136][137]. However, combination therapy can result in periodic vaginal bleeding which may be unacceptable to some postmenopausal patients. Recommended therapy in women who have a uterus is the addition of medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle. This reduces the risk of hyperplasia and endometrial carcinoma [138]. Estrogen replacement therapy exerts stimulatory effects on the postmenopausal endometrium, comparable to premenopausal specimens taken in the proliferative phase [167].

f) A large case-control study has suggested that long-term use of estrogens can increase the risk of both localized and widespread endometrial cancer [140]. Women are at an increased risk of developing endometrial carcinoma for at least 10 years after discontinuing estrogens if they had taken estrogen for 1 or more years. It is suggested that all women who have not had hysterectomies and who have used estrogens for 1 year or more should be considered for long-term gynecologic monitoring regardless of when they received estrogens. Endometrial carcinoma was not associated with estrogen use for a period of less than 1 year. In this study, 31% of 425 women with endometrial carcinoma reported having used estrogens, compared to 15% of 792 controls. Histories were obtained in these patients with regard to noncontraceptive estrogens, and whether patients had used estrogens for numerous indications and not just postmenopausal symptoms (regulation of periods, menstrual problems, infertility, breast conditions, endometriosis or sexual difficulties).

Ovarian cancer

a) The use of hormone replacement therapy (HRT) among postmenopausal women was associated with increased risk of fatal and incident ovarian cancer. In a large cohort UK Million Women Study (n=948,576), postmenopausal women who did not have previous cancer or bilateral oophorectomy (ovariotomy) were followed for an average of 5.3 years (over 5 million woman-years) for ovarian cancer incidence,

and an average of 6.9 years (6.5 million woman-years) for death. The mean age was 57.2 +/- 4.6 years at baseline; and at the time of last contact, 50% participants had ever used HRT while 30% were current users. Ever users of HRT experienced an increased risk of ovarian cancer compared with never users (relative risk (RR) 1.11, 95% confidence interval (CI), 1.02 to 1.21; p=0.02). Unlike past users (RR 0.98, 95% CI, 0.88 to 1.11; p=0.7), current users of HRT exhibited significantly higher ovarian cancer risk relative to never users (RR 1.2, 95% CI, 1.09 to 1.32; p=0.0002); and the difference between the current- and past-users were significant (p=0.01 for heterogeneity). It was estimated that current users developed ovarian cancer after 7.7 years of HRT use overall (9.2 years for estrogen-only and 6.9 years for estrogen-progestagen therapy). Past users, on the other hand, were diagnosed with ovarian cancer 5.6 +/- 4.3 years after discontinuing HRT. The relative risk of ovarian cancer also increased with longer duration of HRT among current users (p=0.04 for trend): 1.05 (95% CI, 0.9 to 1.23) for fewer than 5 years of use, 1.24 (95% CI, 1.09 to 1.41) for 5 to 9 years of use, and 1.31 (95% CI, 1.12 to 1.53) for 10 years or more of use; but did not differ significantly by type of preparation used, constituents, or route of administration. While 95% of the malignant ovarian cancers were epithelial, HRT was greater for serous (RR 1.53, 95% CI, 1.31 to 1.79) than for mucinous (RR 0.72, 95% CI, 0.52 to 1), endometroid (RR 1.05, 95% CI, 0.77 to 1.43), or clear cell tumors (RR 0.77, 95% CI, 0.48 to 1.23). Current users of HRT also exhibited higher mortality risk than never users (RR 1.23, 95% CI, 1.09 to 1.38; p=0.0006), but past users did not (RR 0.97, 95% CI, 0.84 to 1.11). Over 5 years, the standardized incidence and mortality rates for ovarian cancer for never users were 2.2 (2.1 to 2.3) and 1.3 (1.2 to 1.4) per 1000, respectively, and 2.6 (2.4 to 2.9) and 1.6 (1.4 to 1.8) per 1000, respectively, for current users; resulting in a projected 1 extra ovarian cancer case in every 2500 users, and 1 extra death from the malignancy in every 3300 users [126].

b) Results of the Women's Health Initiative (WHI) randomized, double-blind, placebo-controlled trial indicate continuous combined estrogen and progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. Postmenopausal women with a uterus (n=16,608) were randomized to treatment with conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone 2.5 mg or placebo. After 5.6 years follow-up, the hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval (CI) 0.77 to 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years [129][55].

c) Results from a cohort study of former participants in the Breast Cancer Detection Demonstration Project indicate short-term estrogen-progestin use did not increase the risk for ovarian cancer but further study is warranted. Of 44,241 women, 329 developed ovarian cancer during follow-up. After adjustment for age, menopause type, and oral contraceptive use, the results were:

TYPE OF HORMONE REPLACEMENT	RATE RATIO (RR) and 95% CONFIDENCE INTERVAL (CI)
Ever use of estrogen	RR=1.6; 95% CI, 1.2 to 2.0
Estrogen only for 10 to 19 years	RR=1.8; 95% CI, 1.1 to 3.0*
Estrogen only for 20 or more years	RR=3.2; 95% CI, 1.7 to 5.7*
Estrogen-progestin use after estrogen	RR=1.5; 95% CI, 0.91 to 2.4
Estrogen-progestin use only	RR=1.1; 95% CI, 0.64 to 1.7
Estrogen-progestin use only, less than 2 yrs	RR=1.6; 95% CI, 0.78 to 3.3**
Estrogen-progestin use only, 2 or more yrs	RR=0.8; 95% CI, 0.35 to 1.8**

* p value for trend less than 0.001

** p value for trend equal to 0.30

d) A 7% increase in rate ratio (RR) per year of estrogen-only use was observed (95% confidence interval, 2% to 13%). Also observed were significantly elevated RRs with increasing duration of estrogen-only use across all degrees of other ovarian cancer risk factors [164].

Black Box Warning

1) Estradiol

a) Oral (Tablet)

1) Estrogens Increase the Risk of Endometrial Cancer

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than "synthetic" estrogens at equivalent estrogen doses.

2) Cardiovascular and Other Risks

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo.

The Women's Health Initiative Memory (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age and older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy.

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [62].

b) Transdermal (Gel/Jelly)

1) Endometrial Cancer, Cardiovascular Disorders, Probable Dementia, and Breast Cancer

Estrogen-Alone Therapy

Endometrial Cancer - There is an increased risk of cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Use adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.
Cardiovascular Disorders and Probable Dementia - Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia.
Cardiovascular Disorders and Probable Dementia - The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo.
Cardiovascular Disorders and Probable Dementia - The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.
Cardiovascular Disorders and Probable Dementia - Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile.
Cardiovascular Disorders and Probable Dementia - Prescribe estrogens with or without progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia - Do not use estrogen plus progestin therapy for the prevention of cardiovascular disease or dementia. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with combined medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo.
Cardiovascular Disorders and Probable Dementia - The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.
Breast Cancer - The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer.
Breast Cancer - Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus

progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestin products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestin therapy, taking into account her individual risk profile.
Breast Cancer - Prescribe estrogens with or without progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [33].

c) Transdermal (Gel/Jelly; Patch, Extended Release)

1) Endometrial Cancer, Cardiovascular Disorders, Breast Cancer, and Probable Dementia

Estrogen-Alone Therapy

Endometrial Cancer - There is an increased risk of cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [63][10][64][65][66][67].
Cardiovascular Disorders and Probable Dementia - Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [63][64][10][65][66][67].
Cardiovascular Disorders and Probable Dementia - The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo [63][10][64][65][66][67].
Cardiovascular Disorders and Probable Dementia - The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [63][10][64][65][66][67].
Cardiovascular Disorders and Probable Dementia - In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens [65][29][67].
Cardiovascular Disorders and Probable Dementia - Only daily oral 0.625 mg CE was studied in the estrogen -alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile [63][68][10][64].
Cardiovascular Disorders and Probable Dementia - Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [63][10][64][65][66][67].

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia - Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [63][10][64][65][66][29][67].
Cardiovascular Disorders and Probable Dementia - The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with combined medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [63][10][64][65][66][67].
Cardiovascular Disorders and Probable Dementia - The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age and older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [63][10][64][65][66][67].
Breast Cancer - The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [63][10][64][65][66][67].
Breast Cancer - In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins [65][67].
Breast Cancer - Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia, and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestogen therapy, taking into account her individual risk profile [63][68][10][64].
Breast Cancer - Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [63][10][64][65][66][67].

d) Transdermal (Spray)

1) Endometrial Cancer, Cardiovascular Disorders, Breast Cancer, Probable Dementia, and Unintentional Secondary Exposure to Estrogen

Estrogen Alone Therapy

Endometrial Cancer- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed and random endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal genital bleeding.
Cardiovascular Disorders and Probable Dementia - Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia.
Cardiovascular Disorders and Probable Dementia - The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] alone, relative to placebo.
Cardiovascular Disorders and Probable Dementia - The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women .
Cardiovascular Disorders and Probable Dementia - In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.
Cardiovascular Disorders and Probable Dementia - Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia - Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia.
Cardiovascular Disorders and Probable Dementia - The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo.
Cardiovascular Disorders and Probable Dementia - The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.
Breast Cancer - The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer.
Breast Cancer - In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins.
Breast Cancer - Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Unintentional Secondary Exposure

Breast budding and breast masses in prepubertal females and gynecomastia and breast masses in prepubertal males have been reported following unintentional secondary exposure to estradiol transdermal spray by women using this product. In most cases, the condition resolved with the removal of the estradiol transdermal spray exposure. Women should ensure that children should not come in contact with the site(s) where estradiol transdermal spray is applied. Healthcare providers should advise patients to strictly adhere to recommended instructions for use [69].

e) Vaginal (Cream; Insert, Extended Release)

1) Endometrial Cancer, Cardiovascular Disorders, Breast Cancer, and Probable Dementias

Estrogen Alone Therapy

Endometrial Cancer - There is an increased risk of cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [70][71][72][73].
Cardiovascular Disorders and Probable Dementia - The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo [70][71][72][73].
Cardiovascular Disorders and Probable Dementia - The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [70][71][72][73].

Cardiovascular Disorders and Probable Dementia - Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia [70][71][72][73].
Cardiovascular Disorders and Probable Dementia - Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile [70][71].
Cardiovascular Disorders and Probable Dementia - In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens[72][73].
Cardiovascular Disorders and Probable Dementia - Prescribe estrogens with or without progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [70][71][72][73].

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia - The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with combined medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [70][71][72][73].
Cardiovascular Disorders and Probable Dementia - The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [70][71][72][73].
Cardiovascular Disorders and Probable Dementia - Do not use estrogen and progestin therapy for the prevention of cardiovascular disease or dementia [70][71][72][73].
Breast Cancer - The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [70][71][16][72][73].
Breast Cancer - Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia, and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestogen therapy, taking into account her individual risk profile [70][71].
Breast Cancer - Prescribe estrogens with or without progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [70][71][72][73].

2) Estradiol Acetate

a) Oral (Tablet)

1) Estrogens Increase the Risk of Endometrial Cancer

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

2) Cardiovascular and Other Risks

Estrogens with or without progestins should not be used for the preventions of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and DVT in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE) 0.625 mg combined with medroxyprogesterone acetate (MPA) 2.5 mg relative to placebo.

The WHI Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral CE plus MPA relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy.

Other doses of oral CE with MPA, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [61].

b) Vaginal (Insert, Extended Release)

1) Estrogen Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia.
The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risk of stroke and DVT in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) 0.625 mg-alone, relative to placebo.
The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE 0.625 mg-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.
In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.
Estrogens with or without progestins should be described at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [59].

2) Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia.
The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE 0.625 mg combined with medroxyprogesterone acetate (MPA) 2.5 mg, relative to placebo.
The WHIMS estrogen plus progestin ancillary study of the WHI reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [59].

3) Estradiol Cypionate

a) Intramuscular (Oil)

1) Estrogens Increase the Risk of Endometrial Cancer

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that the use of "natural" estrogens results in a different endometrial risk profile than "synthetic" estrogens at equivalent estrogen doses.

2) Cardiovascular and Other Risks

Estrogens with and without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo.

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen-alone therapy.

Other doses of conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [55].

4) Estradiol Valerate

a) Intramuscular (Oil)

1) Estrogens Increase the Risk of Endometrial Cancer

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

2) Cardiovascular and Other Risks

Estrogens and progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo.

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy.

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [58].

REMS

No results available

Drug Interactions (single)

Drug-Drug Combinations

Abametapir

1) Interaction Effect: increased exposure of CYP3A4 substrate
2) Summary: Avoid use of CYP3A4 substrates within 2 weeks after application of abametapir. If this is not feasible, avoid use of abametapir[230].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid use of CYP3A4 substrates within 2 weeks after application of abametapir. If this is not feasible, avoid use of abametapir[230].
7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by abametapir

Amifampridine

1) Interaction Effect: increased risk of seizures
2) Summary: Concomitant use of amifampridine and this drug may increase the risk of seizures. Consider this risk if these agents are to be used concomitantly[364].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of amifampridine and this drug may increase the risk of seizures. Consider this risk if these agents are to be used concomitantly[364].
7) Probable Mechanism: unknown

Amiodarone

1) Interaction Effect: increased hormonal contraceptive exposure
2) Summary: The concomitant use of hormonal contraceptives (CYP3A4 substrates) and amiodarone, a CYP3A4 inhibitor and substrate[445], may increase the exposure of the hormonal contraceptive. If amiodarone is used concomitantly with hormonal contraceptives, monitor for adverse effects related to the hormonal contraceptive.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If hormonal contraceptives (CYP3A4 substrates) are used concomitantly with amiodarone, a CYP3A4 inhibitor and substrate[445], the oral contraceptive exposure may be increased. If amiodarone is used concomitantly with hormonal contraceptives, monitor for adverse effects related to the hormonal contraceptive.

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of the hormonal contraceptive by amiodarone

Amitriptyline

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily.

Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Amoxapine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

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mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Amoxicillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Amoxicillin may alter intestinal flora, possibly leading to lower estrogen reabsorption and decreased oral combination contraceptive efficacy[354]. Concomitant use has been associated with unintended pregnancies and menstrual changes [356][357] [358]. However, systemic exposure to ethinyl estradiol/etonogestrel was not different when the vaginal ring was used with or without a 10-day course of amoxicillin during a randomized, crossover study (n=15) [355]. Furthermore, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins.. The OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If a 1% to 3% contraceptive failure rate is unacceptable, recommend an additional form of contraception [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of amoxicillin and combination contraceptives may result in decreased contraceptive efficacy[354]; however, significant differences in contraceptive failure rates were not demonstrated during a study of oral contraceptives with or without antibiotics [183] and no significant difference in exposure was observed with the use of the vaginal ring with or without amoxicillin [355]. If a typical failure rate of 1% to 3% is a concern for the patient, consider additional or alternative forms of birth control.
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) Systemic exposure of ethinyl estradiol/etonogestrel with use of the vaginal ring contraceptive was not affected by concomitant use of amoxicillin in a randomized, 2-way crossover study in healthy women volunteers (n=15). Following synchronization of menstrual cycles by 21 to 28 days and a 7-day ring-free period, volunteers received the vaginal ring for 21 days with or without amoxicillin 875 mg orally twice daily for 10 days (mean age, 29.9 +/- 5.8 years). After a 7-day ring-free washout period, subjects crossed over to the opposite treatment arm. With administration of the vaginal ring alone, the mean AUC of ethinyl estradiol, measured at 12 hours, day 9 to 10, day 10, and day 21, was 0.328 +/- 0.092 nanograms x hr/mL, 0.266 +/- 0.0874 nanograms x hr/mL, 5.86 +/- 1.77 nanograms x hr/mL, and 11.7 +/- 3.86 nanograms x hr/mL, respectively. With administration of the ring plus amoxicillin, the mean AUC of ethinyl estradiol was 0.328 +/- 0.0757 nanograms x hr/mL, 0.252 +/- 0.0935 nanograms x hr/mL, 5.49 +/- 1.67 nanograms x hr/mL, and 11.3 +/- 3.57 nanograms x hr/mL, respectively. The AUC interaction/control ratio (ring with amoxicillin to ring alone) also showed absence of drug interaction. At 12 hours, day 9 to 10, day 10, and day 21, the interaction/control ratio was 1.01 (90% CI, 0.87 to 1.18), 0.96 (90% CI, 0.84 to 1.09), 0.95 (90% CI, 0.85 to 1.06), and 0.98 (90% CI, 0.88 to 1.09), respectively. The etonogestrel plasma concentrations and interaction/control ratio demonstrated similar findings at all time points [355].

b) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial

difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Ampicillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183]. Another study showed concurrent ampicillin administration did not to diminish the effectiveness of the oral contraceptive studied [184].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ampicillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) In a study of 11 regularly menstruating women, ages 21 to 39, concurrent ampicillin administration appeared not to diminish the effectiveness of the oral contraceptive studied. Demulen(R) (1 mg ethynodiol diacetate and 50 mcg ethinyl estradiol) was given to each subject for 2 consecutive menstrual cycles, 21 days on and 7 days off. Ampicillin 250 mg or placebo was given 4 times/day from day 1 through day 16 of each study cycle. Two subjects experienced breakthrough bleeding while taking ampicillin. One subject reported spotting with Demulen(R)/placebo combination, but not with Demulen(R)/ampicillin. There was no difference in quantity of menstrual flow between the two study cycles. One subject reported mid-cycle abdominal pain while on Demulen(R)/ampicillin. All cycles appeared to be anovulatory with no significant difference in follicle-stimulating hormone, luteinizing hormone, and steroid hormone levels in patients on Demulen(R)/ampicillin compared with patients on Demulen(R)/placebo [184].

Amprenavir

1) Interaction Effect: decreased serum concentrations of amprenavir and loss of contraceptive efficacy
2) Summary: A loss of virologic response and possible resistance to amprenavir may occur when hormonal contraceptives (containing ethinyl estradiol/norethindrone) are used concomitantly. Alternate methods of non-hormonal contraception are recommended[231]. Significant changes (increase and decrease) in the mean AUCs of the estrogen and progestin may occur with concomitant administration of protease inhibitors [232]. Concomitant administration of ethinyl estradiol/norethindrone 0.035 mg/1 mg for one cycle and amprenavir 1200 mg twice daily for 28 days in 10 patients resulted in a decrease in AUC by 22% and a decrease minimum plasma concentration (Cmin) by 20% [233].

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Those taking amprenavir should be instructed not to use hormonal contraceptives because some oral contraceptives (containing ethinyl estradiol/norethindrone) have been found to decrease the concentration of amprenavir. Likewise, concomitant use of oral contraceptives with protease inhibitors may result in increases or decreases of estrogen and progestin serum drug levels.
7) Probable Mechanism: induction of contraceptive metabolism

Apalutamide

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of a CYP3A4 inducer, such as apalutamide, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure[197]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of apalutamide [197].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a CYP3A4 inducer, such as apalutamide, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of apalutamide[197].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives by apalutamide
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Aprepitant

1) Interaction Effect: reduced efficacy of contraceptives
2) Summary: Concomitant use of aprepitant or fosaprepitant with hormonal contraceptives may result in decreased contraceptive efficacy. Studies have demonstrated a significant decrease in the AUC and minimum concentration of ethinyl estradiol and norethindrone with concomitant administration. Patients should be advised to use an alternative or back-up method of contraception during therapy and for 1 month after the last dose[342].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for reduced efficacy of hormonal contraceptives in patients receiving aprepitant or fosaprepitant, alternative or back-up methods of contraception should be used during treatment and for 1 month after the last dose[342].
7) Probable Mechanism: unknown
8) Literature Reports

a) When oral aprepitant 100 mg was given once daily for 14 days with an oral contraceptive containing ethinyl estradiol 35 mcg and norethindrone 1 mg, the ethinyl estradiol AUC decreased by 43%, and the norethindrone AUC decreased by 8%. In a separate study, a daily dose of a combination contraceptive containing ethinyl estradiol and norethindrone was administered for 21 days. On day 8, oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral dexamethasone 12 mg were administered. On days 9 and 10, oral aprepitant 80 mg/day and dexamethasone 8 mg/day were given. On day 11, oral dexamethasone 8 mg was administered alone. The AUC of ethinyl estradiol decreased 19% and there was no change in the norethindrone AUC on day 10. The minimum concentration of ethinyl estradiol decreased as much as 64% and norethindrone decreased up to 60% during days 9 through 21 [342].

Armodafinil

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of a CYP3A4 inducer, such as armodafinil, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure[197]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of armodafinil [197].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a CYP3A4 inducer, such as armodafinil, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of armodafinil[197].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives by armodafinil
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Artemether

1) Interaction Effect: reduced hormonal contraceptive plasma concentrations
2) Summary: Artemether is an inducer of CYP3A4 isozymes, and both artemether and lumefantrine are primarily metabolized by CYP3A4. Although not formally studied, concomitant use of artemether/lumefantrine and a hormonal contraceptive may reduce the effectiveness of the hormonal contraceptive. Therefore, patients should be advised to use an additional non-hormonal contraceptive when artemether/lumefantrine and a hormonal contraceptive are coadministered[331].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of artemether/lumefantrine and a hormonal contraceptive may decrease the hormonal contraceptive plasma concentrations. Therefore, advise patients to use an additional non-hormonal method of birth control when artemether/lumefantrine and a hormonal contraceptive are coadministered[331].
7) Probable Mechanism: induction of hormonal contraceptive metabolism by artemether

Atazanavir

1) Interaction Effect: an increase in exposure to the combination contraceptive
2) Summary: Concomitant use of atazanavir (with/without ritonavir) and a combination ethinyl estradiol/norgestimate or norethindrone oral contraceptive has resulted in a substantial increase in progesterone exposure and both increases and decreases in ethinyl estradiol exposure[307] In a study in healthy HIV-negative women (n=20), coadministration of atazanavir/ritonavir and an oral contraceptive containing ethinyl estradiol and norgestimate resulted in increased exposure of norgestimate and decreased exposure of ethinyl estradiol; however, the reduction in ethinyl estradiol levels was not expected to decrease contraceptive efficacy. Results of this study indicate that an oral contraceptive containing at least 30 mcg of ethinyl estradiol would be sufficient to maintain adequate exposure of ethinyl estradiol [308]. Use caution when prescribing oral contraceptives in patients receiving atazanavir. A combination oral contraceptive with the appropriate dose of ethinyl estradiol (at least 35 mcg with concomitant atazanavir plus ritonavir and no more than 30 mcg with concomitant atazanavir) is recommended. An alternate method of contraception is recommended when the patient is using other hormonal contraceptives (eg, patch, vaginal ring, injection), oral contraceptives that contain progestins other than norethindrone or norgestimate, or oral contraceptives that contain less than 25 mcg of ethinyl estradiol, as studies have not been conducted [307].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Use caution when coadministering atazanavir (with or without ritonavir) and a combination ethinyl estradiol/norgestimate or norethindrone oral contraceptive as concomitant use has resulted in substantial increases in progesterone exposure and both reductions and elevations in ethinyl estradiol exposure[307][308]. If an oral contraceptive is administered with atazanavir plus ritonavir, the oral contraceptive should contain at least 35 mcg of ethinyl estradiol. If administered with atazanavir alone, the oral contraceptive should contain no more than 30 mcg of ethinyl estradiol. An alternative method of contraception is recommended if atazanavir (with or without ritonavir) is being considered for a patient who is using other hormonal contraceptives (eg, patch, vaginal ring, or injection), oral contraceptives that contain progestins other than norethindrone or norgestimate, or oral contraceptives that contain less than 25 mcg of ethinyl estradiol, as studies have not been conducted in these cases [307].
7) Probable Mechanism: unknown
8) Literature Reports

a) Concomitant use of atazanavir (with or without ritonavir) and a combination ethinyl estradiol/norgestimate or norethindrone oral contraceptive has resulted in substantial increases in progesterone exposure. Long-term effects of increases in progestational agent bioavailability are not known and could result in an increased risk of insulin resistance, dyslipidemia, and acne. Concomitant use of atazanavir 300 mg plus ritonavir 100 mg once daily with an ethinyl estradiol/norgestimate oral contraceptive resulted in decreased ethinyl estradiol and increased norgestimate exposure. Coadministration of atazanavir 400 mg once daily with an ethinyl estradiol/norethindrone contraceptive resulted in increased exposure to both ethinyl estradiol and norethindrone. No studies have been conducted on the concomitant use of atazanavir (with or without ritonavir) with other hormonal contraceptives (eg, patch, vaginal ring, or injection), with oral contraceptives that contain progestins other than norethindrone or norgestimate, or with oral contraceptives that contain less than a 25-mcg dose of ethinyl estradiol [307].

b) In a pharmacokinetic study in healthy HIV-negative women (n=20; mean age 28 years), coadministration of atazanavir/ritonavir and an oral contraceptive containing ethinyl estradiol (EE) and norgestimate (NGM) resulted in increased exposure of norgestimate and decreased exposure of ethinyl estradiol; however the reduction in ethinyl estradiol levels was not expected to decrease contraceptive efficacy. In this open-label, three-period study, participants received in the lead-in period a full 28-day cycle of Ortho Tri-CyClen(R) (EE 0.035 mg plus NGM 0.18/0.215/0.25 mg). This was followed by period 1 in which participants received a second cycle of daily Ortho Tri-CyClen(R) (treatment A). Participants with satisfactory safety assessments began a third cycle on day 29 of Ortho Tri-Cyclen LO(R) (EE 0.025 mg plus NGM 0.18/0.215/0.25 mg) coadministered with atazanavir 300 mg/ritonavir 100 mg once daily for 14 days (treatment B). A dose normalization was performed to account for the different EE doses in the 2 treatments and to estimate the magnitude of reduction in EE exposures. Coadministration of atazanavir/ritonavir plus dose-normalized EE/NGM resulted in geometric mean reductions in EE of 16%, 19%, and 37% for Cmax, AUC, and Cmin, respectively. For NGM exposure, Cmax, AUC, and Cmin were increased by 68%, 85%, and 102%, respectively. Results of this study indicate that an oral contraceptive containing at least 30 mcg of EE would be sufficient to maintain adequate exposure of EE. Since the contraceptive efficacy of Ortho Tri-Cyclen(R) is primarily dependent on progestin, the contraceptive efficacy was not expected to be compromised [308].

Bacampicillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186][443]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of bacampicillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183]. Another study indicated that alternative contraceptive methods are not required during combined therapy, as ampicillin had no significant effect on plasma levels of oral contraceptives [437].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) Concomitant ampicillin and oral contraceptive therapy has been reported to result in menstrual irregularity and unplanned pregnancy, as well as reduced urinary excretion of endogenous estrogens [438][439][440][441][442].

c) Ampicillin had no significant effect on plasma levels of ethinyl estradiol, levonorgestrel, follicle-stimulating hormone, or progesterone when given in combination with oral contraceptives. The authors indicate that alternative contraceptive methods are not required during combined therapy [437].

d) The interaction between oral contraceptives and ampicillin may be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [443].

e) In a study of 11 regularly menstruating women, ages 21 to 39 years, concurrent ampicillin administration appeared not to diminish the effectiveness of the oral contraceptive studied. Demulen(R) (1 mg ethynodiol diacetate and 50 mcg ethinyl estradiol) was given to each subject for 2 consecutive menstrual cycles, 21 days on and 7 days off. Ampicillin 250 mg or placebo was given 4 times a day from day 1 through day 16 of each study cycle. Two subjects experienced breakthrough bleeding while taking ampicillin. One subject reported spotting with Demulen(R)/placebo combination, but not with Demulen(R)/ampicillin. There was no difference in quantity of menstrual flow between the two study cycles. One subject reported mid-cycle abdominal pain while on Demulen(R)/ampicillin. All cycles appeared to be anovulatory with no significant difference in follicle-stimulating hormone, luteinizing hormone, and steroid hormone levels in patients on Demulen(R)/ampicillin compared with patients on Demulen(R)/placebo [444].

Belzutifan

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of belzutifan and a hormonal contraceptive may decrease plasma concentrations of the contraceptive leading to contraceptive failure or an increase in breakthrough bleeding. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with belzutifan and for 1 week after the last dose[382].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of belzutifan and a hormonal contraceptive may decrease plasma concentrations of the contraceptive leading to contraceptive failure or an increase in breakthrough bleeding. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with belzutifan and for 1 week after the last dose[382].
7) Probable Mechanism: induction of CYP450-mediated hormonal contraceptive metabolism by belzutifan

Betamethasone

1) Interaction Effect: increased corticosteroid effects
2) Summary: Combination oral contraceptives have been demonstrated to alter the pharmacokinetics of hydrocortisone and prednisone, thereby potentially enhancing therapeutic effect. The half-lives of these steroids increase by 2 to 3 times and their clearance may decrease 2- to 5-fold[297][298][299].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients should be monitored for increased corticosteroid effects; the betamethasone dose may need to be reduced.
7) Probable Mechanism: inhibition of corticosteroid metabolism by the combination contraceptive

Bexarotene

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Bexarotene can potentially increase the rate of metabolism and reduce plasma concentrations of other substrates metabolized by CYP3A4, including hormonal contraceptives. If concomitant use cannot be avoided, two reliable forms of contraception are strongly recommended, one of which should be non-hormonal[359].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: During administration of bexarotene, the use of hormonal contraceptives is not recommended. If concurrent administration cannot be avoided, it is strongly recommended that one of the two reliable forms of contraception be non-hormonal.
7) Probable Mechanism: induction of metabolic enzymes by bexarotene

Bosentan

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of bosentan (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive. Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when coadministered. Coadministration of bosentan and a combination oral hormonal contraceptive decreased mean norethindrone levels and ethinyl estradiol levels as much as 56% and 66% in individual patients. Do not use a hormonal contraceptive as the sole means of contraception[276] Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Use a non-hormonal contraceptive back-up method during coadministration and for 28 days after discontinuing a CYP3A4 inducer [250].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of bosentan (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive. Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when coadministered. Do not use a hormonal contraceptive as the sole means of contraception[276]. Use a non-hormonal back-up contraceptive method during coadministration and for 28 days after discontinuing a CYP3A4 inducer [250].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) Coadministration of bosentan and a combination oral hormonal contraceptive decreased mean norethindrone levels by 14% and ethinyl estradiol levels by 31% in a study. However, decreases in exposure were as high as 56% and 66%, in individual patients [276].

Bupropion

1) Interaction Effect: increased risk of seizures
2) Summary: BuPROPion is associated with a dose-related risk of seizures and when used concomitantly with other seizure threshold-lowering agents there is an increased risk. Use extreme caution when coadministering bupropion with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic corticosteroids). Begin treatment with a low initial buPROPion dose and increase the dose gradually. If a patient experiences a seizure, discontinue buPROPion and do not reinitiate[424][425].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: BuPROPion is associated with a dose-related risk of seizures and when used concomitantly with other seizure threshold-lowering agents there is an increased risk. Use extreme caution when coadministering buPROPion with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic corticosteroids). Begin treatment with a low initial buPROPion dose and increase the dose gradually. If a patient experiences a seizure, discontinue buPROPion and do not

reinitiate[424][425].
7) Probable Mechanism: additive lowering of the seizure threshold

Carbamazepine

1) Interaction Effect: a decrease in plasma concentrations of hormonal contraceptives and contraceptive failure and breakthrough bleeding
2) Summary: Carbamazepine is a strong CYP3A4 inducer and concomitant use with hormonal contraceptives may significantly decrease exposure and contraceptive efficacy. Coadministration of carbamazepine and oral ethinyl estradiol/norethindrone significantly decreased AUC and increased clearance of the contraceptive in a randomized study[179]. Concomitant use of a CYP3A4 inducer disproportionally increased unplanned pregnancy rate with oral and implanted contraceptives, but not with intrauterine devices or intravaginal rings [177]. Because breakthrough bleeding and significantly increased pregnancy rates have been reported with coadministration, consider an alternative to carbamazepine, or employ alternative or backup contraceptive methods [175] during coadministration and for at least 28 days after discontinuation of carbamazepine [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of carbamazepine (a strong CYP3A4 inducer) with hormonal contraceptives (oral and subdermal implant) has resulted in breakthrough bleeding and pregnancies. Consider an alternative to carbamazepine, or employ alternative or backup contraceptive methods[175] during coadministration and for at least 28 days after discontinuation of carbamazepine [176].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) In a study in healthy women (N=10 evaluable; 18 to 45 years) using an etonogestrel implant for 13 to 34 months, 3 weeks of coadministered carbamazepine titrated up to 300 mg twice daily resulted in a significant median 61% decrease in etonogestrel levels from 158 picogram (pg)/mL (range, 127.9 to 347.3 pg/mL) to 50.8 pg/mL (range 39.4 to 202.3 pg/mL). In 8 women, the etonogestrel level was below the threshold for ovulatory suppression (less than 90 pg/mL) after carbamazepine coadministration. There was no significant change in the number of ovarian follicle-like structures or endometrial thickness. No pregnancies were reported during the study period [178].

c) A randomized, open-label, five-group study concluded that carbamazepine significantly decreased the mean AUC and Cmax values of oral contraceptives containing ethinyl estradiol and norethindrone. In two, 28-day cycles, five groups of female subjects received oral doses of ethinyl estradiol and norethindrone (Ortho-Novum 1/35(R)) alone in the first cycle and then in combination with topiramate or carbamazepine during the second cycle. When carbamazepine 600 mg/day was coadministered with ethinyl estradiol and norethindrone, a significant 42% and 58% decrease was observed in the mean AUC of both oral contraceptives, respectively, as was the mean Cmax by 19.2%. However, oral clearance significantly increased in both contraceptives by 127% and 69%, respectively. Coadministration of topiramate at daily doses for nonobese (50 mg, 100 mg, and 200 mg) and obese (200 mg) women resulted in a nonsignificant change in the AUC of ethinyl estradiol by -12%, +5%, -11% and -9%, respectively, when compared with the oral contraceptive alone. Norethindrone results were similar with plasma levels and AUC not significantly changed [179].

d) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, primarily phenobarbital, phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contraception. The benzodiazepines and valproic acid have not been associated with increased failure rates in women receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives may diminish breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may also increase the risk of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended that low doses of estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; however, if unplanned pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be

considered. If breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestranol or its equivalent (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be discontinued, but rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Switching to a lower dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women receiving moderate or high-dose contraceptives [180].

e) Carbamazepine reduced the AUC of ethinyl estradiol by 6% to 60% in 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norgestrel AUCs were also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding can be controlled for most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol [181].

f) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus carbamazepine 400 mg daily. The plasma concentration of levonorgestrel in this patient was very low (107 to 120 picograms (pg)/mL) when compared with controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma levonorgestrel concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel should not be relied upon as the sole means of contraception in patients on anticonvulsant therapy [182].

Carbenicillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of carbenicillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefaclor

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives, which could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefaclor and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefadroxil

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives, which could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefadroxil and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefdinir

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that

cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives, which could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefdinir and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefditoren

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives, which could result in unintended pregnancies and menstrual changes[185][186]. However, multiple doses of cefditoren had no effect on the pharmacokinetics of ethinyl estradiol [416]. Additionally, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183]. In addition, cefditoren given in multiple doses had no effect on the pharmacokinetics of ethinyl estradiol (the estrogenic component in most contraceptive combinations) [416].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics; however, multiple doses of cefditoren had no effect on the pharmacokinetics of ethinyl estradiol[416] Additionally, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics

for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefixime

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives, which could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefixime and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefpodoxime

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefpodoxime and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].

7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefprozil

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefprozil and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Ceftazidime

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Similar to other antibiotics, ceftazidime may alter intestinal flora, which may lead to lower reabsorption of estrogen and decreased effectiveness of combination oral estrogen/progesterone contraceptives[330]. Patients should be advised to use an additional form of birth control if these agents are used concomitantly.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ceftazidime and a combination oral estrogen/progesterone-containing contraceptive may result in decreased contraceptive effectiveness[330]. Counsel patients to use an additional form of birth control if these agents are used concomitantly.

7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption

Ceftibuten

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ceftibuten and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefuroxime

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of cefuroxime and combination contraceptives may result in decreased contraceptive efficacy . The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives[344] resulting in unintended pregnancies and menstrual changes [185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefuroxime and combination contraceptives may result in decreased contraceptive efficacy[344]; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up

survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cenobamate

1) Interaction Effect: reduced hormonal contraceptive plasma concentrations and reduced contraceptive efficacy
2) Summary: Because of a potential for reduced efficacy, women should use additional or alternative non-hormonal birth control when used concomitantly with cenobamate (a CYP3A4 inducer)[290]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cenobamate and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive. Women should use additional or alternative non-hormonal birth control while taking cenobamate[290].
7) Probable Mechanism: unknown
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Ceritinib

1) Interaction Effect: increased exposure of CYP3A substrate
2) Summary: Concomitant use of ceritinib (a strong CYP3A inhibitor) and a CYP3A substrate may increase exposure of the substrate. Coadministration with midazolam (a sensitive CYP3A substrate) has resulted in an increase in the midazolam AUC by 5.4-fold and Cmax by 1.8-fold. Avoid use of sensitive CYP3A substrates and if other CYP3A substrates are coadministered, consider dose reductions of the CYP3A substrate[422].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ceritinib (a strong CYP3A inhibitor) and a CYP3A substrate may increase exposure of the substrate. Avoid use of sensitive CYP3A substrates and if other CYP3A substrates are coadministered, consider dose reductions of the CYP3A substrate[422].
7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of drug by ceritinib
8) Literature Reports

a) Coadministration of a single dose of midazolam (a sensitive CYP3A substrate) following 3 weeks of ceritinib 750 mg daily under fasted conditions increased the midazolam AUC by 5.4-fold and Cmax by 1.8-fold compared to midazolam administered alone [422]

Clavulanic Acid

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Ticarcillin/clavulanic acid may alter intestinal flora, which may lead to lower reabsorption of estrogen and decreased effectiveness of combination oral estrogen/progesterone contraceptives[345]. Concomitant use has been associated with unintended pregnancies and menstrual changes [346] [347] However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure

rate is unacceptable to the patient, an additional form of contraception should be recommended [183]
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ticarcillin/clavulanic acid and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Clobazam

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Administration of clobazam, a CYP3A4 inducer, with hormonal contraceptives, which are CYP3A4 substrates, may decrease plasma concentrations of the contraceptives. During concurrent use and for 28 days following use of clobazam and hormonal contraceptives, effective additional non-hormonal forms of birth control should be used throughout clobazam therapy[281].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Administration of clobazam with hormonal contraceptives may decrease plasma concentrations of the contraceptive. During concurrent use and for 28 days following use of clobazam and hormonal contraceptives, effective use of additional non-hormonal forms of birth control is recommended[281].
7) Probable Mechanism: induction of CYP3A4-mediated hormonal contraceptive metabolism by clobazam

Clomipramine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients

taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Cloxacillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cloxacillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral

contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Colesevelam

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concurrent use of an oral contraceptive containing ethinyl estradiol/norethindrone and colesevelam was associated with decreased bioavailability of the oral contraceptive. If co-treatment with colesevelam and an oral contraceptive containing ethinyl estradiol/norethindrone is necessary, patients should take the contraceptive at least 4 hours prior to colesevelam[198].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: If concomitant use of colesevelam and an oral contraceptive containing ethinyl estradiol and norethindrone is necessary, patients should usually take the contraceptive at least 4 hours prior to colesevelam[198].
7) Probable Mechanism: reduced absorption of contraceptive by nonspecific binding with colesevelam
8) Literature Reports

a) Concurrent administration of colesevelam in participants receiving an oral contraceptive containing ethinyl estradiol and norethindrone significantly reduced the exposure of the contraceptive. Coadministration of colesevelam 3.75 g with ethinyl estradiol 0.035 mg/norethindrone 1 mg resulted in reductions of 24% in both ethinyl estradiol AUC and Cmax, and a 1% and 20% reduction in norethindrone AUC and Cmax, respectively. When the combination contraceptive was administered 1 hour prior to colesevelam, the AUC and Cmax were changed by -18% and -1%, respectively, for ethinyl estradiol, and by 5% and -3%, respectively, for norethindrone. Administration of the combination contraceptive 4 hours prior to colesevelam, led to a -12% change in ethinyl estradiol AUC, and changes of 6% and 7% in norethindrone AUC and Cmax, respectively [198].

Conivaptan

1) Interaction Effect: increased exposure of CYP3A substrate
2) Summary: Avoid concomitant use of conivaptan (strong CYP3A inhibitor) with drugs eliminated primarily by CYP3A-mediated metabolism, as this may result in increased exposure of the CYP3A substrate. Conivaptan increased the AUC of CYP3A substrates midazolam, simvastatin, and amlodipine. The CYP3A substrate may be initiated no sooner than 1 week after completion of conivaptan therapy[386].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of conivaptan (strong CYP3A inhibitor) with drugs eliminated primarily by CYP3A-mediated metabolism, as this may result in increased exposure of the CYP3A substrate. The CYP3A substrate may be initiated no sooner than 1 week after completion of conivaptan therapy[386].
7) Probable Mechanism: inhibition of CYP3A-mediated substrate metabolism by conivaptan
8) Literature Reports

a) The strong CYP3A inhibitor conivaptan 40 mg/day IV increased the AUC of midazolam, a CYP3A substrate, by approximately 100% with a 1-mg IV dose and by 200% with a 2-mg oral dose [386].

b) Conivaptan 30 mg/day IV tripled the AUC of simvastatin, a CYP3A substrate [386].

c) Conivaptan 40 mg orally twice daily doubled the AUC and half-life of amlodipine, a

CYP3A substrate [386].

Cyclacillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cyclacillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cyclosporine

1) Interaction Effect: an increased risk of cycloSPORINE toxicity (renal dysfunction, cholestasis, paresthesias)
2) Summary: Concurrent use of cycloSPORINE and combination contraceptives has resulted in higher cycloSPORINE concentrations[335] according to several case reports [336][337]. These reports have demonstrated that androgens, estrogens, and progestins increase cycloSPORINE concentrations, probably through reduced hepatic cycloSPORINE metabolism [338][339][336].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When possible, this combination should be avoided. If cycloSPORINE and combination oral contraceptives are used concurrently, cycloSPORINE serum levels and the patients clinical response should be monitored carefully.
7) Probable Mechanism: decreased cycloSPORINE metabolism
8) Literature Reports

a) Concomitant administration of cycloSPORINE and an oral contraceptive doubled plasma cycloSPORINE concentrations compared with baseline in a 32-year-old woman. The oral contraceptive contained levonorgestrel 150 mcg and ethinyl estradiol 30 mcg. The level declined after the preparation was discontinued, but the same sequence occurred on rechallenge [333].

b) Norethindrone was associated with increased cycloSPORINE levels in a 15-year-old female renal transplant patient. The cycloSPORINE level decreased after norethindrone was discontinued [334].

Dabrafenib

1) Interaction Effect: decreased plasma concentrations and loss of efficacy of the hormonal contraceptive
2) Summary: Concomitant use of dabrafenib and hormonal contraceptives could decrease the plasma concentrations of the contraceptives and render them ineffective. Because dabrafenib can cause fetal harm, advise patient to use nonhormonal forms of

contraception during dabrafenib therapy and for 4 weeks after treatment. If concomitant use is unavoidable, monitor for loss of efficacy of the hormones[363].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of dabrafenib and hormonal contraceptives could decrease the plasma concentrations of the contraceptives and render them ineffective. Because dabrafenib can cause fetal harm, advise patient to use nonhormonal forms of contraception during dabrafenib therapy and for 4 weeks after treatment. If concomitant use is unavoidable, monitor for loss of efficacy of the hormones[363].
7) Probable Mechanism: altered metabolism of contraceptives by dabrafenib

Darunavir

1) Interaction Effect: reduced exposure to hormonal contraceptives and reduced hormonal contraceptive efficacy
2) Summary: Coadministration of darunavir/ritonavir with estrogen-based contraceptives led to significantly decreased plasma concentrations of ethinyl estradiol and norethindrone in 1 study[236]. Consider supplementary or non-hormonal contraception options for women of childbearing potential during darunavir therapy, as no data are available to provide guidance on coadministration of darunavir with oral or other hormonal contraceptives [235].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider supplementary or non-hormonal contraception options for women of childbearing potential during darunavir therapy, as no data are available to provide guidance on coadministration of darunavir with oral or other hormonal contraceptives[235].
7) Probable Mechanism: unknown
8) Literature Reports

a) An open-label, randomized, crossover study in 19 healthy, HIV-negative females aged 18 to 43 years (median, 34 years) revealed that coadministration of ethinyl estradiol/norethindrone with darunavir/ritonavir resulted in significantly lower exposure and mean plasma concentrations of ethinyl estradiol and norethindrone. Compared to administration of ethinyl estradiol and norethindrone alone, coadministration with darunavir/ritonavir led to decreases in ethinyl estradiol Cmin, Cmax, and AUC of 62%, 32%, and 44%, respectively. Similarly, norethindrone Cmin, Cmax, and AUC decreased by 30%, 10%, and 14%, respectively. There were no significant changes in darunavir or ritonavir pharmacokinetic parameters [236].

Dehydroepiandrosterone

1) Interaction Effect: increased risk of estrogenic adverse effects
2) Summary: Combining dehydroepiandrosterone (DHEA) with estrogen may result in symptoms of estrogen excess. DHEA has increased endogenous estrogen levels in postmenopausal women[283]. Pre- and post-menopausal women have effective enzymatic systems for the biotransformation of DHEA to C-19 and C-18 sex steroids [283], suggesting that increased estrogen levels may occur in all women regardless of menopausal status.
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dehydroepiandrosterone (DHEA) and estrogen is not recommended. Monitor for symptoms and adverse effects of estrogen excess in those patients who elect to combine therapies. Such symptoms include (but are not limited to) nausea, headache, intolerance to contact lenses, insomnia, chorea, cholasma, colitis, acute breakthrough or withdrawal bleeding, changes in menstrual flow, leukorrhea, and pancreatitis.
7) Probable Mechanism: additive estrogenic effect since dehydroepiandrosterone is enzymatically converted into C-19 and C-18 sex steroids
8) Literature Reports

a) Estrone and estradiol levels increased to two-times the basal value following four weeks of dehydroepiandrosterone (DHEA) 400 milligrams (mg) four times daily for 28 days in six postmenopausal women in a double-blind, placebo-controlled, crossover study. Subjects received DHEA or placebo for 28 days, followed by a 2-week washout period, then crossed over to the other treatment (DHEA or placebo). Estrone increased from 58.7 +/- 11.0 to 167.4 +/- 66.6 picomole/liter (pmol/L) and estradiol increased from 36.7 +/- 3.7 to 121.1 +/- 25.7 pmol/L. This corresponds to a maximal percent change of 214 +/- 67 percent and 181 +/- 29 percent for estrone and estradiol, respectively [282].

Desipramine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical

importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased

clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Dexamethasone

1) Interaction Effect: decreased plasma levels of hormonal contraceptive and prolonged dexamethasone effect
2) Summary: Concomitant use of dexamethasone and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of dexamethasone[176]. Combination contraceptives have altered the pharmacokinetics of hydrocortisone and prednisone, potentially enhancing the therapeutic effect. The half-lives of these steroids increase by 2 to 3 times and their clearance may decrease 2- to 5-fold [291][292][293]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dexamethasone and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of dexamethasone[176]. Combination contraceptives have altered the pharmacokinetics of hydrocortisone and prednisone, potentially enhancing the therapeutic effect [291][292][293].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism; decreased dexamethasone clearance
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Diazepam

1) Interaction Effect: diazepam toxicity (CNS depression, hypotension)
2) Summary: Combination contraceptives may decrease the metabolism of diazepam, alprazolam, triazolam and chlordiazepoxide. Combination contraceptives may increase the effect of diazepam on psychomotor performance[252][253][254]. Therefore, diazepam dosage reduction may be necessary in patients receiving both diazepam and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between diazepam's plasma concentration and its clinical effectiveness has not clearly been established [251].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and diazepam for an increased response to the benzodiazepine.
7) Probable Mechanism: inhibition of oxidative diazepam metabolism by the contraceptive
8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair diazepam clearance and significantly increase the elimination half-life of diazepam. Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of diazepam 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in diazepam clearance or protein binding between the two groups. However, apparent elimination half-life of diazepam was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with diazepam plus contraceptives compared with diazepam alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [251]. Although these results refer only to intravenous

administration of diazepam, it is likely that experience with oral administration of diazepam would be similar since diazepam is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the diazepam/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated diazepam metabolism by the estrogen. This would subsequently reduce the oxidation of diazepam in the liver [251].

Dicloxacillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dicloxacillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Dicumarol

1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Concomitant combination contraceptive and dicumarol therapy may result in diminished or enhanced dicumarol activity. Combination contraceptives may increase Factor VII, IX, X and XII while decreasing Factor III[190][191].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR should be closely monitored with the addition or withdrawal of treatment with combination contraceptives, and should be reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in order to maintain the desired level of anticoagulation.
7) Probable Mechanism: unknown

Donepezil

1) Interaction Effect: reduced seizure threshold
2) Summary: Seizure threshold lowering effects have been associated with donepezil[385]. Use extreme caution when prescribing donepezil with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Seizure threshold lowering effects have been associated with donepezil[385]. Use extreme caution when prescribing donepezil with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic

corticosteroids). Begin treatment with a low initial dose and increase dose gradually.
7) Probable Mechanism: unknown

Dothiepin

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily.

Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Doxepin

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120

mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Doxycycline

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of doxycycline and oral combination contraceptives (OC) may reduce contraceptive efficacy because tetracyclines alter intestinal flora which, in turn, may alter enterohepatic circulation of the contraceptive[204]. In a review of 163 cases of OC failure in reliable pill takers, 23% were attributed to concurrent use of antibiotics; 4% included a concurrent tetracycline [361]. Absence of interaction was shown in a study (N=15) of concurrent use of ethinyl estradiol/etonogestrel vaginal ring contraceptive and doxycycline [355]. A retrospective review (N=356) showed no difference in OC failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines. Failure rate did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to a patient, an additional form of contraception is recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of doxycycline and combination oral contraceptives (OC) may result in decreased contraceptive efficacy. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracyclines, tetracycline and its derivatives may interact with low-dose estrogen contraceptives[202]. Absence of interaction was also shown in a study (N=15) of concurrent use of ethinyl estradiol/etonogestrel vaginal ring combination contraceptive and doxycycline [355]. A retrospective review (N=356) showed no difference in OC failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception is recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) Systemic exposure of ethinyl estradiol/etonogestrel with use of the vaginal ring contraceptive was not affected by concomitant use of doxycycline in a randomized, 2-way crossover study in healthy volunteers (n=15). Following synchronization of menstrual cycles by 21 to 28 days and a 7-day ring-free period, volunteers received the vaginal ring for 21 days with or without doxycycline 200 mg orally on day 1 then, 100 mg daily for 10 days. After a 7-day ring-free washout period, subjects crossed over to the opposite treatment arm. With administration of the vaginal ring alone, the mean AUC of ethinyl estradiol, measured at 24 hours, day 9 to 10, day 10, and day 21, was 0.638 nanograms x hr/mL, 0.538 nanograms x hr/mL, 5.51 nanograms x hr/mL, and 11.2 nanograms x hr/mL, respectively. With administration of the ring plus doxycycline, the mean AUC of ethinyl estradiol was 0.6 nanograms x hr/mL, 0.512 nanograms x hr/mL, 5.35 nanograms x hr/mL, and 10.9 nanograms x hr/mL, respectively. The AUC interaction/control ratio (ring with doxycycline to ring alone) also showed absence of drug interaction. At 24 hours, day 9 to 10, day 10, and day 21, the interaction/control ratio was 0.95, 0.92, 0.95, and 0.95, respectively. The etonogestrel plasma concentrations and interaction/control ratio demonstrated similar findings at all time points [355].

b) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure

rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

c) There was no increased risk of contraceptive failure with concomitant antibiotic use in a study of 34 patients with acne who used oral antibiotics, including tetracycline (n=17) and erythromycin (n=20), concomitantly with low-dose estrogen oral contraceptives for a total period of 71 women-years. The calculated contraceptive failure rate was 1.4 per 100 women-years for the study, which was not significantly different than an accepted and documented contraceptive failure rate of 0.27 per 100 women-years (p=0.17). Of the 34 patients, one became pregnant while using the norethindrone, ethinyl estradiol, and mestranol combination concomitantly with oral tetracycline (12 months duration of use); the patient stated that she did not miss any doses of the contraceptive combination or had any changes in her menstrual cycle. Two other patients reported menstrual irregularities; one reported spotting while using the ethinyl estradiol and ethynodiol diacetate combination concomitantly with terfenadine and minocycline treatment, and another reported heavy cramping while using the norethindrone acetate and ethinyl estradiol combination concomitantly with tetracycline. Although this study determined that there was no increased risk of contraceptive failure with concomitant antibiotic use, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202].

d) The effect of doxycycline on serum levels of estradiol and norethindrone was studied in 24 women taking oral contraceptives. The subjects had been taking an oral contraceptive containing 1 mg norethindrone and 35 mcg ethinyl estradiol for at least 2 months prior to the study. Administration of doxycycline 100 mg daily for 7 days starting on day 14 of the 28-day cycle had no significant effect on the average serum levels of estradiol and norethindrone, however, there was substantial variability. Progesterone levels indicated that ovulation had not occurred in any of these subjects [360]. Although no significant effect was observed in this study, antibiotics may have an effect in patients with unusually low oral contraceptive hormone levels.

e) A study which documented 163 cases of oral contraceptive failure in reliable pill takers found that 23% (37 cases) of these failures were associated with antibiotic use. Of these 163 cases, 6 were attributed to the use of tetracyclines, including doxycycline, minocycline, and lymecycline. The authors recommended a 7-day abstinence period or a barrier method of contraceptive following a course of antibiotics [270].

f) The interaction between oral contraceptives and tetracyclines has been suggested to be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [204].

Efavirenz

1) Interaction Effect: loss of contraceptive efficacy
2) Summary: Coadministered efavirenz may result in increased or reduced serum concentrations of hormonal contraceptives[391]. In healthy women, coadministration of efavirenz and an oral contraceptive (ethinyl estradiol/norgestimate) did not increase ethinyl estradiol exposure; however, exposure to the progestin components (norgestimate and levonorgestrel) was significantly decreased [390]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Contraceptive failure with etonogestrel in patients receiving efavirenz has been reported. A reliable method of barrier contraception is indicated when efavirenz and a hormonal contraceptive are coadministered. Continue adequate contraceptive measures for 12 weeks upon discontinuation of efavirenz [389].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Based on clinical studies, decreased progestin levels may be expected if efavirenz is coadministered with hormonal contraceptives including oral contraceptives, implants, and injections. Advise patients to use a reliable method of barrier contraception when efavirenz and a hormonal contraceptive are coadministered. Continue adequate contraceptive measures for 12 weeks upon discontinuation of efavirenz[389].
7) Probable Mechanism: altered metabolism of the hormonal contraceptive
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to

all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) In a pharmacokinetic study in healthy HIV-negative women (n=28; mean age 26 years), coadministration of efavirenz (600 mg daily) and an oral contraceptive containing ethinyl estradiol (EE) and norgestimate (NGM) resulted in similar exposure for ethinyl estradiol to that seen when given alone; however, exposure to the progestin components (norgestimate and levonorgestrel) was significantly decreased. In this open-label, three-period, four-treatment study, participants received in period 1 (treatment A) Ortho Tri-Cyclen LO(R) (EE 0.025 mg plus NGM 0.18 mg on days 1 to 7 (phase 1); EE 0.025 mg plus NGM 0.215 mg on days 8 to 14 (phase 2); and EE 0.025 mg plus NGM 0.25 mg on days 15 to 21 (phase 3)). This was followed by period 2 (days 29 to 56) where participants with acceptable baseline safety assessments received a full cycle of Ortho-CyClen(R) (EE 0.035 mg plus NGM 0.25 mg (phases 1 to 3; treatment B)). Participants with satisfactory safety assessments began a second cycle of Ortho-CyClen(R) (days 57 to 77; period 3) coadministered with efavirenz 600 mg/day for 14 days (days 57 to 70; treatment C). Ethinyl estradiol pharmacokinetic parameters (Cmax, AUC, and Cmin) were not significantly different when efavirenz was given concurrently. However, norgestimate exposure was significantly decreased in the presence of efavirenz. The adjusted geometric means for Cmax, AUC, and Cmin were reduced by 46% (90% confidence interval (CI), 39% to 52%), 64% (90% CI, 62% to 67%), and 82% (90% CI, 79% to 85%), respectively. Post-hoc analysis also showed similar results with levonorgestrel exposure (adjusted geometric means for Cmax, AUC, and Cmin reduced by 80% to 86% in the presence of efavirenz) [390].

Elagolix

1) Interaction Effect: increased estrogen exposure, reduced progestin efficacy, and reduced elagolix efficacy
2) Summary: Concomitant use of elagolix 200 mg twice daily with an estrogen-containing contraceptive is not recommended as it may increase estrogen exposure and increase the risk of thromboembolic and vascular adverse events. Estrogen-containing contraceptives are also expected to decrease the efficacy of elagolix. Additionally, coadministration of elagolix and progestin-containing oral contraceptives may reduce contraceptive efficacy. In a study, coadministration of a single-dose of a combined oral contraceptive containing ethinyl estradiol and levonorgestrel following administration of elagolix 200 mg twice daily increased the ethinyl estradiol AUC by 2.18-fold and Cmax by 1.36-fold, and decreased the levonorgestrel AUC and Cmax by 27% and 3%, respectively. Progestin-containing intrauterine contraceptive systems have not been studied. Use effective non-hormonal contraception during treatment with elagolix and for 28 days after discontinuing therapy[247].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of elagolix 200 mg twice daily with an estrogen-containing contraceptive is not recommended as it may increase estrogen exposure and increase the risk of thromboembolic and vascular adverse events. Estrogen-containing contraceptives are also expected to decrease the efficacy of elagolix. Additionally, coadministration of elagolix and progestin-containing oral contraceptives may reduce contraceptive efficacy; progestin-containing intrauterine contraceptive systems have not been studied. Use effective non-hormonal contraception during treatment with elagolix and for 28 days after discontinuing therapy[247].
7) Probable Mechanism: unknown
8) Literature Reports

a) Coadministration of a single-dose of combined oral contraceptive (COC) (containing ethinyl estradiol 20 mcg/levonorgestrel 0.1 mg) following administration of elagolix 200 mg twice daily for 15 days in 20 subjects increased the ethinyl estradiol AUC by 2.18-fold and Cmax by 1.36-fold compared to the COC alone. Additionally, levonorgestrel AUC and Cmax were decreased by 27% and 3%, respectively [247].

b) Coadministration of a combined oral contraceptive (COC) (containing ethinyl estradiol 35 mcg/triphasic norgestimate 0.18/0.215/0.25 mg) once daily together with elagolix 150 mg once daily in 21 subjects increased the ethinyl estradiol AUC by 1.3-fold and Cmax by 1.15-fold compared to the COC alone. Additionally, norelgestromin AUC and Cmax were decreased by 15% and 13%, and norgestrel by 8% and 11%, respectively [247].

Elvitegravir

1) Interaction Effect: altered contraceptive effectiveness and risk of side effects
2) Summary: Caution is advised when using elvitegravir as the combination product elvitegravir/cobicistat/emtricitabine/tenofovir in combination with hormonal contraceptives as this has resulted in a rise in norgestimate concentrations and a decrease in ethinyl estradiol concentrations. Increased progestin concentrations may lead to an increased risk for insulin resistance, dyslipidemia, acne, or venous thrombosis. Coadministration with other hormonal contraceptives (ie, patches, rings, injectable contraceptives) has not been studied and thus nonhormonal alternatives may be considered. If concomitant use is indicated, consider the potential risks and benefits, especially in women with additional risk factors for progestin-related adverse events[228].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: In combined use with elvitegravir, as part of the combination product elvitegravir/cobicistat/emtricitabine/tenofovir, norgestimate concentration was increased and ethinyl estradiol concentration was decreased. Increased progestin concentrations may lead to an increased risk for insulin resistance, dyslipidemia, acne, or venous thrombosis. If concomitant use of elvitegravir and a hormonal contraceptive is indicated, consider the potential risks and benefits, especially in women with additional risk factors for these events. Coadministration with other hormonal contraceptives (ie, patches, rings, injectable contraceptives) has not been studied and thus nonhormonal alternatives may be considered[228].
7) Probable Mechanism: unknown
8) Literature Reports

a) Administration of elvitegravir/cobicistat/emtricitabine/tenofovir with ethinyl estradiol and norgestimate resulted in a more than 2-fold increase in AUC, Cmax, and Cmin of norgestimate and a 25% and 44% reduction in ethinyl estradiol AUC and Cmin, respectively [229].

Encorafenib

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Use of encorafenib (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly. Avoid concomitant use. Advise women of reproductive potential to use an effective non-hormonal method of contraception during treatment with encorafenib and for 2 weeks after the final dose[383].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use of encorafenib (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly. Avoid concomitant use. Advise women of reproductive potential to use an effective non-hormonal method of contraception during treatment with encorafenib and for 2 weeks after the final dose[383].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism

Enzalutamide

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of enzalutamide (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness or increase breakthrough bleeding[176]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of enzalutamide [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of enzalutamide (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness or increase breakthrough bleeding. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of enzalutamide[176].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted

etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Eslicarbazepine Acetate

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of a CYP3A4 inducer, such as eslicarbazepine, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure[197]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of eslicarbazepine [197].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a CYP3A4 inducer, such as eslicarbazepine, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of eslicarbazepine[197].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives by eslicarbazepine
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Etravirine

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of a CYP3A4 inducer, such as etravirine, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure[197]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of etravirine [197].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a CYP3A4 inducer, such as etravirine, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of etravirine[197].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives by etravirine
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted

etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Fedratinib

1) Interaction Effect: increased exposure of substrate
2) Summary: Concomitant use of fedratinib (an inhibitor of CYP3A4, CYP2C19, and CYP2D6) with a substrate of CYP3A4, 2C19, or 2D6 may increase substrate concentrations and the risk of adverse reactions of those drugs. In single-dose pharmacokinetic studies, fedratinib increased midazolam (CYP3A4 substrate) AUC by 4-fold, omeprazole (CYP2C19 substrate) AUC by 3-fold, and metoprolol (CYP2D6 substrate) AUC by 2-fold. If coadministration is necessary, monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates[381].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of fedratinib (a CYP3A4, CYP2C19, and CYP2D6 inhibitor) with a substrate of CYP3A4, 2C19, or 2D6 may increase substrate concentrations and the risk of adverse reactions of those drugs. If coadministration is necessary, monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates[381].
7) Probable Mechanism: inhibition of CYP-mediated substrate metabolism by fedratinib
8) Literature Reports

a) Coadministration of a single dose of midazolam 2 mg (CYP3A4 substrate) with fedratinib increased midazolam AUC by 4-fold [381].

b) Coadministration of a single dose of omeprazole 20 mg (CYP2C19 substrate) with fedratinib increased omeprazole AUC by 3-fold [381].

c) Coadministration of a single dose of metoprolol 100 mg (CYP2D6 substrate) with fedratinib increased metoprolol AUC by 2-fold [381].

Fexinidazole

1) Interaction Effect: increased exposure of CYP3A4 substrate
2) Summary: Avoid concomitant use of fexinidazole (a CYP3A4 inhibitor) with CYP3A4 substrates as there is an increased risk for adverse reactions associated with increased concentrations of these drugs[393].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of fexinidazole (a CYP3A4 inhibitor) with CYP3A4 substrates as there is an increased risk for adverse reactions associated with increased concentrations of these drugs[393].
7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by fexinidazole

Fosamprenavir

1) Interaction Effect: altered hormonal levels and an increased risk of liver enzyme elevations
2) Summary: Fosamprenavir is the prodrug of amprenavir. Reduced exposure to amprenavir and altered hormonal levels occurred when combined oral contraceptives (containing ethinyl estradiol/norethindrone) were used concomitantly with amprenavir. Coadministration of ethinyl estradiol/norethindrone and fosamprenavir/ritonavir has resulted in significant decreases in ethinyl estradiol and norethindrone levels and may also result in hepatic transaminase elevations. Therefore, patients receiving oral contraceptives should be instructed to use alternative methods of non-hormonal contraception[332].
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concomitant administration of amprenavir, the active metabolite of fosamprenavir, and oral contraceptives (containing ethinyl estradiol/norethindrone) has resulted in decreased amprenavir concentrations and altered hormonal levels. Additionally, coadministration of fosamprenavir with ritonavir, and oral contraceptives led to altered hormonal levels and may result in hepatic transaminase elevations. Alternative methods of non-hormonal contraception are recommended in patients receiving fosamprenavir with or without ritonavir[332].
7) Probable Mechanism: unknown
8) Literature Reports

a) Concomitant administration of ethinyl estradiol 0.035 mg/norethindrone 0.5 mg once daily for 21 days and fosamprenavir 700 mg/ritonavir 100 mg twice daily for 21 days in 25 patients resulted in decreases (90% confidence interval) of 34% (30% to 37% decrease), 38% (32% to 44% decrease), and 26% (20% to 32% decrease) in norethindrone AUC, Cmax, and Cmin, respectively. The corresponding decreases in ethinyl estradiol were 37% (30% to 42% decrease), 28% (21% to 35% decrease), and

minimal or no change, respectively. No change was noted in amprenavir pharmacokinetics [332].

b) Concomitant administration of ethinyl estradiol 0.035 mg/norethindrone 1 mg for one cycle and amprenavir 1200 mg twice daily for 28 days in 10 patients resulted in a decrease in AUC (90% confidence interval (CI)) by 22% (8% to 35% decrease) and a decrease minimum plasma concentration (Cmin) (90% CI) by 20% (41% decrease to a 8% increase) of amprenavir. No change was noted in the Cmax of amprenavir. No change was noted in the Cmax or AUC of ethinyl estradiol, but the Cmin increased 32% (3% decrease to 79% increase). No change was noted in the Cmax of norethindrone, but the AUC increased 18% (1% to 38% increase) and the Cmin increased 45% (13% to 88% increase) [332].

Fosaprepitant

1) Interaction Effect: reduced efficacy of contraceptives
2) Summary: Concomitant use of aprepitant or fosaprepitant with hormonal contraceptives may result in decreased contraceptive efficacy. Studies have demonstrated a significant decrease in the AUC and minimum concentration of ethinyl estradiol and norethindrone with concomitant administration. Patients should be advised to use an alternative or back-up method of contraception during therapy and for 1 month after the last dose[342].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for reduced efficacy of hormonal contraceptives in patients receiving aprepitant or fosaprepitant, alternative or back-up methods of contraception should be used during treatment and for 1 month after the last dose[342].
7) Probable Mechanism: unknown
8) Literature Reports

a) When oral aprepitant 100 mg was given once daily for 14 days with an oral contraceptive containing ethinyl estradiol 35 mcg and norethindrone 1 mg, the ethinyl estradiol AUC decreased by 43%, and the norethindrone AUC decreased by 8%. In a separate study, a daily dose of a combination contraceptive containing ethinyl estradiol and norethindrone was administered for 21 days. On day 8, oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral dexamethasone 12 mg were administered. On days 9 and 10, oral aprepitant 80 mg/day and dexamethasone 8 mg/day were given. On day 11, oral dexamethasone 8 mg was administered alone. The AUC of ethinyl estradiol decreased 19% and there was no change in the norethindrone AUC on day 10. The minimum concentration of ethinyl estradiol decreased as much as 64% and norethindrone decreased up to 60% during days 9 through 21 [342].

Fosnetupitant

1) Interaction Effect: increased exposure of CYP3A4 substrate
2) Summary: Coadministration of netupitant, a moderate inhibitor of CYP3A4, with a CYP3A4 substrate may increase the plasma concentration of the CYP3A4 substrate. The mean AUC and Cmax of the CYP3A4 substrate erythromycin was increased following the coadministration of netupitant in a pharmacokinetic study. Increases in the AUC of dexamethasone, a CYP3A4 probe substrate, remained for up to 8 days following a single dose of netupitant. The concomitant use of CYP3A4 substrates with netupitant should be avoided for 1 week. If a CYP3A4 substrate must be administered within 1 week of netupitant, consider reducing the dose of the CYP3A4 substrate[304].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of CYP3A4 substrates with netupitant (a moderate inhibitor of CYP3A4) for 1 week. If a CYP3A4 substrate must be administered within 1 week of netupitant, consider reducing the dose of the CYP3A4 substrate[304].
7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by netupitant
8) Literature Reports

a) In one study where the duration of CYP3A4 inhibition was assessed using dexamethasone as a CYP3A4 probe substrate, the mean AUC of dexamethasone increased by 1.6-fold on day 1, 2.4-fold on day 4, 1.5-fold on day 6, and 1.2-fold on day 8 after a single dose of the combination netupitant 300 mg/palonosetron 0.5 mg was coadministered to participants on day 1. The participants had been treated with a dexamethasone regimen of 12 mg on day 1 followed by 8 mg on days 2, 3, 4, 6, 8, and 10 [304].

b) A pharmacokinetic study demonstrated that when erythromycin 500 mg was coadministered with netupitant 300 mg, the mean AUC of erythromycin increased by 56% and the Cmax increased by 92% [304].

Fosphenytoin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of phenytoin and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive[176]. Breakthrough bleeding, spotting, and pregnancy have been reported in women taking phenytoin concurrently with hormonal contraceptives [263]. Oral contraceptives have also been reported to

increase or decrease phenytoin levels [268]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of phenytoin [176]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of phenytoin and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive[176]. Breakthrough bleeding, spotting, and pregnancy have been reported in women taking phenytoin concurrently with hormonal contraceptives [263]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of phenytoin [176].
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, primarily phenobarbital, phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contraception [264]. One study found that the use of phenytoin and/or phenobarbital increased the frequency of pregnancy 25-fold in patients taking oral contraceptives [265]. The benzodiazepines and valproic acid have not been associated with increased failure rates in women receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives may diminish breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may also increase the risk of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended that low doses of estrogen and progestin be given initially in patients receiving an enzyme-inducing anticonvulsant; however, if unplanned pregnancy is a particular concern, a moderate dose formulation (ethinyl estradiol 50 mcg) should be considered. If breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestranol or its equivalent (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be discontinued, but rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Switching to a lower dose oral contraceptive is recommended if enzyme-inducing anticonvulsants are discontinued in women receiving moderate or high-dose contraceptive steroids to reduce the risk of vascular disease [264].

c) Contraception by levonorgestrel subdermal capsules is not reliable in patients on anticonvulsant therapy. In addition to levonorgestrel therapy, 2 patients took phenytoin, 3 took phenytoin plus carbamazepine, 2 used carbamazepine only, 1 used clonazepam, and 1 used phenytoin plus sodium valproate. At 3 to 12 months, the mean plasma levonorgestrel concentration was significantly lower in the 6 patients with epilepsy using phenytoin alone or in combination with other anticonvulsants (203 +/- 128 picograms/milliliter [pg/mL]) than in controls using levonorgestrel implants only (325 +/- 135 pg/mL). Two of the 9 patients with epilepsy became pregnant; 1 was taking phenytoin 250 mg daily and the second phenytoin 400 mg daily and carbamazepine 400 mg daily [266]. A 26-year-old woman receiving phenytoin 300 mg/day became pregnant after 9 months of implant use. It appears that phenytoin, and probably carbamazepine, decrease plasma levonorgestrel concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction [267]. Phenytoin also induces sex hormone binding globulin (SHBG) and thereby decreases the amounts of biologically active levonorgestrel. Levonorgestrel should not be relied upon as the sole means of contraception in patients on anticonvulsants.

Ginseng

1) Interaction Effect: additive estrogenic effects
2) Summary: Case reports suggest estrogen-like activity of ginseng[378][379][380]. The exact type of ginseng (i.e. Panax, Siberian, American, etc) was not reported. Concomitant use of ginseng with conjugated estrogens may result in symptoms of estrogen excess or interference. Avoid concomitant use if possible until further information characterizing

this interaction is available.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Since estrogenic effects have been noted with topical and oral estrogen, either dosage form should be treated with the same caution when coadministered with ginseng. If estrogenic symptoms such as mastalgia and breakthrough menstrual bleeding occur, decreased the ginseng dosage. Because of the apparent estrogen-like effect, avoid ginseng in patients with breast cancer, undiagnosed abnormal genital bleeding, active thrombophlebitis or thromboembolic disorders, or if the woman is pregnant.
7) Probable Mechanism: saponin glycoside constituents of ginseng may stimulate liver RNA and protein synthesis mimicking the effect of ovarian steroids
8) Literature Reports

a) A 72-year-old woman ingested one tablet daily of a Swiss-Austrian geriatric formula which contained 200 mg of ginseng (Geriatric Pharmaton, Bernardgass, Austria). This resulted in vaginal bleeding and what was described as a "moderate estrogen effect" [374].

b) A 70-year-old woman experienced swollen tender breasts with diffuse nodularity after 3 weeks of "regular" ingestion of ginseng powder. The breast symptoms resolved upon discontinuation of the ginseng powder, although a time period is not provided. With two subsequent rechallenges, the symptoms reappeared. Neither dose nor time period were provided in the case report. Serum prolactin levels were measured both during ginseng powder use as well as when the patient was not using the powder; these levels were reported as normal although exact levels were not provided [375].

c) Five women aged 25 to 40 who had been taking ginseng for varying periods reported to their doctor the development of breast symptoms, including nipple enlargement, and an increased sexual responsiveness [376].

d) A 62-year-old woman (14 years post-menopausal) had a vaginal smear exhibiting a strong estrogenic effect with a maturation index of 0/65/35 (parabasal/intermediate/superficial cells) which was attributed to her intake of "Rumanian ginseng in an unspecified dose. The ginseng product was analyzed and was shown not to contain any estrogen, nor was the woman taking any estrogen product. Within 3 weeks of discontinuing the ginseng use, the vaginal smear displayed a maturation index of 9/95/5. Within 2 weeks of ginseng rechallenge, the vaginal smear maturation index was 0/90/10. Throughout periods of ginseng use and abstinence, the serum concentrations of estrone, estradiol, and estriol remained essentially unchanged within the normal range (0.32 nanomoles/liter (nmol/L), 0.03 nmol/L and less than 0.01 nmol/L, respectively). The authors theorize the saponin content of ginseng interacts with estrogen receptor proteins in a manner similar to ovarian steroids [377].

Griseofulvin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Griseofulvin may decrease the effectiveness of hormonal contraceptives and produce contraceptive failure, breakthrough bleeding[176][417][418], or irregular menstruation [417][418]. The mechanism of action is thought to be an enhanced hepatic metabolism of contraceptive steroids by griseofulvin [419][420][421]. Limited data suggest that the effects of this interaction may be more prevalent with combination contraceptives that contain a lower dose of estrogen [420]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation griseofulvin [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Griseofulvin may decrease the effectiveness of hormonal contraceptives and produce contraceptive failure, breakthrough bleeding[176][417][418], or irregular menstruation [417][418]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of griseofulvin [176].
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports

a) A case report described pregnancy occurring in a 25-year-old woman receiving griseofulvin and oral contraceptives concurrently. The woman, who had been taking the oral contraceptive (OC), Triphasil(R), for 4 years with no menstrual irregularities, was treated with ultramicrocrystalline griseofulvin 330 mg twice daily while continuing to use oral contraception. Two month after initiation of griseofulvin, her nails were greatly improved but she reported transient headaches. Two months later, the patient was found to be pregnant. Her last menstrual period had occurred 2 months after initiation of griseofulvin. The patient claimed to have taken her OC regularly and did not take any other medications during this period. It was postulated the pregnancy probably resulted from failure of the oral contraceptive due to an interaction between the oral contraceptive and griseofulvin [419].

b) A case report described oligomenorrhea and irregular menses in a 32-year-old woman receiving concomitant griseofulvin and oral contraceptive therapy with norethindrone 0.5 and 1 mg plus ethinyl estradiol 0.035 mg (Ortho Novum 7/7/7(R)). The woman, who

had two normal pregnancies and subsequent deliveries from 1981 to 1984 and who had been taking the oral contraceptive for the preceding four months with no abnormalities in menstruation, was diagnosed with tinea unguium. She was treated with griseofulvin 250 mg daily for 14 days, then increased to 500 mg daily for the remainder of the 6-month regimen. No other drugs were given. Following griseofulvin therapy initiation, the woman presented with oligomenorrhea and irregular menses. As a result, the patient's gynecologist changed her oral contraceptive to norgestrel 0.5 mg plus ethinyl estradiol 0.05 mg (Ovral-28(R)), providing a 57% increase in the estrogen component. Six months following the oral contraceptive change, the patient reported regular menses with normal menstrual flow [420].

c) The Safety of Medicines in the United Kingdom committee and the Netherlands Centre for Monitoring of Adverse Reactions to Drugs received 22 reports of a possible oral contraceptive (OC) and griseofulvin interaction. Among the 22 women using long-term OC who began receiving griseofulvin 0.5 to 1 g/day, 15 women (mean age, 26 years; range, 17 to 42 years; mean griseofulvin dose, 550 mg/day) reported transient intermenstrual bleeding and 5 women (mean age, 33.4 years; range, 17 to 44 years; mean griseofulvin dose, 880 mg/day) reported amenorrhea in the first and second cycles following griseofulvin initiation. In 7 of the intermenstrual bleeding cases and one of the amenorrhea cases, the women were using OCs with less than 50 mcg estrogen. Of the 20 women reporting menstrual irregularities, 14 women received no other drugs during the time of griseofulvin treatment and 3 women used drugs not known to interfere with OCs (ie, miconazole ointment, grass pollen vaccine, tetanus vaccine). In the 3 remaining patients, details of concurrent drug administration were not reported. In 2 patients with intermenstrual bleeding and 2 with amenorrhea, the original reaction recurred upon rechallenge with griseofulvin. Two unintended pregnancies were also reported among the 22 cases. In one case, the patient had been using a high-dose OC for 15 months and griseofulvin 500 mg/day for 2.5 months. One month after starting griseofulvin, she received a 1-week course of cotrimoxazole and became pregnant in that time period. In the second case, conception occurred when a patient was taking an unspecified OC, griseofulvin, and a combination of sulfonamides [421].

Guar Gum

1) Interaction Effect: reduced contraceptive effectiveness
2) Summary: Women receiving oral contraceptives have been advised to take additional contraceptive precautions during guar gum therapy, due to potential effects on oral contraceptive absorption[201]. Clinical studies evaluating this interaction are lacking.
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Advise patients to use additional contraceptive methods while taking guar gum with oral contraceptives.
7) Probable Mechanism: reduced contraceptive absorption

Hydrocortisone

1) Interaction Effect: prolonged hydrocortisone effect
2) Summary: Combination oral contraceptives have been demonstrated to increase the antiinflammatory effect of hydrocortisone and prednisone. The half-lives of these steroids may increase by 2 to 3 times[456][457][458].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor closely for increased corticosteroid effects and adjust hydrocortisone dose as needed.
7) Probable Mechanism: unknown

Imipramine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150

mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Insulin

1) Interaction Effect: may decrease blood glucose lowering effect of insulin
2) Summary: Concurrent use of estrogens and insulin may decrease the blood glucose lowering effect of insulin. Dose adjustments and increase frequency of glucose monitoring may be required[404][405].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of estrogens and insulin may decrease the blood glucose lowering effect of insulin. Dose adjustments and increase frequency of glucose monitoring may be required[404][405].
7) Probable Mechanism: unknown

Insulin Lispro, Recombinant

1) Interaction Effect: may decrease blood glucose lowering effect of insulin lispro
2) Summary: Concurrent use of estrogens and insulin lispro may decrease the blood glucose lowering effect of insulin lispro. Dose adjustments and increase frequency of glucose monitoring may be required[394][395][396].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of estrogens and insulin lispro may decrease the blood glucose lowering effect of insulin lispro. Dose adjustments and increase frequency of glucose monitoring may be required[394][395][396].
7) Probable Mechanism: unknown

Isotretinoin

1) Interaction Effect: decreased effectiveness of hormonal contraceptives
2) Summary: When coadministered with isotretinoin, pharmacokinetic and pharmacodynamic changes to estrogens and progestins are small but highly variable and unpredictable. Pregnancy has been reported in women who have used combined oral contraceptives, as well as topical/injectable/implantable/insertable hormonal birth control products. Such reports have occurred more frequently in those using a single form of contraception. Micro-dosed progestin-only pills elevate the risk of contraceptive failure during concomitant treatment with isotretinoin. During isotretinoin therapy, female patients of child bearing potential must use 2 forms of contraception simultaneously, one form should include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, or topical/injectable/implantable/insertable hormonal birth control products[367][368][369].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Advise patients to use 2 forms of contraception simultaneously during isotretinoin therapy, unless patient has agreed to absolute abstinence or has had a hysterectomy. One form should include one of the following: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, or topical/injectable/implantable/insertable hormonal birth control products. Micro-dosed progesterone preparations (minipills than do not contain an estrogen) may be inadequate. Counsel patients about contraception and behaviors that increase the risk of pregnancy[367][368][369].
7) Probable Mechanism: unknown
8) Literature Reports

a) Isotretinoin did not interact with oral contraceptives in a study. Nine women taking isotretinoin 0.5 mg/kg for severe pustular acne received oral contraceptives (brand unknown) for at least three months prior to starting isotretinoin therapy. Plasma concentrations of ethinyl estradiol and levonorgestrel in the control cycle and in two cycles after starting isotretinoin were similar as determined by radioimmunoassay [370].

b) Pharmacokinetic and pharmacodynamic changes were inconsistent and relatively small when isotretinoin was given with a combination ethinyl estradiol/norethindrone product. In a single-center, open-label drug interaction study, 26 healthy women completed a study in which they were given ethinyl estradiol/norethindrone oral contraceptive (OC) triphasic tablets (35 micrograms and 0.5/0.75/1 milligrams, respectively) daily. At the start of the third month and after the possibility of pregnancy was ruled out, participants were also given isotretinoin 1 milligrams/kilogram/day in two divided doses to complete 16 to 20 weeks of isotretinoin treatment for severe, recalcitrant nodular acne. Ethinyl estradiol and norethindrone plasma concentrations were slightly reduced (9% and 11%, respectively) during the OC plus isotretinoin phase compared with the OC alone phase; patient variability was high, however. Follicle stimulating hormone concentration declined 44% (p=0.03) when isotretinoin was added to the regimen, again with a high degree of variability; serum progesterone and luteinizing hormone levels were unchanged. No pregnancies were reported [371].

Ivosidenib

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Use of ivosidenib (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly. Advise women of reproductive potential to use an effective non-hormonal method of contraception[329].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use of ivosidenib (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly. Advise women of reproductive potential to use an effective non-hormonal method of contraception[329].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism

Lamotrigine

1) Interaction Effect: decreased lamotrigine plasma concentrations
2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in significant decreases in plasma lamotrigine levels[237]. A sudden change

in a patient's clinical condition and altered plasma levels of lamotrigine may occur with the use, or changes in the use, of oral contraceptives [239][241][240]. There have been reports of decreased lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations following withdrawal of oral contraceptives in women taking lamotrigine. Dosage adjustments may be necessary to maintain clinical response when starting or discontinuing oral contraceptives during lamotrigine therapy [238].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine plasma concentrations during concomitant use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal contraception[237][238].
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that oral contraceptives induce the metabolism of lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contraceptives at study enrollment. They were then allocated in a crossover fashion to receive either placebo or contraceptive (ethinyl estradiol 35 mcg/norgestimate 250 mcg) over 4 periods (21 days of treatment followed by a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose) and urine samples were collected between the evening and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%) after placebo for 21 days compared with oral contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glucuronide/lamotrigine ratio, was decreased by 31% (95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 patients during oral contraceptive therapy while no seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of glucuronidation pathways involved in the metabolism of lamotrigine and ethinyl estradiol [239].

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the patient's clinical condition have been reported. Five patients who were seizure-free (1 with epilepsy, 2 with complex partial seizures, and 2 with absence epilepsy) had decreased lamotrigine serum concentrations after oral contraceptives were initiated. Two other patients, 1 with simple partial seizures and 1 with complex partial seizures, had discontinued their oral contraceptives. Plasma levels of lamotrigine in these 2 patients had increased significantly as well. Oral contraceptives reduce the plasma levels of lamotrigine 41% to 64% (mean, 49%). As a result, seizure control deteriorated when oral contraceptives were added, or side effects occurred when oral contraceptives were discontinued. These effects were independent of whether the oral contraceptives contained desogestrel, ethinyl estradiol, or norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lamotrigine doses in women with epilepsy who use combination contraceptives [240].

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive coadministration. A retrospective study evaluated 52 women, 22 who used oral contraceptives and 30 who did not. The mean lamotrigine dose was 349 mg/day among women taking oral contraceptives and 327 mg/day among those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives and 28 mcmol/L in patients without oral contraceptives (p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine [241].

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (ethinyl estradiol 30 mcg/levonorgestrel 150 mcg) increased the apparent clearance of lamotrigine 300 mg/day by approximately 2-fold with a mean decrease in AUC of 52% and in Cmax of 39%. Trough serum lamotrigine concentrations gradually increased and were approximately 2-fold higher at the end of the week of inactive treatment ("pill-free" week) compared with trough serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in women not taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lamotrigine will be necessary in women taking estrogen-containing oral contraceptives [238].

Lesinurad

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Coadministration of lesinurad and hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may result in decreased effectiveness of the contraceptive. Additional methods of contraception are recommended[326].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of lesinurad and hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may result in decreased effectiveness of the contraceptive. Additional methods of contraception are recommended[326].

7) Probable Mechanism: interference with metabolism of hormonal contraceptive by lesinurad

Levothyroxine

1) Interaction Effect: decrease in serum-free thyroxine concentration
2) Summary: Estrogens, including those in oral combined hormonal contraceptives and in hormone-replacement therapy, may raise serum concentrations of thyroxine-binding globulin, necessitating an increase in the dose of replacement thyroid hormone therapy[249][272][273].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Estrogens, including those in oral combined hormonal contraceptives and in hormone-replacement therapy, may raise serum concentrations of thyroxine-binding globulin, necessitating an increase in the dose of replacement thyroid hormone therapy[249][272][273].
7) Probable Mechanism: estrogen-induced increases in serum thyroxine-binding globulin concentration
8) Literature Reports

a) Women with hypothyroidism who are treated with thyroxine, who then receive estrogen, may experience a decrease in the concentration of serum-free thyroxine, thereby increasing serum thyrotropin concentrations and increasing the need for thyroxine. Thirty-six women were evaluated for the effects of estrogen administration on pituitary-thyroid function. Twenty-five of these women were receiving thyroxine therapy for chronic hypothyroidism, 18 of these patients received thyroid replacement therapy and 7 received thyroxine for thyrotropin suppression for thyroid cancer. In women with normal thyroid function, serum-free thyroxine and thyrotropin concentrations did not change. The mean serum thyroxine concentration increased 30% and serum thyroxine-binding globulin level increased 54%. In women with hypothyroidism, the serum-free thyroxine concentration decreased 18% and the serum thyrotropin concentration increased 256%. Thyrotropin levels increased to greater than 7 mcU/mL in seven women receiving thyroid replacement therapy and to greater than 1mcU/mL in three women in the thyrotropin-suppression group, necessitating increases in thyroxine doses [274].

Licorice

1) Interaction Effect: increased risk of fluid retention and elevated blood pressure
2) Summary: Elevated blood pressure and fluid retention has been associated with concomitant use of licorice and oral contraceptives in case reports[350][351], which may be related to estrogen and/or progesterone. The glycyrrhetinic acid component of licorice is metabolized to 3-monoglucuronyl-glycyrrhetinic acid (3MGA), which inhibits 11-beta-hydroxysteroid dehydrogenase and reduces cortisol breakdown, resulting in a hypermineralocorticoid effect [352][353].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution is advised if licorice is taken with estrogen. If the patient develops fluid retention and increased blood pressure, discontinue licorice.
7) Probable Mechanism: increased mineralocorticoid effect
8) Literature Reports

a) A 21-year-old female developed headache and hypertension (190/120 mmHg), associated with licorice consumption (100 grams daily) along with an oral contraceptive. She was advised to discontinue eating licorice. Blood pressure remained elevated with treatment combining atenolol, lisinopril, hydrochlorothiazide, and amlodipine. Drug treatment was discontinued, and 2 weeks later blood pressure was 180/110 mmHg, potassium 2.6 mmol/L (normal 3.8 to 5.0 mmol/L), bicarbonate 35.9 mmol/L (normal 23 to 29 mmol/L). Plasma aldosterone was 160 picomoles/liter (pmol/L) (normal 320 to 2000 pmol/L). The patient then admitted to replacing her licorice intake with two packets of Stimerolol Sugar Free(R) chewing gum per day. This chewing gum contains 585 mg licorice in each 15 gram packet, which equals 8% to 12% glycyrrhizinic acid. Her glycyrrhizinic acid intake was calculated to be 120 mg daily. Within 3 weeks of discontinuing the gum, her blood pressure and potassium level normalized [348].

b) A 35-year-old woman taking an oral contraceptive and chlorothiazide experienced hypokalemia (2.2 mmol/L). Her blood pressure was 140/80 mmHg. Chlorothiazide was stopped and potassium chloride 600 mg three times daily was started. After one week, potassium remained abnormal at 2.0 mmol/L, after 2 weeks it decreased further to 1.5 mmol/L. Intravenous potassium supplementation was started. Although she denied licorice use, it was discovered that she used BenBits Cool Mint(R) chewing gum (Leaf, United Kingdom), 3 packets daily. This product contained 160 mg licorice in each 16 gram packet, of which 10% was glycyrrhizinic acid. After 2 days of intravenous potassium and 15 days of oral potassium, and within 3 weeks of discontinuing the chewing gum, edema disappeared, blood pressure decreased to 110/80 mmHg and potassium increased to 4.2 mmol/L. The authors attributed the hypokalemia to the licorice intake [348].

c) In a study of 4 groups of 6 healthy volunteers administered varying doses of licorice root, the group administered 814 mg of glycyrrhizin experienced a decrease in serum

potassium from 4.25 millimoles/liter (mmol/L) to 3.53 mmol/L (p equals 0.014) after one week. Two of the subjects were taking oral contraceptives concomitantly; all others were taking no other medications. One of the subjects taking an oral contraceptive developed headache, peripheral edema, borderline arterial hypertension (144/91 mmHg), and hypokalemia (2.6 mmol/L) and discontinued treatment. Kaliuresis was noted as well, though not statistically significant. After one week, plasma renin activity significantly decreased in groups taking 380 mg and 814 mg glycyrrhizin (p equals 0.025 and p equals 0.045, respectively). Plasma aldosterone decreased significantly in the group taking 814 mg glycyrrhizin (p equals 0.04). This indicates that volume expansion occurred; however, renal sodium retention was not found to be significant [349].

Lixisenatide

1) Interaction Effect: decreased absorption of oral contraceptives
2) Summary: Concomitant use of lixisenatide with oral contraceptives may decrease absorption of the oral contraceptive. When a single dose of the oral contraceptive, ethinylestradiol/levonorgestrel was administered 1 hour after lixisenatide, ethinylestradiol and levonorgestrel Cmax decreased by approximately half; however, when a single dose of ethinylestradiol/levonorgestrel was administered either 1 hour before or 11 hours after lixisenatide, the Cmax and other absorption parameters of ethinylestradiol and levonorgestrel were not affected. If these agents are coadministered, instruct patients to take oral contraceptives at least 1 hour before lixisenatide or at least 11 hours after lixisenatide administration[384].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lixisenatide with oral contraceptives may result in decreased absorption of the oral contraceptive. If these agents are coadministered, instruct patients to take oral contraceptives at least 1 hour before lixisenatide or at least 11 hours after lixisenatide administration[384].
7) Probable Mechanism: delayed gastric emptying
8) Literature Reports

a) In a drug interaction study, administration of a single dose of the oral contraceptive, ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg one hour or 4 hours after lixisenatide 10 mcg decreased ethinylestradiol Cmax by 52% and 39%, respectively, and levonorgestrel Cmax by 46% and 20%, respectively. The median Tmax of the oral contraceptive was also delayed by 1 to 3 hours. However, the overall exposure (AUC) and mean t(1/2) of ethinylestradiol and levonorgestrel were not affected. When a single dose of ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg was administered either 1 hour before or 11 hours after lixisenatide 10 mcg, the Cmax, AUC, t(1/2), and Tmax of ethinylestradiol and levonorgestrel did not change [384].

Lofepramine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving

only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Lomitapide

1) Interaction Effect: increased exposure of lomitapide
2) Summary: The concomitant use of lomitapide (a CYP3A4 substrate) with oral contraceptives (weak CYP3A4 inhibitors) may cause increased exposure to lomitapide. When the combined oral contraceptive ethinylestradiol/norgestimate was coadministered with lomitapide, the systemic exposure of lomitapide increased by 30%. If concurrent use is required, the maximum lomitapide dosage is 40 mg daily. When initiating an oral contraceptive in a patient already taking lomitapide 10 mg/day or more, decrease the lomitapide dose by 50%. Then carefully titrate based on response and tolerability to a maximum of 40 mg daily[275].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of lomitapide (a CYP3A4 substrate) with oral contraceptives (weak CYP3A4 inhibitors) may cause increased exposure to lomitapide. If concurrent use is required, the maximum lomitapide dosage is 40 mg daily. When initiating an oral contraceptive in a patient already taking lomitapide 10 mg/day or more, decrease the lomitapide dose by 50%. Then carefully titrate based on response and tolerability to a maximum of 40 mg daily[275].
7) Probable Mechanism: inhibition of CYP3A4-mediated lomitapide metabolism
8) Literature Reports

a) The concomitant administration of the combined oral contraceptive, ethinylestradiol 0.035 mg and norgestimate 0.25 mg daily, with a single 20-mg dose of lomitapide was shown to increase the AUC of lomitapide by 30% and Cmax by 40% compared with lomitapide administered alone [275].

Lonapegsomatropin-tcgd

1) Interaction Effect: reduced lonapegsomatropin-tcgd efficacy
2) Summary: Oral estrogens may reduce the serum insulin-like growth factor-1 (IGF-1) response to lonapegsomatropin-tcgd. Patients receiving oral estrogen replacement may require higher lonapegsomatropin-tcgd dosages[312].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients receiving oral estrogen replacement may require higher lonapegsomatropin-tcgd dosages. Oral estrogens may reduce the serum insulin-like growth factor-1 (IGF-1) response to lonapegsomatropin-tcgd.[312].
7) Probable Mechanism: an unknown mechanism

Lorazepam

1) Interaction Effect: decreased lorazepam effectiveness
2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of lorazepam[412][413][414]. Women taking combination contraceptives may require a higher dose of lorazepam [415].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and lorazepam therapy for a reduced response to the benzodiazepine.
7) Probable Mechanism: increased hepatic metabolism of lorazepam
8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of lorazepam, which undergoes glucuronide conjugation [407][408]. In seven healthy women receiving oral contraceptives containing norethindrone 1 mg and ethinyl estradiol 50 mcg for at least six months, the administration of intravenous lorazepam 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of lorazepam. The total clearance of lorazepam was increased 3.7-fold as compared with that of eight healthy control females [409].

b) The half-life resulting from intravenous lorazepam 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [410].

c) Another report indicates that the metabolic clearance of lorazepam (and oxazepam) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [411]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

Lorlatinib

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of a CYP3A4 inducer, such as lorlatinib, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure[197]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of lorlatinib [197].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a CYP3A4 inducer, such as lorlatinib, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of lorlatinib[197].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives by lorlatinib
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not

significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Lumacaftor

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Concomitant use of lumacaftor/ivacaftor with hormonal contraceptives increased menstrual abnormality events and may decrease the exposure of the hormonal contraceptive; lumacaftor is a strong CYP3A inducer. Avoid concomitant use unless the potential benefit outweighs the potential risk, and do not rely on a hormonal contraceptive alone as an effective method of contraception[432]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of a CYP3A inducer [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lumacaftor/ivacaftor with hormonal contraceptives increased menstrual abnormality events and may decrease the exposure of the hormonal contraceptive. Avoid concomitant use unless the potential benefit outweighs the potential risk, and do not rely on a hormonal contraceptive alone as an effective method of contraception[432]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of a CYP3A inducer [176].
7) Probable Mechanism: induction of CYP3A-mediated metabolism by lumacaftor
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Mavacamten

1) Interaction Effect: decreased exposure of hormonal contraceptive
2) Summary: Concomitant administration of mavacamten, a CYP3A4 inducer, and progestin and/or ethinyl estradiol, CYP3A4 substrates, may decrease exposures of progestin and ethinyl estradiol, which may lead to contraceptive failure or an increase in breakthrough bleeding. Patients should use a contraceptive method that is not affected by CYP450 enzyme induction (eg, intrauterine system) or add nonhormonal contraception (eg, condoms) during treatment with mavacamten and for 4 months after the last mavacamten dose[246].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant administration of mavacamten, a CYP3A4 inducer, and progestin and/or ethinyl estradiol, CYP3A4 substrates, may decrease exposures of progestin and ethinyl estradiol, which may lead to contraceptive failure or an increase in breakthrough bleeding. Patients should use a contraceptive method that is not affected by CYP450 enzyme induction (eg, intrauterine system) or add nonhormonal contraception (eg, condoms) during treatment with mavacamten and for 4 months after the last mavacamten dose[246].
7) Probable Mechanism: induction of CYP3A4 mediated metabolism of hormonal contraceptive by mavacamten
8) Literature Reports

a) Concomitant use of a 16-day course of the CYP3A4 inducer mavacamten (25 mg on days 1 and 2, followed by 15 mg for 14 days) with midazolam, a CYP3A4 substrate, resulted in a 13% decrease in midazolam AUC(inf) and a 7% decrease in Cmax, in healthy CYP2C19 normal metabolizers. Following coadministration of mavacamten once daily in patients with hypertrophic cardiomyopathy, midazolam AUC(inf) is predicted to decrease by 21% to 64% and Cmax is predicted to decrease by 13% to 48%, depending on the dose of mavacamten and CYP2C19 phenotype [246].

Minocycline

1) Interaction Effect: decreased contraceptive efficacy
2) Summary: Concomitant use of minocycline and combination oral contraceptives (OC) may result in decreased OC efficacy[277] Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracyclines, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202]. In a retrospective chart review, there was no significant difference in OC failure rates among women who received OC with or without antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% [183]. Despite these findings, minocycline-related changes in plasma levels of estradiol, progestinic hormone, follicle stimulating hormone, and luteinizing hormone, breakthrough bleeding, and contraceptive failure were not ruled out based on the results of a multicenter study. Thus, if concomitant use is required, an additional form of birth control during therapy is recommended [277].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of minocycline and oral combination contraceptives (OC) may result in decreased contraceptive efficacy[277]. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracyclines, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202]. Evidence from a large retrospective chart review showed there was no significant difference in OC failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183]; additionally, it is recommended to advise patients to use an additional form of birth control during concomitant treatment with minocycline and combination contraceptives [277].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) In a multicenter study, hormone levels over 1 menstrual cycle were evaluated in women administered low-dose contraceptives concomitantly with minocycline hydrochloride extended-release formulation (1 mg/kg once daily) and in those who received low-dose contraceptives alone. Minocycline-related changes in plasma levels of estradiol, progestinic hormone, follicle stimulating hormone, and luteinizing hormone, as well as breakthrough bleeding and contraceptive failure cannot be ruled out based on the results of this study. Therefore, women are advised to use an additional form of birth control during concomitant treatment with minocycline [277].

b) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

c) There was no increased risk of contraceptive failure with concomitant antibiotic use in a study of 34 patients with acne who used oral antibiotics, including tetracycline (n=17) and erythromycin (n=20), concomitantly with low estrogen oral contraceptives for a total period of 71 women-years.. The calculated contraceptive failure rate was 1.4 per 100 women-years for the study, which was not significantly different than an accepted and documented contraceptive failure rate of 0.27 per 100 women-years (p=0.17). Of the 34 patients, one became pregnant while using the norethindrone, ethinyl estradiol, and mestranol combination concomitantly with oral tetracycline (12 months duration of use). The patient stated that she did not miss any doses of the contraceptive combination or had any changes in her menstrual cycle. Two other patients reported menstrual irregularities; one reported spotting while using the ethinyl estradiol and ethynodiol diacetate combination concomitantly with terfenadine and minocycline treatment, and another reported heavy cramping while using the norethindrone acetate and ethinyl estradiol combination concomitantly with tetracycline. Although this study determined that there was no increased risk of contraceptive failure with concomitant antibiotic use, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202].

d) In a retrospective cohort study using chart reviews and surveys, the oral contraceptive failure rate for combined use with oral antibiotics was 1.6 pregnancies per 100 woman-years of exposure, compared with a failure rate of 0.96 in the control group. Five pregnancies resulted in the antibiotic-exposed group, and all of these women had been using oral contraceptives for at least 6 months at the time of pregnancy and had been taking antibiotics for at least 3 months. Three of the five pregnancies occurred in women taking minocycline, while the other two pregnancies occurred in women receiving a cephalosporin [278].

e) The interaction between oral contraceptives and tetracycline has been suggested to be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [204].

f) During a four-year period documenting 163 cases of contraceptive failure in reliable pill takers, 37 cases of pill failures (23%) were attributed to the concomitant use of antibiotics. Tetracyclines, including minocycline, were featured in 6 of these 37 cases [279].

Mitapivat

1) Interaction Effect: decreased hormonal contraceptive exposure
2) Summary: Coadministration of mitapivat (CYP3A inducer) and a sensitive CYP3A substrate, such as hormonal contraceptives, decreases the exposure of hormonal contraceptives. If coadministration is required, use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment[280].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of mitapivat (CYP3A inducer) and a sensitive CYP3A substrate, such as hormonal contraceptives, decreases the exposure of hormonal contraceptives. If coadministration is required, use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment[280].
7) Probable Mechanism: induction of CYP3A-mediated metabolism by mitapivat

Mitotane

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of mitotane (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness or increase breakthrough bleeding[176]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of mitotane [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of mitotane (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness or increase breakthrough bleeding. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of mitotane[176].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Mobocertinib

1) Interaction Effect: decreased plasma concentrations of the hormonal contraceptive, which may result in reduced contraceptive efficacy
2) Summary: Coadministration of mobocertinib with hormonal contraceptives may decrease plasma concentrations of the contraceptive, which may lead to reduced

contraceptive efficacy. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with mobocertinib and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with mobocertinib and for 1 week after the last dose of mobocertinib[343].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of mobocertinib with hormonal contraceptives may decrease plasma concentrations of the contraceptive, which may lead to reduced contraceptive efficacy. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with mobocertinib and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with mobocertinib and for 1 week after the last dose of mobocertinib[343].
7) Probable Mechanism: induction of the metabolism of the hormonal contraceptive by mobocertinib

Modafinil

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Use of modafinil (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly and for 1 month after discontinuation of modafinil[234]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptives and for 1 month after discontinuation of modafinil treatment [234].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use of modafinil (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly and for 1 month after discontinuation of modafinil. Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptives and for 1 month after discontinuation of modafinil treatment[234].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Mycophenolate Mofetil

1) Interaction Effect: decreased contraceptive exposure and effectiveness
2) Summary: Coadministration of mycophenolate mofetil with combined oral contraceptives resulted in a significant decrease in exposure to levonorgestrel. Decreased exposure could result in reduced effectiveness of the combination contraceptive. Use additional barrier contraceptive methods when coadministration is required[431].
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of combination oral contraceptives and mycophenolate mofetil may decrease exposure to the progestin component and result in reduced oral contraceptive effectiveness. Use additional barrier contraceptive methods when coadministration is required[431].
7) Probable Mechanism: unknown
8) Literature Reports

a) .In a study involving 18 women with psoriasis, coadministration of mycophenolate mofetil (1 g twice daily) and combined oral contraceptives containing ethinyl estradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg and 0.2 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.1 mg) over 3 consecutive menstrual cycles resulted in a significant decrease in levonorgestrel AUC by approximately 15%. The mean AUC was similar for ethinyl estradiol and 3-keto desogestrel. There was large interpatient

variability (%CV in the range of 60% to 70%) in the data, especially for ethinyl estradiol. The mean serum levels of luteinizing hormone, follicle-stimulating hormone, and progesterone were not significantly affected [431].

Mycophenolic Acid

1) Interaction Effect: decreased contraceptive efficacy
2) Summary: Concomitant use of mycophenolic acid or mycophenolic sodium and oral contraceptives may result in reduced oral contraceptive effectiveness. In a drug interaction study, mean levonorgestrel AUC was decreased by 15% when coadministered with mycophenolic mofetil, the prodrug of mycophenolic acid. Use of additional barrier contraceptive methods is required when coadministered with hormonal contraceptives (such as birth control pills, transdermal patch, vaginal ring, injection, and implant)[426].
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of mycophenolic acid or mycophenolic sodium and oral contraceptives may result in reduced oral contraceptive effectiveness. Use of additional barrier contraceptive methods is required when coadministered with hormonal contraceptives (such as birth control pills, transdermal patch, vaginal ring, injection, and implant)[426].
7) Probable Mechanism: unknown
8) Literature Reports

a) In a study involving 18 women with psoriasis, coadministration of mycophenolate mofetil (1 g twice daily), the prodrug of mycophenolic acid, and combined oral contraceptives containing ethinyl estradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg and 0.02 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.1 mg) resulted in a significant decrease in levonorgestrel AUC by approximately 15%. The mean AUC was similar for ethinyl estradiol and 3-keto desogestrel. There was a large interpatient variability (%CV in the range of 60% to 70%) in the data, especially for ethinyl estradiol. The mean serum levels of luteinizing hormone, follicle-stimulating hormone, and progesterone were not significantly affected [427].

Nafcillin

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as nafcillin, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased efficacy or an increase in breakthrough bleeding[249][250]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of nafcillin [249] [250].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as nafcillin, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased efficacy or an increase in breakthrough bleeding. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of nafcillin[249][250].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism by nafcillin
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Nelfinavir

1) Interaction Effect: contraceptive failure
2) Summary: Coadministration of protease inhibitors, such as nelfinavir, and combination contraceptives may cause significant changes (increase and decrease) in the mean AUC of the estrogen and progestin[310]. Coadministered nelfinavir may decrease serum concentrations of contraceptives, which could cause a reduction in their effectiveness.

Patients should be instructed to use alternate or additional contraceptive measures when taking nelfinavir [311].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving concurrent combination oral contraceptives and nelfinavir should be counseled to use alternative or additional contraceptive measures.
7) Probable Mechanism: increased estrogen and progestin metabolism
8) Literature Reports

a) Nelfinavir 750 mg every eight hours for seven days has been shown to decrease the AUC of norethindrone (0.4 mg daily for 15 days) by 18%. When ethinyl estradiol 35 mcg daily for 15 days was administered to 12 patients on the same nelfinavir regimen, the AUC and Cmax of ethinyl estradiol were decreased by 47% and 28%, respectively [309].

Netupitant

1) Interaction Effect: increased exposure of CYP3A4 substrate
2) Summary: Coadministration of netupitant, a moderate inhibitor of CYP3A4, with a CYP3A4 substrate may increase the plasma concentration of the CYP3A4 substrate. The mean AUC and Cmax of the CYP3A4 substrate erythromycin was increased following the coadministration of netupitant in a pharmacokinetic study. Increases in the AUC of dexamethasone, a CYP3A4 probe substrate, remained for up to 8 days following a single dose of netupitant. The concomitant use of CYP3A4 substrates with netupitant should be avoided for 1 week. If a CYP3A4 substrate must be administered within 1 week of netupitant, consider reducing the dose of the CYP3A4 substrate[304].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of CYP3A4 substrates with netupitant (a moderate inhibitor of CYP3A4) for 1 week. If a CYP3A4 substrate must be administered within 1 week of netupitant, consider reducing the dose of the CYP3A4 substrate[304].
7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by netupitant
8) Literature Reports

a) In one study where the duration of CYP3A4 inhibition was assessed using dexamethasone as a CYP3A4 probe substrate, the mean AUC of dexamethasone increased by 1.6-fold on day 1, 2.4-fold on day 4, 1.5-fold on day 6, and 1.2-fold on day 8 after a single dose of the combination netupitant 300 mg/palonosetron 0.5 mg was coadministered to participants on day 1. The participants had been treated with a dexamethasone regimen of 12 mg on day 1 followed by 8 mg on days 2, 3, 4, 6, 8, and 10 [304].

b) A pharmacokinetic study demonstrated that when erythromycin 500 mg was coadministered with netupitant 300 mg, the mean AUC of erythromycin increased by 56% and the Cmax increased by 92% [304].

Nevirapine

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as nevirapine, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased contraceptive efficacy or an increase in breakthrough bleeding[249][250].Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of nevirapine [249][250].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as nevirapine, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased contraceptive efficacy or an increase in breakthrough bleeding. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of nevirapine[249][250].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism by nevirapine
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were

administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Nortriptyline

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless,

and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Octreotide

1) Interaction Effect: decreased bioavailability and decreased efficacy of combined oral contraceptives or increased breakthrough bleeding
2) Summary: Concomitant use of octreotide and combined oral contraceptives (COCs) may decrease bioavailability and decrease efficacy of COCs or increase breakthrough bleeding. In a single-dose study, coadministration of levonorgestrel 0.3 mg and octreotide 40 mg orally significantly decreased levonorgestrel AUC and Cmax by 24% and 38%, respectively; coadministration of ethinyl estradiol 0.06 mg and octreotide 40 mg orally did not significantly change ethinyl estradiol AUC or Cmax. If concomitant use is required, an alternative non-hormonal method of contraception or a back-up method should be used[406].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of octreotide and combined oral contraceptives (COCs) may decrease bioavailability and decrease efficacy of COCs or increase breakthrough bleeding. If concomitant use is required, an alternative non-hormonal method of contraception or a back-up method should be used[406].
7) Probable Mechanism: unknown
8) Literature Reports

a) In a single-dose study, coadministration of levonorgestrel 0.3 mg and octreotide 40 mg orally significantly decreased levonorgestrel AUC by 24% (mean ratio, 0.76; 90% CI, 0.67 to 0.86) and Cmax by 38% (mean ratio, 0.62; 90% CI, 0.54 to 0.71). Coadministration of ethinyl estradiol 0.06 mg and octreotide 40 mg orally did not significantly change ethinyl estradiol AUC (mean ratio, 0.94; 90% CI, 0.86 to 1.03) or Cmax (mean ratio, 0.92; 90% CI, 0.83 to 1.01) [406].

Oxacillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of oxacillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183]
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years

or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) A case of potential oral contraceptive failure was reported in an 18-year-old female receiving concurrent oxacillin (500 mg every 6 hours for six weeks) and a combination oral contraceptive agent (norethindrone 1 mg/0.035 mg estradiol) [398].

Oxcarbazepine

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of oxcarbazepine (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and may diminish effectiveness. In 2 studies, oxcarbazepine decreased the AUC of ethinyl estradiol by 48% and 52% and of levonorgestrel by 32% and 52%[455][176]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration [455] and for at least 28 days after discontinuation of oxcarbazepine [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of oxcarbazepine (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and may diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration[455][176] and for at least 28 days after discontinuation of oxcarbazepine [176].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Coadministration of oxcarbazepine with an oral contraceptive containing ethinyl estradiol and levonorgestrel has resulted in an mean decrease in AUC of ethinyl estradiol by 48% and 52% and of levonorgestrel by 32% and 52% in 2 studies [455].

b) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Oxytetracycline

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of oxytetracycline and oral combination contraceptives (OC) may reduce contraceptive efficacy. The mechanism of interaction is thought that tetracyclines may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives[204]. Isolated cases of contraceptive failure with oxytetracycline have been reported [206]. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracycline, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202]. In a large retrospective chart review, there was no significant difference in OC failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of oxytetracycline and oral combination contraceptives (OC) may result in decreased contraceptive efficacy. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracyclines, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives[202]. Evidence

from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) There was no increased risk of contraceptive failure with concomitant antibiotic use in a study of 34 patients with acne who used oral antibiotics, including tetracycline (n=17) and erythromycin (n=20), concomitantly with low estrogen oral contraceptives for a total period of 71 women-years.. The calculated contraceptive failure rate was 1.4 per 100 women-years for the study, which was not significantly different than an accepted and documented contraceptive failure rate of 0.27 per 100 women-years (p=0.17). Of the 34 patients, one became pregnant while using the norethindrone, ethinyl estradiol, and mestranol combination concomitantly with oral tetracycline (12 months duration of use); the patient stated that she did not miss any doses of the contraceptive combination or had any changes in her menstrual cycle. Two other patients reported menstrual irregularities; one reported spotting while using the ethinyl estradiol and ethynodiol diacetate combination concomitantly with terfenadine and minocycline treatment, and another reported heavy cramping while using the norethindrone acetate and ethinyl estradiol combination concomitantly with tetracycline. Although this study determined that there was no increased risk of contraceptive failure with concomitant antibiotic use, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202].

c) In a study of 24 women taking the oral contraceptive Ortho-Novum 1/35, serum concentrations of ethinyl estradiol, norethindrone, and endogenous progesterone measured on days 18 to 20 of the menstrual cycle were not significantly different on the same days the following cycle during which doxycycline 100 mg twice daily was coadministered [203].

d) The interaction between oral contraceptives and tetracyclines has been suggested to be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [204].

e) A 20-year-old woman taking an oral contraceptive containing ethinyl estradiol 30 mcg and D-norgestrol 150 mcg became pregnant after receiving tetracycline 500 mg every 6 hours for 3 days followed by 250 mg every 6 hours for 2 days [205].

Penicillin G

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of penicillin G and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral

contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Penicillin G Procaine

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of penicillin G and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Penicillin V

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins;

and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of penicillin V and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Phenobarbital

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as phenobarbital, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased contraceptive efficacy or an increase in breakthrough bleeding[249][250]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of phenobarbital [249][250].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as phenobarbital, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased contraceptive efficacy or an increase in breakthrough bleeding. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of phenobarbital[249][250].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism by phenobarbital
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Phenylbutazone

1) Interaction Effect: reduced contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with drugs that increase the metabolism of contraceptive steroids,

such as phenylbutazone. This could result in unintended pregnancy or breakthrough bleeding[341].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with medications, such as phenylbutazone, that increase the metabolism of contraceptive steroids.
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports

a) No alterations were found in phenylbutazone serum concentrations when a single-dose of phenylbutazone was coadministered with low-estrogen combination contraceptives. Seven volunteers using oral contraceptives containing norethindrone 1 mg plus ethinyl estradiol 30 mcg received one dose of phenylbutazone 400 mg. Phenylbutazone serum levels were not affected (the same study reported that oral contraceptives lowered aspirin concentrations) [340]. Although phenylbutazone has been demonstrated to interact with oral contraceptives in animal studies, no interaction has been reported in humans.

Phenytoin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of phenytoin and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive[176]. Breakthrough bleeding, spotting, and pregnancy have been reported in women taking phenytoin concurrently with hormonal contraceptives [263]. Oral contraceptives have also been reported to increase or decrease phenytoin levels [268]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of phenytoin [176]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of phenytoin and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive[176]. Breakthrough bleeding, spotting, and pregnancy have been reported in women taking phenytoin concurrently with hormonal contraceptives [263]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of phenytoin [176].
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, primarily phenobarbital, phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contraception [264]. One study found that the use of phenytoin and/or phenobarbital increased the frequency of pregnancy 25-fold in patients taking oral contraceptives [265]. The benzodiazepines and valproic acid have not been associated with increased failure rates in women receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives may diminish breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may also increase the risk of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended that low doses of estrogen and progestin be given initially in patients receiving an enzyme-inducing anticonvulsant; however, if unplanned pregnancy is a particular concern, a moderate dose formulation (ethinyl estradiol 50 mcg) should be considered. If breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestranol or its equivalent (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be discontinued, but rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Switching to a lower dose oral contraceptive is recommended if enzyme-inducing

anticonvulsants are discontinued in women receiving moderate or high-dose contraceptive steroids to reduce the risk of vascular disease [264].

c) Contraception by levonorgestrel subdermal capsules is not reliable in patients on anticonvulsant therapy. In addition to levonorgestrel therapy, 2 patients took phenytoin, 3 took phenytoin plus carbamazepine, 2 used carbamazepine only, 1 used clonazepam, and 1 used phenytoin plus sodium valproate. At 3 to 12 months, the mean plasma levonorgestrel concentration was significantly lower in the 6 patients with epilepsy using phenytoin alone or in combination with other anticonvulsants (203 +/- 128 picograms/milliliter [pg/mL]) than in controls using levonorgestrel implants only (325 +/- 135 pg/mL). Two of the 9 patients with epilepsy became pregnant; 1 was taking phenytoin 250 mg daily and the second phenytoin 400 mg daily and carbamazepine 400 mg daily [266]. A 26-year-old woman receiving phenytoin 300 mg/day became pregnant after 9 months of implant use. It appears that phenytoin, and probably carbamazepine, decrease plasma levonorgestrel concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction [267]. Phenytoin also induces sex hormone binding globulin (SHBG) and thereby decreases the amounts of biologically active levonorgestrel. Levonorgestrel should not be relied upon as the sole means of contraception in patients on anticonvulsants.

Pitolisant

1) Interaction Effect: reduced effectiveness of hormonal contraceptive
2) Summary: Avoid concomitant use of pitolisant with oral contraceptives, as pitolisant may reduce the effectiveness of hormonal contraceptives. Women of childbearing potential should use an alternative method of non-hormonal contraception during treatment and for at least 21 days after discontinuation[365].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of pitolisant with oral contraceptives, as pitolisant may reduce the effectiveness of hormonal contraceptives. Women of childbearing potential should use an alternative method of non-hormonal contraception during treatment and for at least 21 days after discontinuation[365].
7) Probable Mechanism: induction of contraceptive metabolism

Pixantrone

1) Interaction Effect: increased exposure of CYP1A2 substrates
2) Summary: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[399].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[399].
7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism by pixantrone

Prednisolone

1) Interaction Effect: an increased risk of corticosteroid side effects (neuropsychiatric reactions, fluid and electrolyte disturbances, hypertension, hyperglycemia)
2) Summary: Combination contraceptives may decrease prednisoLONE clearance significantly[470][471][472][473].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor closely for increased corticosteroid effects and adjust prednisoLONE dose as required.
7) Probable Mechanism: may decrease hepatic metabolism
8) Literature Reports

a) Chronic contraceptive and steroid use results in a marked decrease in prednisoLONE clearance. Six females using chronic oral contraceptives received prednisoLONE 0.53 (high dose) and 0.14 mg/kg (low dose) intravenously. Six females (controls) received only prednisoLONE. A significant decrease in clearance occurred for each of the prednisoLONE doses in women receiving oral contraceptives as compared with the control values (p less than 0.01). There is a significant decrease in unbound prednisoLONE clearance for women taking oral contraceptives compared with 0 control subjects at both doses (p less than 0.01). The results presented in this study demonstrate that an approximate 3.5-fold increase in prednisoLONE dose resulted in an increase, observed in each subject, in clearance by a factor of 1.96 +/- 0.52 for the control subjects and by a factor of 1.44 +/- 0.33 for the oral contraceptives group. Dose-dependent prednisoLONE kinetics and marked decreases in prednisoLONE clearance in women taking oral contraceptives results from concomitant synthetic estrogen dosing. Women taking oral contraceptives who are currently undergoing prednisoLONE therapy should be monitored carefully. The author expects lower doses of prednisoLONE to yield clinical efficacy in these patients [468].

b) The clearance of free prednisoLONE is reduced in women taking oral contraceptives compared to women who do not. The study evaluated eight female subjects who used

oral combination contraceptives and eight female control subjects who did not. Each subject received prednisoLONE phosphate equivalent to 0.1 mg/kg intravenous of prednisoLONE and 1.0 mg/kg of prednisoLONE. Free prednisoLONE clearance was reduced approximately 30% in oral contraceptive users compared with control subjects (p less than 0.001). Pre-dose plasma cortisol concentrations were elevated two-fold (p less than 0.001) in oral contraceptive users compared with control subjects. The authors conclude that inhibition of prednisoLONE clearance by cortisol may be the mechanism for circadian variations in free prednisoLONE clearance. This mechanism could contribute the inhibition of prednisoLONE clearance by oral contraceptives. This study demonstrated that there is a reduction in the dose dependency of free prednisoLONE clearance in oral contraceptive users compared to control subjects [469].

Prednisone

1) Interaction Effect: decreased plasma levels of hormonal contraceptive; increased risk of corticosteroid side effects (neuropsychiatric reactions, fluid and electrolyte disturbances, hypertension, hyperglycemia)
2) Summary: Concomitant use of predniSONE and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness[176].Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of predniSONE [176]. Hormonal contraceptives have been demonstrated to alter the pharmacokinetics of hydrocortisone and predniSONE, thereby potentially enhancing therapeutic effect [255]. The half-lives of these steroids increase by 2 to 3 times and their clearance may decrease by 2- to 5-fold [258][259][260]. Combination oral contraceptives may also decrease prednisolone clearance by 20% to 80% [261][262].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of predniSONE and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of predniSONE[176]. Hormonal contraceptives have also altered the pharmacokinetics of hydrocortisone and predniSONE, potentially enhancing therapeutic effect [255].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism; decreased predniSONE metabolism
8) Literature Reports

a) Concomitant oral contraceptive and prednisolone therapy can result in reduced corticosteroid elimination [256][257]. In a study by [256], the plasma clearance of prednisolone was decreased by approximately 50% with a corresponding rise in the AUC for free prednisolone. It is not known if this effect is due to the estrogen component alone. Studies using progestogen oral contraceptives have not been performed.

b) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Primidone

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as primidone, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased efficacy or an increase in breakthrough bleeding[249][250]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of primidone [249][250].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a hormonal contraceptive with a CYP3A

inducer, such as primidone, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased efficacy or an increase in breakthrough bleeding. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of primidone[249][250].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism by primidone
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Protriptyline

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Red Clover

1) Interaction Effect: altered estrogenic effects or increased side effects
2) Summary: Red clover isoflavones have affinity for estradiol-alpha and -beta receptors and may act as both agonists and antagonists[300][301]. Red clover may enhance the estrogenic effects of estrogens [302][303].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if red clover is taken with estrogens. Monitor the patient for symptoms of estrogen excess or loss of efficacy.
7) Probable Mechanism: red clover extract may act as an estrogen agonist or antagonist, and may have antiprogestin effects

Rifabutin

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Coadministered rifabutin may induce hormonal contraceptive metabolism, resulting in reduced contraceptive efficacy[195]. During an crossover study, rifabutin altered the disposition of an oral contraceptive and resulted in a higher incidence of spotting compared with controls [196]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of rifabutin [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of rifabutin and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of rifabutin[176].
7) Probable Mechanism: induction of CYP450-mediated hormonal contraceptive metabolism by rifabutin
8) Literature Reports

a) In 22 healthy women maintained on hormonal combination contraceptives (ethinyl estradiol/norethindrone), the administration of rifabutin resulted in a decrease of AUC and Cmax of both contraceptive components [192].

b) An open-label, randomized, three-way crossover study of healthy females (n=28) was undertaken to determine the impact of concomitant rifabutin and rifampin therapy on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norethindrone (Ortho-Novum 1/35(R)). Twenty-two women completed all three phases of the study. All women received the oral contraceptive for 21 days for the first cycle, which served as the control. They were then randomized to one of two sequences to receive concomitant rifampin or rifabutin 300 mg daily for 10 days. When evaluating the

pharmacokinetics of ethinyl estradiol, women receiving rifabutin had a decreased Cmax (333.4 picograms (pg)/mL vs. 416.1 pg/mL) and a decreased AUC (2192.6 pg/hr/mL vs. 3362 pg/hr/mL) when compared with controls. Similarly, the Cmax of norethindrone was 15.37 nanograms (ng)/mL in the rifabutin group and 22.61 ng/mL in control, and the AUC of norethindrone was 86.19 ng/hr/mL during the rifabutin phase and 159.09 ng/hr/mL during control. The incidence of spotting was 3.7% during the control cycle and increased to 21.7% during rifabutin therapy. However, there was no clear evidence of ovulation in this study [193].

c) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

d) The effects of rifampin and rifabutin on an oral contraceptive were examined in a randomized, 2-period, crossover trial involving 12 females. All subjects were on a stable contraceptive regimen that contained ethinyl estradiol 35 mcg and norethindrone 1 mg (Ortho-Novum(R) 1/35). Each participant was randomized to receive 14 days of therapy with rifampin 600 mg daily or rifabutin 300 mg daily on days 7 through 21 of their menstrual cycle. Rifabutin decreased the mean trough ethinyl estradiol concentration (Cmin) by 50%, but the mean Cmax was not significant. Mean norethindrone Cmin values decreased by 32%, while Cmax did not significantly change. Luteinizing hormone and follicle stimulating hormone levels were not statistically altered by rifabutin. All subjects remained anovulatory after rifabutin therapy as indicated by undetectable progesterone levels [194].

Rifampin

1) Interaction Effect: decreased plasma levels of hormonal contraceptive
2) Summary: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with drugs that increase the metabolism of contraceptive steroids, such as rifampin. This could result in unintended pregnancy or breakthrough bleeding[448][227].Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Rifampin may alter intestinal flora, which alters the enterohepatic circulation of oral contraceptives. Concomitant use has been associated with unintended pregnancies and menstrual changes [449]. An alternative method of contraception should be used [450] during coadministration and for at least 28 days after discontinuation of rifampin [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of rifampin and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of rifampin[176].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) An open-label, randomized, three-way crossover study was conducted on 28 healthy females to determine the impact of concomitant rifabutin and rifampin therapy on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norethindrone

(Ortho-Novum 1/35(R)). Twenty-two women completed all three phases of the study. All women received the oral contraceptive for 21 days for the first cycle, which served as the control. They were then randomized to one of two sequences to receive concomitant rifampin or rifabutin 300 mg daily for 10 days. When evaluating the pharmacokinetics of ethinyl estradiol, women receiving rifampin had a decreased Cmax (243.1 picograms (pg)/mL vs. 416.1 pg/mL) and a decreased AUC (1220.7 pg/hr/mL vs. 3362 pg/hr/mL) when compared with controls. Similarly, the Cmax of norethindrone was 16.5 nanograms (ng)/mL in the rifampin group and 22.61 ng/mL in control, and the AUC of norethindrone was 65.08 ng/hr/mL during the rifampin phase and 159.09 ng/hr/mL during control. The incidence of spotting was 3.7% during the control cycle and increased to 36.4% during rifampin therapy. However, there was no clear evidence of ovulation in this study [446].

c) The effects of rifampin and rifabutin on an oral contraceptive were examined in a randomized, 2-period crossover trial involving 12 females. All subjects were on a stable contraceptive regimen that contained ethinyl estradiol 35 mcg and norethindrone 1 mg (Ortho-Novum(R) 1/35). Each participant was randomized to receive 14 days of therapy with rifampin 600 mg daily or rifabutin 300 mg daily on days 7 through 21 of their menstrual cycle. Rifampin decreased the mean trough ethinyl estradiol concentration (Cmin) by 79% and decreased the mean Cmax by 43%. Mean norethindrone Cmin values decreased by 89%, while Cmax did not significantly change. Luteinizing hormone levels were not statistically altered by rifampin, while follicle stimulating hormone values increased by 69%. Despite these profound pharmacokinetic alterations, all subjects remained anovulatory after rifampin therapy as indicated by undetectable progesterone levels [447].

Rifapentine

1) Interaction Effect: loss of hormonal contraceptive efficacy
2) Summary: Systemic concentrations of the estrogen or progestin component of a combination hormonal contraceptive may be reduced with concomitant use of a metabolic enzyme inducer of CYP3A[249] such as rifapentine, and thus reduce the effectiveness of hormonal contraceptives. Changing to non-hormonal methods of birth control is advised in patients using oral, transdermal patch, or other systemic hormonal contraceptives [435]. Continue back-up contraception for 28 days after discontinuing the enzyme inducer to maintain contraceptive reliability [249]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Systemic concentrations of the estrogen or progestin component of a combination hormonal contraceptive may be reduced with concomitant use of a metabolic enzyme inducer of CYP3A[249] such as rifapentine, and thus reduce the effectiveness of hormonal contraceptives. Changing to non-hormonal methods of birth control is advised in patients using oral, transdermal patch, or other systemic hormonal contraceptives [435]. Continue back-up contraception for 28 days after discontinuing the enzyme inducer to maintain contraceptive reliability [249].
7) Probable Mechanism: induction of metabolism of hormonal contraceptives
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Ritonavir

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of ritonavir and combination hormonal contraceptives may decrease efficacy of the contraceptive. The AUC of a single 50 mcg dose of ethinyl estradiol declined by 40% on average when given concomitantly with ritonavir 500 mg twice daily. Cmax of ethinyl estradiol also decreased by 32%[187]. In a study, the AUC of ethinyl estradiol decreased from 1670 pg/mL/hr to 993 pg/mL/hr when coadministered with ritonavir [188]. If concomitant use is necessary, alternate methods of contraception should be considered [187].
3) Severity: major
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Concomitant use of ritonavir and combination hormonal contraceptives may decrease efficacy of the contraceptive. Alternative methods of contraception should be considered[187].
7) Probable Mechanism: decreased plasma ethinyl estradiol levels
8) Literature Reports

a) Twenty-three female study participants received a single oral dose of an oral contraceptive containing ethinyl estradiol 50 mcg and ethynodiol diacetate 1 mg on study days 1 and 29. From days 15 through 30, ritonavir was administered twice daily. Cmax of ethinyl estradiol was 104 picograms (pg)/mL when administered alone, and decreased to 70.7 pg/mL in the presence of ritonavir. Likewise, the AUC of ethinyl estradiol decreased from 1670 pg/mL/hr to 993 pg/mL/hr when coadministered with ritonavir. These results are consistent with an increase in ethinyl estradiol clearance from hepatic enzyme induction of glucuronidation and/or cytochrome P450 hydroxylation caused by ritonavir [188].

b) Ritonavir is an inhibitor of CYP3A4, which is involved in the metabolism of both estrogens and levonorgestrel. As such, inhibition of metabolism may result in increase plasma concentrations of estrogen and/or levonorgestrel and risk of related side effects [189].

c) The AUC of a single 50 mcg dose of ethinyl estradiol declined by 40% on average when given concomitantly with ritonavir 500 mg twice daily. Cmax of ethinyl estradiol also decreased by 32% [187].

Rufinamide

1) Interaction Effect: reduced efficacy of combination contraceptives
2) Summary: Concomitant use of rufinamide with hormonal contraceptives may result in decreased contraceptive efficacy. One study demonstrated a decrease in the AUC and Cmax of ethinyl estradiol and norethindrone when rufinamide was administered concurrently. Patients should be advised to use an alternative or backup method of contraception during rufinamide therapy[474] and for 28 days after discontinuation of rufinamide [250].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for reduced efficacy of hormonal contraceptives in patients receiving rufinamide, alternative or backup methods of contraception should be used during treatment with rufinamide[474] and for 28 days after discontinuation of rufinamide [250].
7) Probable Mechanism: unknown
8) Literature Reports

a) When oral rufinamide 800 mg was given twice daily for 14 days with an oral contraceptive containing ethinyl estradiol 35 mcg and norethindrone 1 mg, the mean ethinyl estradiol AUC and Cmax decreased by 22% and 18%, respectively, and the mean norethindrone AUC and Cmax decreased by 14% and 18%, respectively [474].

Secobarbital

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant combination contraceptive and chronic barbiturate therapy may lead to an increased metabolism of contraceptive steroids, thus decreasing their effectiveness as a contraceptive[451][452][453]. This may result in unintended pregnancy or breakthrough bleeding [454].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients taking secobarbital chronically should use alternative methods of birth control along with the hormonal contraceptive.
7) Probable Mechanism: induction of estrogen metabolism

Selegiline

1) Interaction Effect: an increase in selegiline oral bioavailability and an increased risk of selegiline adverse reactions
2) Summary: During a randomized study to determine the dose relationship of selegiline and its main metabolite, desmethylselegiline, female subjects who were receiving oral contraceptives had a Cmax and AUC that was 10- to 20-fold higher than subjects not receiving oral contraceptives. The marked elevation in the bioavailability of selegiline may result in a loss of selective inhibition of monoamine oxidase (MAO) type B, which would predispose the patient to hypertensive reactions after the intake of amines[328].
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concomitant use of selegiline and a combination contraceptive should be avoided. Alternately, the selegiline dose should be reduced to minimize the risks of selegiline adverse effects, including hypertensive reactions.
7) Probable Mechanism: inhibition of selegiline first-pass metabolism to desmethylselegiline
8) Literature Reports

a) Eight healthy females, four using oral contraceptives, entered an open, four-period randomized study to characterize the dose relationship of selegiline and desmethylselegiline pharmacokinetics. Subjects ingested a single dose of 5 mg, 10 mg, 20 mg, or 40 mg of selegiline, with a washout period of at least two weeks between treatment phases. Although researchers were not looking for differences in the pharmacokinetics of selegiline between oral contraceptive users and non-users, there was a 20-fold increase in selegiline AUC in oral contraceptive users as compared with non-users. The median Cmax was more than 10 times higher in the group taking oral steroids. Desmethylselegiline AUC values were also higher in contraceptive users, although the increase was smaller in magnitude and did not reach statistical significance. The difference in the metabolic ratio between the two groups suggests that oral contraceptives inhibit the N-demethylation of selegiline to desmethylselegiline. The increase in selegiline bioavailability in oral contraceptive users may lead to loss of selective inhibition of monoamine oxidase type B, predisposing the patient to hypertensive reactions [327].

Somapacitan-beco

1) Interaction Effect: decreased somapacitan-beco efficacy
2) Summary: Treatment with somapacitan-beco and oral estrogens may decrease the serum IGF-1 response to somapacitan-beco. Patients receiving oral estrogen replacement may require higher somapacitan-beco dosages. If coadministration with oral estrogens is required, increase initial dose to somapacitan-beco 2 mg subQ once weekly[207].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Treatment with somapacitan-beco and oral estrogens may decrease the serum IGF-1 response to somapacitan-beco. Patients receiving oral estrogen replacement may require higher somapacitan-beco dosages. If coadministration with oral estrogens is required, increase initial dose to somapacitan-beco 2 mg subQ once weekly[207].
7) Probable Mechanism: decreased serum IGF-1 response to somapacitan-beco

Somatropin

1) Interaction Effect: decreased somatropin efficacy
2) Summary: Treatment with somatropin and oral estrogens may decrease the serum IGF-1 response to somatropin. Patients receiving oral estrogen may require higher somatropin dosages[366].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Treatment with somatropin and oral estrogens may decrease the serum IGF-1 response to somatropin. Patients receiving oral estrogen may require higher somatropin dosages[366].
7) Probable Mechanism: decreased serum IGF-1 response to somatropin

St John's Wort

1) Interaction Effect: decrease in estrogen plasma concentrations and in contraceptive effectiveness
2) Summary: Pregnancy and breakthrough bleeding have been reported when St. John's wort was taken concurrently with hormonal contraceptives[217][218][219][220][221]. St. John's wort significantly increased the metabolism of norethindrone in a clinical trial [222], likely through induction of CYP3A4 and p-glycoprotein metabolism [223][224] [225]. The effect of St. John's wort on transdermal and injectable contraceptives is unknown, though caution is advised [226].Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use an alternate nonhormonal contraceptive method [227] during coadministration and for at least 28 days after discontinuation of St. John's wort [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of St. John's wort and hormonal contraceptives may decrease plasma concentrations of the contraceptive and diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of St. John's wort[176].
7) Probable Mechanism: induction of CYP3A4-mediated hormone metabolism and induction of intestinal P-glycoprotein drug transporter by St. John's wort
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of

total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) In a systematic review of studies of pharmacokinetic interactions involving St John's Wort, concomitant use with ethinyl estradiol in 4 studies resulted in no change in ethinyl estradiol AUC with products containing hyperforin dosages of 0.4 mg/day, and a decrease in ethinyl estradiol AUC of 10% to 34% with hyperforin dosages of 2.4 to 33 mg/day [210].

c) In a systematic review of studies of pharmacokinetic interactions involving St John's Wort, concomitant use with norethindrone in 2 studies resulted in a 11% to 12% decrease in norethindrone AUC with products containing hyperforin dosages of 27 to 33 mg/day [210].

d) In a systematic review of studies of pharmacokinetic interactions involving St John's Wort, concomitant use with desogestrel in 2 studies resulted in a 42% decrease in the AUC of ketodesogestrel, the active desogestrel metabolite with products containing hyperforin dosages of 4.8 to 7.5 mg/day and no change in AUC with 0.4 mg/day [210].

e) There have been 8 reports of breakthrough bleeding and 1 case of changed menstrual bleeding by women 23 to 31 years of age who were taking St. John's wort and oral contraceptives. Most of the women had been taking oral contraceptives for a long time. The time between coadministration of St. John's wort and onset of problems was approximately 1 week for most patients. Induction of CYP3A4, which metabolizes steroids, is suggested to be the cause [211].

f) Three case reports detail women taking ethinyloestradiol and desogestrel combination contraceptives who experienced breakthrough bleeding while taking hypericum. The author cites the possible mechanism of this interaction as a CYP3A4 induction by St. John's wort, causing increased metabolism and consequent lowering of ethinyloestradiol concentrations [212].

g) St. John's wort caused breakthrough bleeding in 7 of 12 women taking oral contraceptives. Twelve healthy female subjects received a combination oral contraceptive (ethinyl estradiol/norethindrone) for three months. During months 2 and 3, St. John's wort 300 mg was administered 3 times daily. Follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, ethinyl estradiol, and norethindrone concentrations as well as CYP3A enzyme activity were assessed in months 1 and 3. FSH, LH and progesterone concentrations on days 11 through 16 were not altered by St. John's wort. St. John's wort significantly increased the oral clearance of norethindrone from 8.2 to 9.5 L/hr . Seven of 12 subjects experienced breakthrough bleeding during month 3, compared with 2 of twelve in month 1. The authors conclude that long-term St. John's wort administration alters the efficacy and disposition of combination oral contraceptives due to the ability of St. John's wort to induce intestinal wall CYP3A [213].

h) Two women experienced unintended pregnancy within 5 months of starting St. John's wort. Both had used oral contraceptives for more than 8 years [214].

i) A 36-year-old female experienced an unplanned pregnancy associated with the concomitant use of St. John's wort and an oral hormonal contraceptive (ethinyl estradiol/dienogest (Valette(R))). She had self-medicated with St. John's wort extract (Helarium(R) 425, Bionorica) up to 1700 mg daily for approximately 3 months before conception. She was on no other medications [215].

j) Seven reports of pregnancy have been received by the United Kingdom since February 2000 associated with concomitant use of St. John's wort and oral contraceptives [216].

Succinylcholine

1) Interaction Effect: prolongation of neuromuscular blockade
2) Summary: The chronic use of oral contraceptives has been reported to reduced plasma cholinesterase activity by approximately 20%[387]. Plasma cholinesterase rapidly hydrolyzes succinylcholine to succinylmonocholine, which possesses insignificant muscle relaxant properties. By reducing the activity of plasma cholinesterase, the neuromuscular blocking effect of succinylcholine may be enhanced [388]. The enhanced response to succinylcholine may be more pronounced in patients who have a pathologically depressed cholinesterase activity.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients receiving chronic combination contraceptive therapy should be monitored for prolongation of neuromuscular blockade when administered succinylcholine. The enhanced response to succinylcholine may be more pronounced in patients who have a pathologically depressed cholinesterase activity.
7) Probable Mechanism: inhibition of plasma cholinesterase activity

Sugammadex

1) Interaction Effect: decreased contraceptive serum concentration and efficacy
2) Summary: Concomitant use of sugammadex and hormonal contraceptives may result in decreased contraceptive serum concentrations and efficacy due to binding of progestogen by sugammadex. An additional, nonhormonal contraceptive method or backup method of contraception (such as condoms and spermicides) is recommended for 7 days after sugammadex administration in patients who are on non-oral hormonal contraceptives or in patients who took an oral contraceptive on the same day as the sugammadex administration[248].
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of sugammadex and hormonal contraceptives may result in decreased contraceptive serum concentrations and efficacy due to binding of progestogen by sugammadex. An additional, nonhormonal contraceptive method or backup method of contraception (such as condoms and spermicides) is recommended for 7 days after sugammadex administration in patients who are on non-oral hormonal contraceptives or in patients who took an oral contraceptive on the same day as the sugammadex administration[248].
7) Probable Mechanism: binding of progestogen by sugammadex

Sultamicillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183]. Another study showed concurrent ampicillin administration did not to diminish the effectiveness of the oral contraceptive studied [184].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ampicillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) In a study of 11 regularly menstruating women, ages 21 to 39, concurrent ampicillin administration appeared not to diminish the effectiveness of the oral contraceptive studied. Demulen(R) (1 mg ethynodiol diacetate and 50 mcg ethinyl estradiol) was given to each subject for 2 consecutive menstrual cycles, 21 days on and 7 days off. Ampicillin 250 mg or placebo was given 4 times/day from day 1 through day 16 of each study cycle. Two subjects experienced breakthrough bleeding while taking ampicillin. One subject reported spotting with Demulen(R)/placebo combination, but not with Demulen(R)/ampicillin. There was no difference in quantity of menstrual flow between the two study cycles. One subject reported mid-cycle abdominal pain while on Demulen(R)/ampicillin. All cycles appeared to be anovulatory with no significant difference in follicle-stimulating hormone, luteinizing hormone, and steroid hormone

levels in patients on Demulen(R)/ampicillin compared with patients on Demulen(R)/placebo [184].

Tacrine

1) Interaction Effect: an increased risk of tacrine adverse effects
2) Summary: Hormone replacement therapy (HRT) with estradiol valerate and levonorgestrel significantly increased tacrine concentrations in ten healthy female volunteers. HRT reduces the metabolic conversion of tacrine to its main metabolite, 1-hydroxytacrine, by inhibiting cytochrome P450 1A2 enzymes during the first-pass phase, which may increase the likelihood of enhanced tacrine efficacy and adverse effects[430].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for enhanced tacrine adverse effects during long-term treatment in conjunction with estradiol. Smaller doses of tacrine may be appropriate.
7) Probable Mechanism: inhibition of cytochrome P450 1A2-mediated conversion of tacrine to 1-hydroxytacrine
8) Literature Reports

a) Ten healthy female volunteers participated in a randomized, double-blind crossover study which evaluated the effects of hormone replacement therapy (HRT) on the pharmacokinetics of tacrine. Each subject received HRT with estradiol valerate 2 mg and levonorgestrel 0.25 mg or matching placebo once daily for ten days. One hour after the last dose of HRT on day 10, a single dose of tacrine 40 mg was administered. HRT increased the area under the concentration-time curve (AUC) of tacrine by 60% and increased the mean maximum concentration (Cmax) by 46%. The mean apparent oral clearance of tacrine was reduced by 31% in the presence of HRT. No significant pharmacokinetic effects were seen on 1-hydroxytacrine during the HRT phase, indicating that HRT reduces the 1-hdyroxylation of tacrine by cytochrome P450 1A2. While this drug interaction may enhance the efficacy of tacrine in the treatment of Alzheimer's disease, the incidence and severity of adverse effects may also increase, which could contribute to decreased patient compliance [429].

Tazemetostat

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of tazemetostat and with CYP3A substrates, including hormonal contraceptives, may result in decreased concentrations and reduced efficacy of CYP3A substrates. Coadministration of tazemetostat with midazolam (a sensitive CYP3A substrate) decreased midazolam AUC by 40% and Cmax by 21%. Tazemetostat may render some hormonal contraceptives ineffective. Advise females of reproductive potential using tazemetostat to use effective non-hormonal contraception during treatment and for 6 months after the final dose[362].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of tazemetostat with CYP3A substrates, including hormonal contraceptives, may result in decreased concentrations and reduced efficacy of CYP3A substrates. Tazemetostat may render some hormonal contraceptives ineffective. Advise females of reproductive potential using tazemetostat to use effective non-hormonal contraception during treatment and for 6 months after the final dose[362].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of tazemetostat 800 mg twice daily with oral midazolam (a sensitive CYP3A substrate) in patients decreased midazolam AUC(0 to12) by 40% and Cmax by 21% [362].

Telaprevir

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Administration of telaprevir with ethinyl estradiol may significantly decrease plasma concentrations of ethinyl estradiol. Norethindrone concentrations were minimally effected. In a drug interaction study, concurrent administration of ethinyl estradiol and telaprevir led to significant decreases in ethinyl estradiol Cmax, AUC, and Cmin[306]. During concurrent use of telaprevir and combination contraceptives, 2 effective non-hormonal forms of birth control should be used throughout telaprevir therapy and until approximately 2 weeks following the discontinuation of telaprevir, at which time hormonal contraceptives may be used as 1 of the 2 contraceptive measures required during ribavirin and peginterferon alfa therapy; however, specific contraceptive prescribing guidelines should be followed. Patients who are using estrogens as hormone replacement therapy should be monitored for signs of estrogen deficiency [305].
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Administration of telaprevir with ethinyl estradiol may significantly decrease plasma concentrations of ethinyl estradiol. During concurrent use of telaprevir and combination contraceptives, 2 effective non-hormonal forms of birth control should be used throughout telaprevir therapy and until approximately 2 weeks following the discontinuation of telaprevir, at which time hormonal contraceptives may be

used as 1 of the 2 contraceptive measures required during ribavirin and peginterferon alfa therapy; however, specific contraceptive prescribing guidelines should be followed. Patients who are using estrogens as hormone replacement therapy should be monitored for signs of estrogen deficiency[305].
7) Probable Mechanism: unknown
8) Literature Reports

a) In a pharmacokinetic study (n=24), the concomitant administration of telaprevir 750 mg every 8 hours with an oral contraceptive containing ethinyl estradiol 0.035 mg and norethindrone 0.5 mg daily resulted in a 26% to 33% reduction in ethinyl estradiol exposure. Female volunteers 18 and 45 years old who were taking ethinyl estradiol 0.035 mg/norethindrone 0.5 mg for at least 3 months were enrolled. During the study, study participants received this combination contraceptive regimen for 21 days followed by a 7-day washout period, then ethinyl estradiol 0.035 mg/norethindrone 0.05 mg plus telaprevir for 21 days followed by telaprevir alone for 7 days. The mean Cmax, AUC at steady state, and Cmin for ethinyl estradiol decreased by 26%, 28% and 33%, respectively, after the administration of telaprevir. The least-squares mean ratios for ethinyl estradiol were all outside the no-effect boundaries of 0.8 to 1.25 (0.74 (90% confidence interval (CI); 0.68 to 0.80), 0.67 (90% CI; 0.63 to 0.71), and 0.72 (90% CI 0.69 to 0.75) for Cmax, Cmin, and AUC at steady state, respectively). Norethindrone and telaprevir exposures were found not to be significantly affected by the coadministration of both agents [306].

b) In 2 drug interaction studies (n=23 and n=24), administration of telaprevir 750 mg every 8 hours for 21 days concurrently with ethinyl estradiol 0.035 mg and norethindrone 0.5 mg daily for 21 days did not significantly change norethindrone concentrations. The norethindrone ratio estimate (norethindrone with telaprevir to norethindrone without) was 1 (90% confidence interval (CI), 0.93 to 1.07) for Cmax, 0.99 (90% CI, 0.93 to 1.05) for AUC and 1 (90% CI, 0.93 to 1.08) for Cmin for one study (n=23). In the second study (n=24), the ratio estimates were 0.85 (90% CI, 0.81 to 0.89), 0.89 (90% CI, 0.86 to 0.93), and 0.94 (0.87 to 1), respectively [305].

Temazepam

1) Interaction Effect: decreased temazepam effectiveness
2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of temazepam[296] and increase the clearance of temazepam [294]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and temazepam for a reduced response to the benzodiazepine should be considered.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of temazepam and combination oral contraceptives may increase temazepam clearance[294]. Consider monitoring patients receiving concurrent combination contraceptives and temazepam for a reduced response to temazepam.
7) Probable Mechanism: increased temazepam clearance
8) Literature Reports

a) Concomitant oral contraceptive and temazepam therapy has been reported to alter the metabolism of temazepam. In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of temazepam following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of temazepam may be less effective in women using oral contraceptives [295].

Tetracycline

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of tetracycline and combination oral contraceptives may result in decreased contraceptive efficacy[269]. The mechanism of interaction is thought that tetracyclines may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives [204]. Although there was no increased risk of contraceptive failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracycline, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202]. In a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of tetracycline and combination oral contraceptives may result in decreased contraceptive efficacy[269]; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3%

contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) There was no increased risk of contraceptive failure with concomitant antibiotic use in a study of 34 patients with acne who used oral antibiotics, including tetracycline (n=17) and erythromycin (n=20), concomitantly with low estrogen oral contraceptives for a total period of 71 women-years. The calculated contraceptive failure rate was 1.4 per 100 women-years for the study, which was not significantly different than an accepted and documented contraceptive failure rate of 0.27 per 100 women-years (p=0.17). Of the 34 patients, one became pregnant while using the norethindrone, ethinyl estradiol, and mestranol combination concomitantly with oral tetracycline (12 months duration of use); the patient stated that she did not miss any doses of the contraceptive combination or had any changes in her menstrual cycle. Two other patients reported menstrual irregularities; one reported spotting while using the ethinyl estradiol and ethynodiol diacetate combination concomitantly with terfenadine and minocycline treatment, and another reported heavy cramping while using the norethindrone acetate and ethinyl estradiol combination concomitantly with tetracycline. Although this study determined that there was no increased risk of contraceptive failure with concomitant antibiotic use, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202].

c) The interaction between oral contraceptives and tetracycline has been suggested to be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [204].

d) A study which documented 163 cases of oral contraceptive failure in reliable pill takers found that 23% (37 cases) of these failures were associated with antibiotic use. Of these 163 cases, 6 were attributed to the use of tetracyclines, including doxycycline, minocycline, and lymecycline. The authors recommended a 7-day abstinence period or a barrier method of contraceptive following a course of antibiotics [270].

e) In a pharmacokinetic study, oral administration of tetracycline 500 mg four times daily for 3 days prior to and 7 days during use of the norelgestromin and ethinyl estradiol combination transdermal did not significantly affect the pharmacokinetics of norelgestromin or ethinyl estradiol [271].

Theophylline

1) Interaction Effect: theophylline toxicity (nausea, vomiting, palpitations, seizures)
2) Summary: Combination hormonal contraceptives containing some synthetic estrogens (ethinyl estradiol) may inhibit the metabolism of theophylline[401]. Combination contraceptives have been reported to decrease theophylline clearance by 34% and increase the half-life by 33% (7.9 vs 5.4 hr) [402]. The distribution of theophylline has not been reported to change. A longer dosing interval may be possible while on combination contraceptives [403].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: During initiation of concurrent therapy, monitor theophylline serum levels and for signs of theophylline toxicity such as nausea, tremors, headache, or rapid, irregular heartbeat. Careful monitoring is also necessary when the combination contraceptive is stopped.
7) Probable Mechanism: decreased theophylline metabolism
8) Literature Reports

a) Low-dose oral contraceptives do not appear to influence single-dose (intravenous) theophylline pharmacokinetics in adolescents [400]. No differences were found in theophylline distribution volume, elimination half-life, or total body clearance between

control subjects (n=10) and subjects who received 3 to 9 months of low-dose oral contraceptives (n=10).

Ticarcillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Ticarcillin/clavulanic acid may alter intestinal flora, which may lead to lower reabsorption of estrogen and decreased effectiveness of combination oral estrogen/progesterone contraceptives[345]. Concomitant use has been associated with unintended pregnancies and menstrual changes [346][347] However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183]
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ticarcillin/clavulanic acid and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Tigecycline

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Tigecycline, a tetracycline derivative, used concomitantly with oral contraceptive combinations (OC) may decrease contraceptive effectiveness[392]. The mechanism of interaction is thought that tetracyclines may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives [204]. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracycline, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202]. In a large retrospective chart review, there was no significant difference in OC failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of tigecycline and oral combination contraceptives (OC) may result in decreased contraceptive efficacy. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracyclines, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives[202]. Evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen

reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) There was no increased risk of contraceptive failure with concomitant antibiotic use in a study of 34 patients with acne who used oral antibiotics, including tetracycline (n=17) and erythromycin (n=20), concomitantly with low estrogen oral contraceptives for a total period of 71 women-years.. The calculated contraceptive failure rate was 1.4 per 100 women-years for the study, which was not significantly different than an accepted and documented contraceptive failure rate of 0.27 per 100 women-years (p=0.17). Of the 34 patients, one became pregnant while using the norethindrone, ethinyl estradiol, and mestranol combination concomitantly with oral tetracycline (12 months duration of use); the patient stated that she did not miss any doses of the contraceptive combination or had any changes in her menstrual cycle. Two other patients reported menstrual irregularities; one reported spotting while using the ethinyl estradiol and ethynodiol diacetate combination concomitantly with terfenadine and minocycline treatment, and another reported heavy cramping while using the norethindrone acetate and ethinyl estradiol combination concomitantly with tetracycline. Although this study determined that there was no increased risk of contraceptive failure with concomitant antibiotic use, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202].

c) Tigecycline is a glycylcycline antibiotic structurally similar to tetracycline antibiotics and may have similar adverse effects [392]. The interaction between oral contraceptives and tetracycline-type antibiotics has been suggested to be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [204].

d) A study which documented 163 cases of oral contraceptive failure in reliable pill takers found that 23% (37 cases) of these failures were associated with antibiotic use. Of these 163 cases, 6 were attributed to the use of tetracyclines, including doxycycline, minocycline, and lymecycline. The authors recommended a 7-day abstinence period or a barrier method of contraceptive following a course of antibiotics [270].

Tipranavir

1) Interaction Effect: decreased estrogen concentration and increased risk of developing a non-serious rash
2) Summary: In pharmacokinetic studies, a single dose of 0.035 milligrams (mg) of ethinyl estradiol coadministered with tipranavir, in combination with ritonavir, dosed as tipranavir/ritonavir 500/100 mg (n=21), 750/200 mg (n=13) twice daily resulted in decreased ethinyl estradiol maximum serum concentrations (Cmax) and area under the concentration-time curve (AUC) by approximately 50%. Alternative methods of nonhormonal contraception should be considered when estrogen-based oral contraceptives are administered concurrently with tipranavir and 200 milligrams of ritonavir. Patients using estrogens as hormone replacement therapy should be monitored for signs of estrogen deficiency. Additionally, there may be an increased risk of developing a non-serious rash when tipranavir is coadministered with estrogens[397].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concurrent administration of ethinyl estradiol with tipranavir and ritonavir results in decreased concentrations of ethinyl estradiol. Consider using alternative methods of nonhormonal contraception when estrogen-based oral contraceptives are administered concurrently with tipranavir and 200 milligrams of ritonavir. Additionally, monitor patients using estrogens as hormone replacement therapy for signs of estrogen deficiency. There may be an increased risk of developing a non-serious rash when tipranavir is coadministered with estrogens[397].
7) Probable Mechanism: unknown

Tirzepatide

1) Interaction Effect: decreased absorption of oral contraceptives
2) Summary: Administration of a combined oral contraceptive (0.35 mg ethinyl estradiol and 0.25 mg norgestimate) and a single dose of tirzepatide 5 mg, reduced mean Cmax and AUC of ethinyl estradiol, norgestimate, and norelgestromin and delayed Tmax. Advise patients to switch to a non-oral contraceptive method, or add a barrier method of contraception for at least 4 weeks after initiation of tirzepatide and for 4 weeks after each tirzepatide dose escalation. Non-oral hormonal contraceptives are not likely to be affected by tirzepatide[423].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of tirzepatide with oral contraceptives may decrease absorption of the oral contraceptive. Advise patients to switch to a non-oral contraceptive method, or add a barrier method of contraception for at least 4 weeks after initiation of tirzepatide and for 4 weeks after each tirzepatide dose escalation. Non-oral hormonal contraceptives are not likely to be affected by tirzepatide[423].
7) Probable Mechanism: delayed gastric emptying
8) Literature Reports

a) Following the administration of a combined oral contraceptive (0.35 mg ethinyl estradiol and 0.25 mg norgestimate) and a single dose of tirzepatide 5 mg, mean Cmax of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%, 66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in Tmax of 2.5 to 4.5 hours also was observed [423].

Tizanidine

1) Interaction Effect: increased tizanidine plasma concentrations resulting in increased hypotensive and sedative effects
2) Summary: The concomitant use of tizanidine and oral contraceptives is not recommended. In a retrospective analysis of population pharmacokinetic data, 50% lower clearance of tizanidine was reported in women taking oral contraceptives than in women not on oral contraceptives following single and multiple 4-mg doses of tizanidine. If coadministration is clinically necessary, initiate tizanidine at a dose of 2 mg and increase daily by 2 to 4 mg based on therapeutic response. Reduce the dose or discontinue tizanidine therapy if hypotension, bradycardia, or excessive drowsiness occurs[475][476].
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of tizanidine and oral contraceptives is not recommended. If coadministration is required, initiate tizanidine at a dose of 2 mg and increase daily by 2 to 4 mg based on response to therapy. Reduce the dose or discontinue tizanidine therapy if hypotension, bradycardia, or excessive drowsiness occurs[475][476].
7) Probable Mechanism: inhibition of CYP1A2-mediated tizanidine metabolism by the contraceptive
8) Literature Reports

a) One study reported higher serum levels of tizanidine in women taking oral contraceptives than in men [477]. In a retrospective analysis of population pharmacokinetic data, 50% lower clearance of tizanidine was reported in women taking oral contraceptives than in women not on oral contraceptives. Patients were given single and multiple 4-mg doses of tizanidine [475][476].

Topiramate

1) Interaction Effect: decreased plasma levels of hormonal contraceptive
2) Summary: Topiramate is a mild inducer of CYP3A4[284]. Coadministration of CYP3A4 inducers, such as topiramate, with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method [285][286][287] during coadministration and for at least 28 days after discontinuation of topiramate [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of topiramate and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if topiramate is used concomitantly with estrogen-containing contraceptives[284]. In women who are taking topiramate concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [285][286][287] during coadministration and for at least 28 days after discontinuation of topiramate [176]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of topiramate with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [288].

7) Probable Mechanism: increased metabolism of hormonal contraceptive
8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that topiramate doses less than or equal to 200 mg/day do not interact with oral contraceptives containing ethinyl estradiol and norethindrone. In two 28-day cycles, 5 groups of female subjects received oral doses of ethinyl estradiol/norethindrone (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with topiramate or carbamazepine during the second cycle. Coadministration of daily topiramate in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; topiramate 200 mg) women resulted in nonsignificant changes in the AUC of ethinyl estradiol and nonsignificant changes in the AUC and plasma concentrations of norethindrone compared with the contraceptive alone. When carbamazepine 600 mg/day was coadministered with ethinyl estradiol/norethindrone (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively. Carbamazepine increased oral clearance in both contraceptives by 127% and 69%, respectively [179].

b) In a study of 12 women with epilepsy who were receiving stable valproic acid monotherapy and oral contraception with ethinyl estradiol 35 mcg/norethindrone 1 mg (21 days on/7 days off), the coadministration of topiramate (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to ethinyl estradiol. Starting on the first 3 days of cycle 2 through cycle 4, topiramate 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of topiramate did not change the norethindrone pharmacokinetic parameters, the mean AUC of ethinyl estradiol was decreased by 18%, 21%, and 30% with daily topiramate doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of ethinyl estradiol was 14.7% to 33% higher. It is suggested that the modest effect of topiramate on ethinyl estradiol pharmacokinetics may be due to topiramate being a weak inducer of cytochrome P450 [289].

Tranexamic Acid

1) Interaction Effect: an increased risk of thrombotic events
2) Summary: Concomitant use of hormonal contraceptives and tranexamic acid is contraindicated due to further increased risk of thrombotic events, especially in women who are obese, or smoke cigarettes, and more so, in smokers over the age of 35 years[199]. Concomitant use of tranexamic acid and all hormonal contraceptives should be avoided, and an effective alternative nonhormonal contraceptive method should be used [200]. Venous and arterial thrombotic events have been reported during postmarketing surveillance of women concomitantly treated with combined hormonal contraceptives and tranexamic acid [199].
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Due to further increased risk of thrombotic events, especially in women who are obese, or smoke cigarettes, and more so, in smokers over the age of 35 years, coadministration of combination hormonal contraceptives and tranexamic acid is contraindicated[199]. Concomitant use of tranexamic acid and all hormonal contraceptives should be avoided, and an effective alternative nonhormonal contraceptive method should be used [200].
7) Probable Mechanism: unknown

Triazolam

1) Interaction Effect: triazolam toxicity (excessive sedation, confusion)
2) Summary: Combination contraceptives may inhibit the oxidative metabolism of triazolam causing an increase in serum levels of the benzodiazepine[373].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and triazolam therapy for an increased response to the benzodiazepine. Reductions in the triazolam dose may be needed.
7) Probable Mechanism: decreased hepatic metabolism of triazolam
8) Literature Reports

a) Low-dose oral contraceptives were shown to cause a 32% decrease in clearance and 44% increase in the AUC of triazolam. The increase in systemic availability of triazolam is similar to that observed after cimetidine or isoniazid, drugs known to inhibit oxidative drug metabolism. Reports of the effect of oral contraceptives on the elimination of oxidized drugs have demonstrated that oral contraceptives impair oxidative metabolism in the liver. This effect was believed to be mediated by the estrogen component of oral contraceptives [372].

Trimipramine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical

importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased

clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Troleandomycin

1) Interaction Effect: altered contraceptive effectiveness and risk of hepatotoxicity
2) Summary: Troleandomycin combined with oral contraceptives has been associated with liver dysfunction[462][463][464][465]; erythromycin may have less propensity for such [466]. Theoretically, macrolide antibiotics may alter intestinal flora and affect enterohepatic circulation of estrogens/progestins; however, contraceptive efficacy was maintained during roxithromycin treatment [467].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor for symptoms of hepatotoxicity or use a less hepatotoxic antibiotic. Advise patients to use a barrier method of birth control in addition to the combination contraceptive.
7) Probable Mechanism: inhibition of combination contraceptive metabolism
8) Literature Reports

a) Concomitant troleandomycin and oral contraceptive therapy may be associated with an increased risk for hepatotoxicity. Twenty-four cases of jaundice have been reported in women taking both troleandomycin and an oral contraceptive. The women had previously taken oral contraceptives for several months to years without evidence of hepatotoxicity. In general, 2 to 15 days after starting troleandomycin 1 to 3 grams daily, intense pruritus developed and was followed by jaundice 2 to 5 days later. Serum bilirubin, alkaline phosphatase, and serum alanine aminotransferase were typically elevated. Eight patients had evidence of cholestasis. After drug therapy was discontinued, jaundice and pruritus gradually disappeared, but persisted more than 1 month in 20 patients and more than 2 months in 6 patients. Twenty patients later resumed taking oral contraceptives without recurrence of the jaundice [459].

b) Twelve patients receiving oral contraceptives developed intrahepatic cholestasis 2 to 20 days after beginning troleandomycin therapy [460]. Three cases of jaundice were reported in women on oral contraceptives and troleandomycin [461].

Ulipristal

1) Interaction Effect: reduced efficacy of ulipristal or progestin-based hormonal contraceptives
2) Summary: Progestin-containing contraceptives may reduce the effectiveness of ulipristal in delaying ovulation. Conversely, ulipristal may reduce hormonal contraceptive effects. Combined oral contraceptive use within 1 day of ulipristal administration did not affect ovulation rates; however, use within 2 days impaired the ability of ulipristal to delay ovulation. Progestin-only contraceptive use within 1 day of ulipristal administration increased the ovulation rate within 6 days of ulipristal administration. Additionally, progestin-only contraceptive use within 2 days of ulipristal administration was associated with a reduction in the ability of the progestin to inhibit cervical mucus permeability. Start hormonal contraception no sooner than 5 days after ulipristal use. A reliable barrier method should also be used until the patient's next menstrual period. Follow instructions on the initiation or resumption of specific hormonal contraceptives after ulipristal intake[433].
3) Severity: major
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Progestin-containing contraceptives may reduce the effectiveness of ulipristal in delaying ovulation. Conversely, ulipristal may reduce hormonal contraceptive effects. Start hormonal contraception no sooner than 5 days after ulipristal use. A reliable barrier method should also be used until the patient's next menstrual period. Follow instructions on the initiation or resumption of specific hormonal contraceptives after ulipristal intake[433].
7) Probable Mechanism: competition for progesterone receptor binding
8) Literature Reports

a) In clinical trials, ovulation rates were similar among women who started ethinyl estradiol 30 mcg/levonorgestrel 150 mcg (COC) within 1 day of ulipristal use during the follicular phase of the menstrual cycle vs women using placebo plus COC. Ovulation occurred in 33.3% of subjects who received ulipristal plus COC vs 32.4% of subjects who received placebo plus COC [434].

b) When a combined oral contraceptive containing ethinyl estradiol 30 mcg/levonorgestrel 150 mcg was started 2 days after ulipristal intake, the ability of ulipristal to delay ovulation, as assessed by transvaginal ultrasound, was reduced; follicular rupture occurred in 27% of subjects in less than 5 days, compared to 3% of subjects after ulipristal alone [433].

c) The effects on ovarian activity of delaying versus immediately resuming combination oral contraceptives (COCs) after ulipristal intake were investigated in women who had been using contraceptives containing ethinyl estradiol 30 mcg/levonorgestrel 150 mcg once daily for 21 days followed by 7 days of placebo pills for at least one cycle (N=49). All subjects missed 3 consecutive pills (Days 5 to 7) during the first week of pills in the subsequent cycle and took ulipristal on the following day (Day 8). These subjects were

randomized to resume their COCs either on the same day as ulipristal intake vs 5 days later. No ovulations with potential risk of pregnancy occurred in either group in the 5 days following ulipristal. However, in the group that waited 5 days to resume taking COCs, 17.4% of women did ovulate later in the cycle (Days 18 to 26) whereas no ovulations occurred in the group that resumed COC intake on the same day as ulipristal [433].

d) Compared with women who used ulipristal alone, more women in the follicular phase of their menstrual cycle ovulated within 6 days of ulipristal use when they started desogestrel 75 mcg within a day of ulipristal intake. Conversely, ulipristal was associated with a reduction in the ability of desogestrel to inhibit cervical mucus permeability; thickening of cervical mucus was slowed by 3 to 4 days among patients who used ulipristal 2 days before desogestrel initiation compared with those who used desogestrel alone [434].

Valproic Acid

1) Interaction Effect: decreased valproate exposure and increased risk of seizures
2) Summary: Concomitant use of valproate, valproic acid, or divalproex sodium and an estrogen-containing hormonal contraceptive may increase the clearance of valproate, which may result in decreased exposure. This may cause an increase in seizure frequency. Monitor serum valproate concentrations and clinical response when adding or discontinuing estrogen containing products[436].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of valproate, valproic acid, or divalproex sodium and an estrogen-containing hormonal contraceptive may increase the clearance of valproate, which may result in decreased exposure. This may cause an increase in seizure frequency. Monitor serum valproate concentrations and clinical response when adding or discontinuing estrogen containing products[436].
7) Probable Mechanism: increased valproate clearance

Voriconazole

1) Interaction Effect: increased levels of voriconazole and of ethinyl estradiol and norethindrone
2) Summary: Coadministration of voriconazole with an oral combination contraceptive containing ethinyl estradiol and norethindrone has resulted in increased plasma concentrations of voriconazole, ethinyl estradiol, and norethindrone. When these agents are coadministered, monitor patients for adverse events related to voriconazole (peripheral edema, visual disturbance) and ethinyl estradiol/norethindrone (abnormal menstruation, breast tenderness, edema)[208][209].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Use caution when prescribing voriconazole to patients who are using oral contraceptives, as concomitant use may cause elevated plasma concentrations of voriconazole, ethinyl estradiol, and norethindrone. Monitor patients for increased adverse effects related to voriconazole (peripheral edema, visual disturbance) and ethinyl estradiol/norethindrone (abnormal menstruation, breast tenderness, edema)[208].
7) Probable Mechanism: altered CYP450-mediated metabolism of voriconazole, ethinyl estradiol, and norethindrone
8) Literature Reports

a) Concomitant administration of voriconazole and an oral contraceptive in 16 healthy women resulted in increased systemic exposure to all analytes relative to monotherapy, according to an open-label, fixed-sequence, three-period study. In period 1, women (mean age, 25.9 years; range, 19 to 36 years) received voriconazole 400 mg every 12 hours on day 1 and 200 mg every 12 hours on days 2 through 4. During period 2, women were given an oral contraceptive containing ethinyl estradiol 0.035 mg/norethindrone 1 mg every 24 hours on days 12 through 32. In period 3, subjects received combination voriconazole 400 mg every 12 hours on day 57, 200 mg every 12 hours on days 58 through 60, and an oral contraceptive every 24 hours on days 40 through 60. With concurrent administration, there were mean increases in voriconazole AUC and Cmax of 46% (90% confidence interval (CI), 32% to 61%) and 14% (90% CI, 3% to 27%), respectively, compared with monotherapy. Ethinyl estradiol AUC and Cmax increased 61% (90% CI, 50% to 72%) and 36% (90% CI, 28% to 45%), respectively. Norethindrone AUC and Cmax increased 53% (90% CI, 44% to 64%) and 15% (90% CI, 3% to 28%), respectively. Regardless of causality, the most commonly-reported adverse events during combination therapy were headache, abnormal vision, dizziness, nausea, and chromatopsia [208].

Warfarin

1) Interaction Effect: decreased or increased anticoagulant effectiveness
2) Summary: Concomitant use of a combination contraceptive and warfarin may result in enhanced or reduced anticoagulant efficacy of warfarin[243][245][242]. One study of 12 patients demonstrated an enhanced response to anticoagulant therapy when given concurrently with oral contraceptive [242]. In one case report, warfarin dose adjustments were required with the concomitant use of 3 different hormonal contraceptives within a 1-year period [243]. In another case report, emergency contraception with progestogen

only in a patient receiving warfarin resulted in an enhanced anticoagulant effect evident by an INR of 8.1 [245]. Although the mechanism of this interaction has not been determined, ethinyl estradiol inhibition of CYP1A2- and CYP2C19-mediated warfarin metabolism is the postulated primary mechanism [243]. Therefore, prothrombin time and INR should be closely monitored when hormonal contraceptive and anticoagulants are coadministered.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of warfarin and a combination oral contraceptive has the potential for decreased or increased anticoagulant efficacy. If these drugs are used together, consider closely monitor prothrombin time or INR.
7) Probable Mechanism: unknown
8) Literature Reports

a) Oral contraceptives potentiated anticoagulant efficacy, as measured by prothrombin time ratio, in 12 women (mean age, 34.5 yr) when treated concomitantly with a combination contraceptive (11, oral; 1, parenteral depot) and an anticoagulant (nicoumalone) compared with an anticoagulant alone. Anticoagulation was being used for Bjork-Shiley valvular prosthesis (n=9) and embolic mitral valve disease (n=3). Patients were followed for a total of 374 patient-months of which 230 months and 144 months were concomitant use with a mean anticoagulant dose of 2.05 mg (phase A) and anticoagulant alone at a mean dose of 2.53 mg (phase B), respectively. Although the anticoagulant dose requirement was lower during phase A (p less than 0.01), prothrombin time ratio was higher at 1.67 during phase A compared with 1.5 during phase B (p less than 0.01). It is postulated that the estrogens in the oral contraceptives may inhibit hepatic cell microsome enzymes. This may enhance the anticoagulant effect due to slowed breakdown of the anticoagulant [242].

b) Warfarin dose requirements were altered when 3 different hormonal contraceptives were used by a 33-year-old woman initially maintained on warfarin 38.5 mg/wk (historical max dose, 42 mg/wk) for long-term anticoagulation after aortic valve replacement. Monophasic ethinyl estradiol 0.02 mg/norethindrone 1 mg/day was also being given. Because of increased thrombosis risk, her oral contraceptive was replaced with an etonogestrel subdermal implant which required a 55.8% warfarin dose increase (60 mg/wk) to obtain goal INR (range, 2.5 to 3.5). After 10 months, the implant was removed due to increased menstrual bleeding. Nine days later, her INR increased to 6.5. During the next 48 days, no systemic contraceptives were used and her warfarin dose was titrated to 55.5 mg/wk. Oral norethindrone 0.35 mg/day was initiated and the warfarin dose stabilized at 53.5 mg/wk; however, norethindrone was discontinued 39 days later. Subsequently, no further warfarin dose adjustments were needed and the patient decided to avoid hormonal contraception. Ethinyl estradiol inhibition of CYP1A2- and CYP2C19-mediated warfarin metabolism is the postulated primary mechanism of this drug interaction which is considered probable based on the Horn Interaction Probability Scale [243].

c) A case report describes an enhanced anticoagulant effect of warfarin after giving a 35-year-old woman levonorgestrel for emergency contraception. The patient had familial type I (quantitative) antithrombin deficiency and a history of deep venous thrombosis and pulmonary thromboembolism. She had been stable on warfarin 7 mg per day with an INR) of 2.1. Three days after receiving emergency contraception, her INR was reported to be 8.1. Warfarin treatment was discontinued for two days and the patient's INR dropped to 2.5. No hemorrhagic complications occurred [244].

Zolmitriptan

1) Interaction Effect: an increased risk of zolmitriptan adverse effects
2) Summary: In a retrospective analysis of pharmacokinetic data, the mean plasma concentrations of zolmitriptan were higher in females taking oral contraceptives compared with those not taking oral contraceptives. Specifically, the Cmax and AUC of zolmitriptan were 30% and 50% higher, respectively, and the time to maximum concentration (Tmax) was prolonged by one-half hour. The effect that zolmitriptan may have on the pharmacokinetics of oral contraceptives has not been evaluated[428].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: When zolmitriptan is administered concurrently to a patient on combination contraceptive therapy, monitor the patient for an increased incidence of zolmitriptan adverse effects, including paresthesias, nausea, dizziness, and chest tightness.
7) Probable Mechanism: inhibition of zolmitriptan metabolism

Drug-Food Combinations

Caffeine

1) Interaction Effect: enhanced CNS stimulation
2) Summary: Concomitant use of combination contraceptives and caffeine ingestion increases the half-life of caffeine by 45% to 90% and decreases the clearance of caffeine by 40% to 65%. The mechanism is thought to involve inhibition by combination

contraceptives of caffeine metabolism[480][481][482]. In some patients, caffeine ingestion may need to be reduced due to excessive CNS stimulation.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Advise patients that consumption of beverages or medications containing caffeine may result in increased CNS stimulation and possible insomnia. Advise patients to decrease caffeine intake while taking combination contraceptives.
7) Probable Mechanism: inhibition of caffeine metabolism by combination contraceptives
8) Literature Reports

a) Caffeine was administered orally to 13 healthy males, 9 healthy females taking no oral contraceptive steroids, and 9 healthy females taking oral contraceptives for more than 6 months. All subjects abstained from drugs, alcohol, and tobacco smoking during the study. In addition, they refrained from drinking caffeine-containing beverages for at least 2 days prior to the study. After an overnight fast, the subjects received 250 mg of caffeine. The half-life of caffeine was significantly prolonged in the oral contraceptive user as compared with the male and female controls (10.7 hours vs 6.2 hours). Total plasma clearance was significantly less in women taking oral contraceptives. Plasma protein binding and volume of distribution of caffeine were similar in both groups of females. Similar pharmacokinetic parameters were observed for men and women not taking oral contraceptives, except for the volume of distribution which was smaller in men [478].

b) The effects of low-dose estrogen (50 mcg or less) oral contraceptives on the pharmacokinetics of caffeine have been studied. Eighteen non-smoking women participated in the study. Nine of these subjects were taking a low-dose oral contraceptive. All patients abstained from drinking caffeine-containing food and beverages for 48 hours prior to the study. After an overnight fast, each subject received 162 mg caffeine base orally [479]. This study demonstrated a prolonged elimination half-life and decreased clearance of caffeine as well as a significant delay in time to peak caffeine concentration in patients taking low-dose estrogen oral contraceptives.

Drug-Lab Modifications

Metyrapone test

1) Interaction Effect: reduced responses to the metyrapone test
2) Summary: Estradiol therapy may resulted in a reduced response to the metyrapone test[483]. Use caution when interpreting results of this test in patients receiving estradiol.
3) Severity: minor
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when interpreting results of the metyrapone test in patients receiving estradiol as a reduced response may occur[483].
7) Probable Mechanism: an unknown mechanism

IV Compatibility (single)

No results available

Pregnancy & Lactation

A) Teratogenicity/Effects in Pregnancy

1) Micromedex Pregnancy Rating: Contraindicated

a) Avoid use of this drug during pregnancy and prescribe an alternative. Evidence has demonstrated fetal abnormalities or risks when used during pregnancy. Advise women of childbearing potential of fetal risk.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) Estradiol is contraindicated during pregnancy [484][485][62].

4) Literature Reports

a) Estradiol is contraindicated during pregnancy. However, inadvertent use of estrogens and progestins as an oral contraceptive during early pregnancy appears to cause little or no increased risk of birth defects (including cardiac anomalies and limb reduction effects) [5][484][19][485][62].

b) Estradiol gel is not indicated for use in pregnant women. Although there are no data regarding the use of estradiol gel during pregnancy, epidemiologic studies and meta-analyses regarding the exposure of combined hormonal contraceptives, containing estrogen and progestins, before conception and during early pregnancy have not reported an increased risk of genital or nongenital

birth defects, including cardiac anomalies and limb-reduction effects. Animal studies have not been conducted with the use of estradiol gel to determine embryo/fetal toxicity [33].

c) The Collaborative Perinatal Project monitored 614 mother-child pairs who had been exposed to estrogens during the first trimester. Forty-eight of these pairs had exposure to estradiol. Although an increase in the expected frequency of congenital anomalies (cardiovascular, eye, ear, Downs syndrome) was observed for estrogens as a group, no such increase was seen with estradiol [486]. A retrospective analysis found a higher number of infants with congenital heart defects were exposed to oral contraceptives when compared with a control group of healthy children. Two out of 18 infants with heart defects were exposed to hormones in utero [487].

d) A retrospective cohort study examined more than 2000 infants exposed to female sex hormones between 1954 and 1963. Compared with a control group, the total number of malformations and malformations of the genitals in male infants were higher among exposed children than unexposed [488]. It is important to note that modern contraceptives contain lower doses of hormones than those used at the time these infants were exposed.

e) A genetically male infant was born with full female genitalia as well as camptomelic syndrome. The mother took oral contraceptives (norethindrone 0.5 to 1 mg plus ethinyl estradiol 0.035 mg) 18 months prior to conception and 6 months into pregnancy. The infant died at 3.5 months of age due to multiple malformations [489].

f) A review and meta-analysis of prospective studies to date of the association between oral contraceptive use during or just prior to pregnancy and the frequency of congenital malformations in offspring was reported. No significant elevations in relative risk were found for all malformations taken together, or for heart defects or limb reduction defects, which were both evaluated separately [490].

g) A case involving neonatal choreoathetosis and maternal use of oral contraceptives throughout pregnancy (0 to 30 weeks gestation) was reported. Diagnosis was made at 10 days of age when the infant was examined for difficulty with feeding secondary to pronounced grimacing and tongue-thrusting. The choreoathetosis resolved without treatment or complications one week later. Other studies have found that injection of 17-beta-estradiol into rats will cause an increase in the number of striatal dopamine receptors and excess dopamine activity is a basis for the development of choreic movements [491].

h) There is no firm evidence linking oral contraceptives with any fetal anomalies except masculinization of the female external genitalia. Exposure after 8 weeks of gestation would presumably be required for this effect to occur [492].

i) Oral contraceptive use immediately prior to or during pregnancy appears to present a risk not exceeding 5% with regard to the incidence of visible malformations. Data on the contraceptive usage of 3,002 mothers of children with malformations was prospectively collected. Compared to matched control mothers, the types of malformations seen were similar among contraceptive users and nonusers. A risk ratio of 0.95 was reported for the oral contraceptive users, which actually represents a slightly smaller risk of malformation in infants [493].

B) Breastfeeding

1) World Health Organization Rating: Avoid breastfeeding if possible. May inhibit lactation.

2) Micromedex Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

3) Clinical Management

a) Estradiol is not indicated for use in women of reproductive potential and should not be used during lactation; however, exercise caution in the event that estradiol is administered to a lactating woman [5][484].

b) Progestin-only oral contraceptives are preferred in breastfeeding and may be started 2 weeks postpartum. Alternatively, depot medroxyprogesterone acetate or hormonal implants can be started after 6 weeks postpartum. Combined estrogen-progestin contraceptives may be started at 6 weeks postpartum; however, the newborn's feedings should be carefully monitored as use of combined oral contraceptives is associated with a reduced quality and quantity of breast milk [499].

4) Literature Reports

a) Estradiol is not indicated for use in women of reproductive potential and should not be used during lactation. Estrogens are excreted into breast milk in small quantities [5][484][495] and have not been associated with adverse effects in the nursing infant. In the past, estrogens were used to suppress postpartum lactation [496][495].

b) Estrogen use in the nursing mother may be associated with decreased milk production and quality of the breast milk [33][5][484], including decreased composition of nitrogen and protein content of the milk [497]. The reduction in milk production may occur at any time during breastfeeding, but is less likely to occur once breastfeeding is well established [33].

c) Transdermal estradiol, administered to nursing women, did not affect estradiol or estrone concentrations in the nursing infant, nor did it affect infant growth, according to a clinical trial involving 19 mothers with post-partum depression, who were randomized to receive either transdermal estradiol, at doses ranging from 50 to 200 mcg/day, sertraline, or placebo [498].

5) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.07 to 0.3 [508]

2) Peak Concentration in Infant

a) Use of estradiol transdermal patches (up to 200 mcg/day) in breastfeeding mothers with postpartum depression produced no significant differences in infant estradiol levels when compared with the use of placebo or sertraline (N=19 mother-infant pairs) [498].

b) Active Metabolites

1) Estrone

a) Peak Concentration in Infant

1) Use of estradiol transdermal patches (up to 200 mcg/day) in breastfeeding mothers with postpartum depression produced no significant differences in infant estrone levels compared with the use of placebo or sertraline (N=19 mother-infant pairs) [498].

Monitoring

A) Estradiol

1) Therapeutic

a) Laboratory Parameters

1) Advanced Androgen-Dependent Carcinoma of the Prostate

a) The effectiveness of estrogen therapy can be assessed by phosphatase determinations and by symptomatic improvement of the patient [7].

2) Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure

a) Most estrogen administration and dosages should be guided by individual patient clinical response rather than by hormone levels [19][7][11][12], however, laboratory parameters, such as estradiol and follicle stimulating hormone, may be useful in some cases [8].

3) Prevention of Postmenopausal Osteoporosis

a) Periodic measurements of bone mineral density and biochemical markers should be assessed [8].

b) Physical Findings

1) Advanced Androgen-Dependent Carcinoma of the Prostate

a) The effectiveness of estrogen therapy can be assessed by phosphatase determinations and by symptomatic improvement of the patient [7].

2) Breast Cancer

a) Estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels [7].

3) Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure

a) Most estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels [19][7][11][12]; however, laboratory parameters, such as estradiol and follicle stimulating hormone, may be useful in some cases [8].

4) Postmenopausal Vasomotor Symptoms

a) Estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels [19][7][13][38][35][8][11][12]. Periodically re-evaluate postmenopausal women to determine if treatment is still necessary [69].

5) Postmenopausal Vulvar and Vaginal Atrophy

a) Estrogen administration and dosage should be guided by individual patient clinical response [5] rather than by hormone levels [19][7][13][8][11][12][14][15].

2) Toxic

a) Laboratory Parameters

1) Monitor serum calcium in patients with pre-existing severe hypocalcemia or in patients with breast cancer and bone metastases [5][7][13][38][35][8][11][12][14][15][94].

2) Monitor plasma triglycerides in patients with pre-existing hypertriglyceridemia [5][7][13][38][35][8][11][12][14][15][94].

3) Monitor thyroid function in patients with pre-existing hypothyroidism in order to maintain free thyroid hormone levels in an appropriate range [5][7][13][38][35][8][19][11][12][69][14][15][94].

b) Physical Findings