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

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].

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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

1) 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 [57].

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

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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 [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].

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)
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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-

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].

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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 [55].

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].

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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

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Disorder of gallbladder

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a) Nausea has been reported with the use of estrogens and/or progestin therapy [55].

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 [55].

Vomiting

a) Vomiting has been reported with the use of estrogens and/or progestin therapy [55].

Estradiol Valerate

Bloating symptom

a) Bloating has been reported with the use of estrogens and/or progestin therapy [57].

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 [57].
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) Nausea has been reported with the use of estrogens and/or progestin therapy [57].

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 [57].

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].

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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].

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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

a) General Information

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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

1) Headache has been reported with estrogen and/or progestin therapy [57].

Impaired cognition

a) General Information

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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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Estradiol Valerate

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].
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Estradiol Valerate

Asthma, acute

a) Estrogen therapy may cause an exacerbation of asthma and should be used with caution in patients with asthma [57].
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

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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

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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].

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].

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

1) Perform yearly breast examinations and patients should perform self-examinations of the breasts every month. Mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results [5][19][7][13][38][35][8][11][12][69][14][15][94].

2) Monitor blood pressure at regular intervals during estrogen use [5][7][13][38][35][8][11][12][14][15][94].

3) Observe carefully for exacerbation of conditions in patients with conditions that may be influenced by fluid retention such as cardiac or renal dysfunction [5][19][7][13][38][35][8][11][12][69][14][15][94].

4) Periodic monitoring of bone maturation and effects on epiphyseal centers is recommended when estrogen is administered to patients whose bone growth is not complete [10][7][8][11][12][14][94].

5) Directed or random endometrial sampling, when indicated, should be performed to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [5].

B) Estradiol Acetate

1) Therapeutic

a) Laboratory Parameters

1) Measurement of serum FSH and estradiol levels have not been shown to be useful [59].

b) Physical Findings

1) Postmenopausal Vasomotor Symptoms

a) Estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels when treating postmenopausal vasomotor symptoms [61]

b) Periodically reevaluate the need for continued treatment [59].

2) Postmenopausal Vulvar and Vaginal Atrophy

a) Improvement in vulvar or vaginal atrophy is indicative of efficacy.

b) Periodically reevaluate the need for continued treatment [59].

2) Toxic

a) Laboratory Parameters

1) Monitor thyroid function in women dependent on thyroid hormone replacement therapy [59].

2) Perform adequate diagnostic measures, including endometrial sampling, as clinically indicated in women with undiagnosed persistent or recurring abnormal vaginal bleeding [59].

b) Physical Findings

1) Carefully evaluate patients for ulceration or erosion of the vaginal or bladder wall [59].

2) Perform yearly breast examinations in all patients and schedule mammography examinations based on patient age, risk factors, and prior mammogram results [59].

3) Carefully observe patients for fluid retention in women who may be affected (eg, cardiac or renal impairment) [59].

C) Estradiol Cypionate

1) Therapeutic

a) Physical Findings

1) Female Hypogonadism

a) Estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels when treating female hypogonadism [55].

2) Postmenopausal Vasomotor Symptoms

a) Estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels when treating postmenopausal vasomotor symptoms [55].

2) Toxic

a) Laboratory Parameters

1) 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 [55].

2) Serum calcium should be monitored in patients with preexisting severe hypocalcemia or in patients with breast cancer and bone metastases [55].

3) Plasma triglycerides should monitored in patients with preexisting hypertriglyceridemia [55].

4) Thyroid function should be monitored in patients with preexisting hypothyroidism in order to maintain free thyroid hormone levels in an appropriate range [55].

b) Physical Findings

1) All women should receive yearly breast examinations by a healthcare provider and should perform self-examinations of the breasts every month. Mammography examinations should be

scheduled based on patient age, risk factors, and prior mammogram results [55].

2) An eye examination should be scheduled if there is a sudden partial or complete loss of vision or a sudden onset of proptosis, diplopia, or migraine. Estrogens should be discontinued pending examination and discontinued permanently if examination reveals papilledema or retinal vascular lesions [55].

3) Blood pressure should be monitored at regular intervals during estrogen use [55].

4) Patients with conditions that may be influenced by fluid retention such as cardiac or renal dysfunction should be carefully observed for exacerbation of their condition [55].

D) Estradiol Valerate

1) Therapeutic

a) Laboratory Parameters

1) Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure

a) Estrogen administration and dosage should be guided by clinical response rather than by serum hormone levels (estradiol, follicle stimulating hormone) [57].

2) Postmenopausal Vasomotor Symptoms

a) Estrogen administration and dosage should be guided by clinical response rather than by serum hormone levels (estradiol, follicle stimulating hormone) [57].

3) Postmenopausal Vulvar and Vaginal Atrophy

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2) Toxic

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2) Serum calcium should be monitored in patients with pre-existing severe hypocalcemia or in patients with breast cancer and bone metastases [57].

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b) Physical Findings

1) All women should receive yearly breast examinations by a healthcare provider and should perform self-examinations of the breasts every month. Mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results [57].

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3) Blood pressure should be monitored at regular intervals during estrogen use [57].

4) Patients with conditions that may be influenced by fluid retention such as cardiac or renal dysfunction should be carefully observed for exacerbation of their condition [57].

5) Periodic monitoring of bone maturation and effects on epiphyseal centers is recommended when estrogen is administered to patients whose bone growth is not complete [57].

Do Not Confuse

No results available

MECHANISM OF ACTION

Mechanism of Action

A) Estradiol

1) Estrogens bind to nuclear receptors in estrogen-responsive tissues. Estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone and follicle stimulating hormone through a negative feedback mechanism. Estrogens reduce the elevated levels of these hormones in postmenopausal women [7][13][38][35][8][92][9][11][12][36][14][15][94].

2) Estrogens are important for developing and maintaining the female reproductive system and secondary sex characteristics. Estrogens promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they stimulate and limit linear skeletal growth. Estrogens have wide-spread effects on metabolism such as transporting of proteins and electrolyte balance [114][509].

3) Estrogens are necessary for maintaining the normal menstrual cycle. During the follicular phase of the menstrual cycle, when estrogen levels are high, there is a proliferation of the vaginal and uterine mucosa and increased cervical secretions. As estrogen levels decline at the end of the cycle, menstruation begins [505][510]; (Naftolin & Tolis, 1978).

4) In non-pregnant women, estrogens (and progesterone) support the physiologic processes resulting in ovulation and preparation of the uterine endometrium to support conception. At the time of menopause, ovarian follicles are incapable of responding to gonadotropin stimulation with progressive maturation. The ovaries cease to produce estrogens and progesterone, and gonadotropin levels rise dramatically as androgen and estrogen levels decrease. Menopause is clinically defined as a duration of amenorrhea of 6 to 12 months in a woman over 45 years of age [511]. In the premenopausal period, estradiol secretion from the ovaries is the major source of estrogen production. Extraglandular production of estrone occurs from androstenedione, derived from both the adrenals and ovaries. In the menopause, ovarian estradiol production diminishes and a peripheral conversion of adrenal androstenedione to estrone becomes the principle source of estrogen [512].

5) All estrogens act similarly and there is no evidence that there are biological differences among various estrogen preparations, other than their ability to bind to receptors once inside target cells. There is no evidence that one estrogen is more carcinogenic than another or that one preparation is safer than another. Differences among various estrogens primarily arise from the dose administered and relative potency (Schiff and Ryan, 1980). All estrogens exert their primary effects on the interphase DNA-protein complex (chromatin) by binding to a receptor usually located in the cytoplasm of a target cell and initiation of translocation of the hormone-receptor complex to the nucleus [513]. The specificity of estrogen action depends upon the presence and concentration of "estrogen targets", which are defined as tissues containing a high concentration of estrogen receptors. These include the endometrium, myometrium, oviduct, vagina, fallopian tube, cervix, brain, liver, placenta, ovarian cells and Leydig's cell. Other tissues reportedly containing estrogen receptors include kidney, prostate, pancreas, heart and skin [513].

6) In breast tissue, estrogens stimulate the growth and differentiation of the ductal epithelium, induce mitotic activity of ductal cylindric cells, and stimulate the growth of connective tissue. In addition, estrogens exert histamine-like effects on the microcirculation of the breast and stimulate the growth of breast cancer cells [514].

7) The mechanism by which estrogens prevent postmenopausal bone loss is not clear. Estrogens cause a clear decrease in calcium excretion and result in a calcium balance indistinguishable from normal premenopausal women [515][516][97]. Though the precise mechanism remains unknown, changes in vitamin D metabolism (increased 1-hydroxylation of 25-OH-D) as well as increased levels of serum calcitonin have been implicated [517][518]; (Taggart et al, 1982). One study has also shown that estrogen therapy reduces the sensitivity of postmenopausal osteoporotic bone to the resorptive effects of parathyroid hormone [519]. Further study is needed.

B) Estradiol Acetate

1) Estrogens bind to nuclear receptors in estrogen-responsive tissues. Estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone and follicle stimulating hormone through a negative feedback mechanism. Estrogens reduce the elevated levels of these hormones in postmenopausal women [170][60].

2) Estrogens are important for developing and maintaining the female reproductive system and secondary sex characteristics. Estrogens promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they stimulate and limit linear skeletal growth. Estrogens have wide-spread effects on metabolism such as transporting of proteins and electrolyte balance [114][509].

3) Estrogens are necessary for maintaining the normal menstrual cycle. During the follicular phase of the menstrual cycle, when estrogen levels are high, there is a proliferation of the vaginal and uterine mucosa and increased cervical secretions. As estrogen levels decline at the end of the cycle, menstruation begins [505][510]; (Naftolin & Tolis, 1978).

4) In non-pregnant women, estrogens (and progesterone) support the physiologic processes resulting in ovulation and preparation of the uterine endometrium to support conception. At the time of menopause, ovarian follicles are incapable of responding to gonadotropin stimulation with progressive maturation. The ovaries cease to produce estrogens and progesterone, and

gonadotropin levels rise dramatically as androgen and estrogen levels decrease. Menopause is clinically defined as a duration of amenorrhea of 6 to 12 months in a woman over 45 years of age [511]. In the premenopausal period, estradiol secretion from the ovaries is the major source of estrogen production. Extraglandular production of estrone occurs from androstenedione, derived from both the adrenals and ovaries. In the menopause, ovarian estradiol production diminishes and a peripheral conversion of adrenal androstenedione to estrone becomes the principle source of estrogen [512].

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C) Estradiol Cypionate

1) Estrogens bind to nuclear receptors in estrogen-responsive tissues. Estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone and follicle stimulating hormone through a negative feedback mechanism. Estrogens reduce the elevated levels of these hormones in postmenopausal women [55].

2) Estrogens are important for developing and maintaining the female reproductive system and secondary sex characteristics. Estrogens promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they stimulate and limit linear skeletal growth. Estrogens have wide-spread effects on metabolism such as transporting of proteins and electrolyte balance [114][509].

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D) Estradiol Valerate

1) Estrogens bind to nuclear receptors in estrogen-responsive tissues. Estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone and follicle stimulating hormone through a negative feedback mechanism. Estrogens reduce the elevated levels of these hormones in postmenopausal women [57].

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PHARMACOKINETICS

Pharmacokinetics

Onset and Duration

A) Onset

1) Estradiol

a) Initial Response

1) Oral

a) Estrogen replacement: 3 days [9].

1) On the third consecutive day of dosing, the mean serum concentration of estradiol and estrone increased to 59 and 302 picograms/milliliter (pg/mL) above baseline, respectively,

after oral estradiol 2 milligrams daily were administered to postmenopausal women [9].

b) Menopausal symptoms: 2 to 4 weeks [500][501]

1) Time to significant improvement of menopausal symptoms relative to baseline was 2 to 4 weeks [500][501].

2) Transdermal

a) Estrogen replacement: 4 hours [9][11][12]

1) After a single application of estradiol transdermal patches that provided 0.05 and 0.1 milligrams of estradiol per day, blood levels of estradiol were increased within 4 hours after administration [9].

2) Following application to the abdomen of estradiol transdermal patches that provided 0.0375 and 0.1 milligrams (mg) of estradiol per day and application to the buttocks of estradiol transdermal patches that provided 0.1 mg of estradiol per day, estradiol levels were increased above baseline within 4 hours after administration [11][12].

2) Estradiol Cypionate

a) Initial Response

1) Menopausal vasomotor symptoms, intramuscular: 1 to 5 days [55].

a) Comparative clinical trials have demonstrated that relief of vasomotor symptoms in menopausal women occurs approximately within 1 to 5 days after a single intramuscular injection of estradiol cypionate 5 milligrams [55].

B) Duration

1) Estradiol

a) Single Dose

1) Transdermal

a) Estrogen replacement: within 24 hours [9]

1) After a single application of estradiol transdermal patches that provided 0.05 and 0.1 milligrams of estradiol per day, mean serum estradiol concentrations of 32 and 67 picograms/milliliter (pg/mL), respectively, were maintained above baseline over the application period. Serum concentration levels of estrone averaged 9 and 27 pg/mL above baseline, respectively. Serum concentrations of estradiol and estrone returned to preapplication levels within 24 hours after removal of the patch [9].

b) Multiple Dose

1) Transdermal

a) Estrogen replacement: 12 to 24 hours [11][12]

1) In a multiple-dose study involving 17 healthy postmenopausal women, estradiol transdermal systems were applied to the abdomen at a dose of 0.05 and 0.1 milligrams (mg)/day) or to the buttocks at a dose of 0.1 mg/day. Plasma concentrations of estradiol and estrone remained slightly above baseline at 12 hours after removal of the transdermal systems. In another study, the levels return to baseline values with 24 hours after the patch removal [11][12].

2) Estradiol Cypionate

a) Single Dose

1) Menopausal vasomotor symptoms, intramuscular: average of 5 weeks [55].

a) Comparative clinical trials have demonstrated that relief of vasomotor symptoms in menopausal women was maintained for 1 to 8 weeks (average 5 weeks) after a single intramuscular injection of estradiol cypionate 5 milligrams [55].

2) Vaginal estrogenic effect, intramuscular: 3 to 4 weeks [55]

a) Comparative clinical trials have demonstrated that after a single intramuscular injection of estradiol cypionate 5 milligrams, the average duration of estrogenic effect, as measured by vaginal smear, was approximately 3 to 4 weeks [55].

Drug Concentration Levels

A) Estradiol

1) Therapeutic Drug Concentration

a) Transdermal Gel

1) Estrogel(R): 28.3 picograms/mL [13]

a) By day 14, the time-averaged serum estradiol and estrone concentrations over the 24-hour dose interval after administration of 1.25 grams estradiol topical gel to one arm were 28.3 and 48.6 picograms/milliliter, respectively. The serum concentrations of estradiol reached steady state after the third daily application of 2.5 grams topical estradiol gel (1.25 grams applied to each arm) [13].

2) Divigel(R): 9.8, 21, 30.5 picograms/mL (0.25, 0.5, and 1 mg daily dose, respectively) [38]

a) The steady state serum concentration of estradiol is achieved by day 12 following daily application of estradiol topical gel 0.1% to the skin of the upper thigh. The mean serum estradiol levels on day 14 after multiple daily doses of estradiol topical gel delivering 0.25 milligram was 9.8 picograms/milliliter (pg/mL). The mean steady state serum concentration of estradiol after multiple daily doses of estradiol topical gel 0.5 milligram was 21 pg/mL. The mean steady state serum concentration of estradiol after multiple daily doses of estradiol topical gel 1 milligram was 30.5 pg/mL[38].

b) Transdermal Patch

1) Alora(R)

a) The average base-line adjusted steady state concentrations of estradiol during a 2 year, randomized, double-blind, controlled trial involving 355 hysterectomized women were 18.6, 35.9, and 50.1 picograms/milliliter for the 0.025, 0.05, and 0.075 milligrams/day dose, respectively [8].

The mean steady state serum concentrations of estradiol after administration of Alora(R) patches are presented below. Studies 1 and 2 were of 3 months duration and Study 3 was of 2 years duration [8]:

Dose (milligrams/day)	Study 1 (pg/mL)	Study 2 (pg/mL)	Study 3 (pg/mL)
0.025	--	--	24.5
0.05	46.9	38.8	42.6
0.075	--	--	56.7
0.1	99.2	97.0	--
pg/mL: picogram/milliliter			

2) Estraderm(R)

a) Steady state serum estradiol levels of 30 picograms/mL and estrone levels of 12 picograms/mL were reported in a 3-week multiple-application study (n=14) receiving Estraderm(R) 0.05 twice a week [9].

3) Vivelle(R) and Vivelle-Dot(R)

a) The mean steady state plasma concentrations of estradiol after administration of Vivelle(R) are summarized below [11][12]:

Dose (milligrams/day)	Application Site	Cavg (picograms/milliliter)
0.0375	Abdomen	34
0.05	Abdomen	57
0.075	Abdomen	72
0.1	Abdomen	89
0.1	Buttock	104
Cavg: average plasma concentration		

4) Transdermal Spray

a) Evamist(TM): 19.6, 30.7, and 30.9 picograms/mL (1, 2, or 3 sprays daily, respectively) [36]

1) By day 14, the mean steady state concentration of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of one 90 microliter (mcL) spray delivering 1.53 milligrams (mg) estradiol was 19.6 picograms/milliliter (pg/mL). The mean steady state concentration of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of two 90 mcL sprays delivering a total of 3.06 mg estradiol was 30.7 pg/mL. The mean steady state concentration of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of three 90 mcL sprays delivering a total of 4.59 mg estradiol was 30.9 pg/mL [36].

5) Vaginal Insert

a) Vaginal, insert (estradiol): 3.6 to 4.6 picograms/mL (pg/mL; Day 14) [5]

1) Following 14 days of once-daily administration in postmenopausal women (n=54), average 24-hour concentration of estradiol was 3.6 +/- 1.8 pg/mL with the 4-mcg insert and 4.6 +/- 2.3 pg/mL with the 10-mcg insert, compared with a placebo level of 4.3 +/- 2.8 mcg/mL [5].

b) Vaginal, insert (estrone): 13.6 to 19.3 picograms/mL (pg/mL; Day 14) [5]

1) Following 14 days of once-daily administration in postmenopausal women (n=54), average 24-hour concentration of estrone was 13.6 +/- 4.8 pg/mL with the 4-mcg insert and 19.3 +/- 10.2 pg/mL with the 10-mcg insert, compared with a placebo level of 17.8 +/- 7.5 mcg/mL [5].

6) Vaginal Ring

a) The steady state concentration values at 48 hours, 4 weeks, and 12 weeks for estradiol and estrone, as well as baseline-adjusted estradiol and estrone following a single estradiol vaginal ring application in 14 healthy postmenopausal women are summarized below [15]:

	Css-48 hr (picograms/milliliter)	Css-4w (picograms/milliliter)	Css-12w (picograms/milliliter
Estradiol	11.2	9.5	8.0
Baseline-adjusted Estradiol	3.6	2	0.4
Estrone	52.5	43.8	47.0
Baseline-adjusted Estrone	6.2	-2.4	0.8
Css: Steady state serum concentration; hr: hours; w: week			

b) The mean steady state serum estradiol concentrations after 1 to 4 estradiol vaginal rings (delivering 2 milligrams estradiol per ring) were inserted at three month intervals during a phase II study involving 222 postmenopausal women were 7.8, 7.0, 7.0, and 8.1 picograms/milliliter at 12, 24, 36, and 48 weeks, respectively. Similar results were seen in estrone concentrations [15].

2) Peak Concentration

a) Transdermal Gel

1) Estrogel(R): 46.4 picograms/mL (1.25 g daily) [13]

a) The mean Cmax of estradiol on day 14 was 46.4 picograms/milliliter after estradiol topical gel 1.25 grams was administered to 24 postmenopausal women once daily on the posterior surface of the arm from wrist to shoulder for 14 days. The mean Cmax of estrone was 64.2 picograms/milliliter [13].

2) Divigel(R): 14.7, 28.4, and 51.5 picograms/mL (0.25, 0.5, and 1.0 mg daily) [38]

a) In postmenopausal women, the mean Cmax of estradiol after multiple daily doses of estradiol topical gel delivering 0.25 milligram was 14.7 picograms/milliliter (pg/mL). The mean Cmax of estradiol after multiple daily doses of estradiol topical gel 0.5 milligram was 28.4 pg/mL. The mean Cmax of estradiol after multiple daily doses of estradiol topical gel 1 milligram was 51.5 pg/mL[38].

b) Transdermal Patch

1) Alora(R): 92 to 144 picograms/mL [8]

The mean Cmax of Alora(R) over an 84-hour dosing interval is presented below (* denotes Cmax for hip was statistically different from Cmax for abdomen) [8]:

Dose (milligrams/day)	Application Site	N	Dosing	Cmax (picograms/milliliter)
0.05	Abdomen	20	Multiple	92
0.075	Abdomen	20	Multiple	120
0.1	Abdomen	42	Multiple	144
0.05	Abdomen	31	Single	53
0.05	Buttock	31	Single	67
0.05	Hip*	31	Single	69
Cmax: Peak serum concentrations				

2) Climara(R): 32 to 174 picograms/mL [92]

a) The average Cmax of estradiol during a 3-week multiple application study in which 24 postmenopausal women wore the 25 square centimeter (cm(2)) Climara(R) system was 100 picograms/milliliter (pg/mL). Serum estrone Cmax level was 60 pg/mL [92].

b) In a single dose study in which 38 postmenopausal women wore a 25 square centimeter (cm(2)) Climara(R) system for one week either on the abdomen or buttocks, the serum Cmax for estradiol was 25% higher with the buttock application than with the abdomen application [92].

A summary of calculated Cmax values for estradiol during evaluation of Climara(R) is outlined in the following table [92]:

Delivery Rate (milligrams/day)	Surface Area (square centimeters)	Application Site	N	Dosing	Cmax (picograms/milliliter)
0.025	6.5	Abdomen	24	Single	32
0.05	12.5	Abdomen	102	Single	71
0.1	25	Abdomen	139	Single	147
0.1	25	Buttock	38	Single	174

3) Vivelle(R), Vivelle-Dot(R): 46 to 145 picograms/mL [11][12]

The mean plasma Cmax values of estradiol after administration of Vivelle(R) at steady state are summarized below [11][12]:

Dose (milligrams/day)	Application Site	Cmax (picograms/milliliter)
0.0375	Abdomen	46
0.05	Abdomen	83
0.075	Abdomen	99
0.1	Abdomen	133
0.1	Buttock	145
Cmax: Peak plasma concentration		

c) Transdermal Spray

1) Evamist(TM): 36.4, 57.4, and 54.1 picograms/mL (1, 2, or 3 sprays daily, respectively) [36]

a) By day 14, the mean Cmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of one 90 microliter (mcL) spray delivering 1.53 milligrams (mg) estradiol was 36.4 picograms/milliliter (pg/mL). The mean Cmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of two 90 mcL sprays delivering a total of 3.06 mg estradiol was 57.4 pg/mL. The mean Cmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of three 90 mcL sprays delivering a total of 4.59 mg estradiol was 54.1 pg/mL [36].

d) Vaginal Ring

1) The Cmax values for estradiol and estrone, as well as baseline-adjusted estradiol and estrone following a single estradiol vaginal ring application in 14 healthy postmenopausal women are summarized below:

	Cmax in picograms/milliliter
Estradiol	63.2
Baseline-adjusted Estradiol	55.6
Estrone	66.3
Baseline-adjusted Estrone	20
Cmax: Peak serum levels	

The initial estradiol Cmax after application of a second ring in the same women resulted in an approximate 38% lower Cmax, thought to be due to reduced systemic absorption via the treated vaginal epithelium [15].

e) Vaginal Insert

1) Vaginal, insert (estradiol): 4.8 to 7.3 picograms/mL (pg/mL; Day 14); 4.3 to 4.8 pg/mL (Day 84) [5]

a) Following 14 days of once-daily administration in postmenopausal women (n=54), mean Cmax of estradiol was 4.8 +/- 2.3 pg/mL with the 4-mcg insert and 7.3 +/- 2.4 pg/mL with the 10-mcg insert, compared with a placebo level of 5.5 +/- 3.4 mcg/mL. After Day 14, women received 1 insert twice weekly. At Day 84, estradiol concentrations compared to baseline concentrations were: 4.3 vs 3.9 pg/mL for 4 mcg; 4.8 vs 5 pg/mL for 10 mcg; and 4.4 vs 4.5 pg/mL for placebo [5].

2) Vaginal, insert (estrone): 16 to 23.9 picograms/mL (pg/mL; Day 14) [5]

a) Following 14 days of once-daily administration in postmenopausal women (n=54), mean Cmax of estrone was16 +/- 5.5 pg/mL with the 4-mcg insert and 23.9 +/- 13.4 pg/mL with the 10-mcg insert, compared with a placebo level of 22.8 +/- 10.9 mcg/mL [5].

f) Vaginal Tablets

1) Vaginal, tablets (estradiol): 47 to 51 picograms/mL [94]

a) During a double-blind, randomized trial, the mean Cmax of estradiol at day 1, 14, and 84 was 51, 47, and 49 picograms/milliliter, respectively, during administration of estradiol 25 mcg vaginal tablets over a 12-week period [94].

2) Vaginal, tablets (estrone): 35 to 39 picograms/mL [94]

a) During a double-blind, randomized trial, the mean Cmax of estrone at day 1, 14, and 84 was 35, 39, and 35 picograms/milliliter, respectively, during administration of estradiol 25 mcg vaginal tablets over a 12-week period [94].

3) Time to Peak Concentration

a) Transdermal Gel

1) Divigel(R): 16, 10, and 8 hr (0.25, 0.5, and 1 mg daily dose, respectively) [38]

a) In postmenopausal women, the median Tmax of estradiol after multiple daily doses of estradiol topical gel delivering 0.25 milligram was 16 hours. The median Tmax of estradiol after multiple daily doses of estradiol topical gel 0.5 milligram was 10 hours. The median Tmax of estradiol after multiple daily doses of estradiol topical gel 1 milligram was 8 hours [38].

b) Transdermal Spray

1) Evamist(TM): 20, 18, and 20 hr (1, 2, or 3 sprays daily, respectively) [36]

a) By day 14, the median Tmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of one 90 microliter (mcL) spray delivering 1.53 milligrams (mg) estradiol was 20 hours (hr). The median Tmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of two 90 mcL sprays delivering a total of 3.06 mg estradiol was 18 hr. The median Tmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of three 90 mcL sprays delivering a total of 4.59 mg estradiol was 20 hr [36].

c) Vaginal Ring

1) Estring(R): 0.5 to 1 hour [15]

a) The time to attain peak serum estradiol levels after insertion of estradiol vaginal ring during a phase 1 study involving 14 postmenopausal women was 0.5 to 1 hour [15].

4) Area Under the Curve

a) Transdermal

1) Divigel(R): 236, 504, and 732 picograms x hr/mL (0.25, 0.5, and 1.0 mg daily dose, respectively) [38]

a) In postmenopausal women, the mean AUC of estradiol after multiple daily doses of estradiol topical gel delivering 0.25 milligram was 236 picograms x hour/milliliter (pg x hr/mL), respectively. The mean AUC of estradiol after multiple daily doses of estradiol topical gel 0.5 milligram was 504 pg x hr/mL. The mean AUC of estradiol after multiple daily doses of estradiol topical gel 1.0 milligram was 732 pg x hr/mL[38].

2) Evamist(TM): 471, 736, and 742 pg x hr/mL (1, 2, or 3 sprays daily dose, respectively) [36]

a) By day 14, the mean AUC of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of one 90 microliter (mcL) spray delivering 1.53 milligrams (mg) estradiol was 471 picograms x hour/milliliter (pg x hr/mL). The mean AUC of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of two 90 mcL sprays delivering a total of 3.06 mg estradiol was 736 pg x hr/mL. The mean AUC of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of three 90 mcL sprays delivering a total of 4.59 mg estradiol was 742 pg x hr/mL [36].

b) Vaginal

1) Vaginal, tablets (estradiol): 538 to 567 picograms x hr/mL [94]

a) During a double-blind, randomized trial, the mean AUC of estradiol at day 1, 14, and 84 was 538, 567, and 563 picograms x hour/milliliter, respectively, during administration of estradiol 25 mcg vaginal tablets over a 12-week period [94].

2) Vaginal, tablets (estrone): 649 to 744 picograms x hr/mL [94]

a) During a double-blind, randomized trial, the mean AUC of estrone at day 1, 14, and 84 was 649, 744, and 681 picograms x hour/milliliter, respectively, during administration of estradiol 25 mcg vaginal tablets over a 12-week period [94].

B) Estradiol Acetate

1) Peak Concentration

a) Oral: estradiol, 56.7, 90.1, and 177.3 pg/mL (0.45, 0.9, and 1.8 mg daily) [170]

b) Oral: baseline adjusted estrone, 155.0, 313.9, and 680.6 pg/mL (0.45, 0.9, and 1.8 mg daily) [170]

1) In 18 healthy postmenopausal women, the mean Cmax of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.45 milligrams was 56.7 and 155.0 picograms/milliliter (pg/mL), respectively. The mean Cmax of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.9 milligrams was 90.1 and 313.9 pg/mL, respectively. The mean Cmax of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 1.8 milligrams was 177.3 and 680.6 pg/mL, respectively [170].

c) Vaginal, ring: estradiol, 1129 to 1665 pg/mL (0.05 mg/day) [60]

d) Vaginal, ring: estrone, 141 pg/mL (0.05 mg/day) [60]

e) Vaginal, ring: estrone sulfate, 2365 pg/mL (0.05 mg/day) [60]

1) The mean Cmax of estradiol, estrone, and estrone sulfate after administration of estradiol acetate vaginal ring which delivered 0.05 milligram/day (mg/day) of estradiol was 1129 to 1665, 141, and 2365 picograms/milliliter (pg/mL) [60].

2) Time to Peak Concentration

a) Oral: estradiol, 0.43 to 0.75 hr [170]

b) Oral: baseline adjusted estrone, 5.0 to 6.0 hr [170]

1) In 18 healthy postmenopausal women, the median Tmax of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.45 milligrams was 0.50 and 6.0 hours, respectively. The median Tmax of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.9 milligrams was 0.43 and 5.0 hours, respectively. The median Tmax of estradiol and baseline-adjusted estrone

after multiple-dose administration of oral estradiol acetate 1.8 milligrams was 0.75 and 6.0 hours, respectively [170].

c) Vaginal, ring: estradiol, 0.7 to 0.9 hr [60]

d) Vaginal, ring: estrone, 6.2 hr [60]

e) Vaginal, ring: estrone sulfate, 9.3 hr [60]

1) The mean Tmax of estradiol, estrone, and estrone sulfate after administration of estradiol acetate vaginal ring which delivered 0.05 milligram/day (mg/day) of estradiol was 0.7 to 0.9, 6.2, and 9.3 hours [60].

3) Area Under the Curve

a) Oral: estradiol, 565.0, 1066.5, and 2211.3 pg x hr/mL (0.45, 0.9, and 1.8 mg daily) [170]

b) Oral: baseline adjusted estrone, 2363.8, 4980.9, and 11510.8 pg x hr/mL (0.45, 0.9, and 1.8 mg daily) [170]

1) In 18 healthy postmenopausal women, the mean AUC of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.45 milligrams was 565.0 and 2363.8 picograms x hour/milliliter (pg x hr/mL), respectively. The mean AUC of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.9 milligrams was 1066.5 and 4980.9 pg x hr/mL, respectively. The mean AUC of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 1.8 milligrams was 2211.3 and 11510.8 pg x hr/mL, respectively [170].

ADME

Absorption

A) Estradiol

1) Bioavailability

a) Transdermal

1) Transdermal, patch: 20 times higher than oral [92][9]

a) The systemic availability of estradiol after transdermal administration is approximately 20 times greater than that after oral administration due to the lack of first pass metabolism during transdermal administration [92][9].

b) Vaginal

1) Vaginal ring: approximately 8% [15]

a) Approximately 8% (95% confidence interval: 2.8 - 12.8%) of the daily amount release locally from Estring(R) was absorbed systemically unchanged in postmenopausal women [15].

2) Transdermal

a) Emulsion: exposure increased by sunscreen use [35]

1) The exposure to estradiol is increased by approximately 35% when sunscreen is applied 10 and 25 minutes prior to application of estradiol emulsion, and by 15% when sunscreen is applied 25 minutes after the application of the estradiol emulsion [35].

b) Gel: passive diffusion [13][38]

1) Estradiol gel is absorbed via a passive diffusion process with the rate of diffusion across the stratum corneum being the rate-limiting factor [13][38].

c) Patch: passive diffusion [8]

1) Estradiol, when administered as a transdermal patch, is absorbed via a passive diffusion process with the rate of diffusion across the stratum corneum being the rate-limiting factor [8].

2) The average daily absorbed dose of estradiol after transdermal estradiol systems (Alora(R)) were worn over a continuous four day interval during 251 separate occasions (n=123) was 0.003 milligrams per square centimeter (cm(2)) active surface area. The nominal mean in vivo daily delivery rates of estradiol from the 9, 18, 27, and 36 cm(2) systems were 0.027, 0.054, 0.081, and 0.11 milligrams/day, respectively [8].

3) Vaginal

a) Ring: rapid for first hour; declines to constant rate for the remaining 3 months [15].

1) Absorption from estradiol occurs rapidly for the first hour but then declines to a steady rate for the remainder of the 3-month dosing interval. Estradiol is rapidly absorbed through the vaginal mucosa [60][15].

B) Estradiol Acetate

1) Bioavailability

a) Oral, rapidly absorbed [170].

1) Estradiol was rapidly absorbed following administration of oral estradiol acetate [170].

b) Vaginal, rapid for first hour; declines to constant rate for the remaining 3 months [60].

1) Absorption from estradiol acetate occurs rapidly for the first hour but then declines to a steady rate for the remainder of the 3-month dosing interval. Estradiol acetate and estradiol are both rapidly absorbed through the vaginal mucosa [60].

2) Effects of Food

a) Oral, no effect on systemic availability [170]

1) Compared to the fasted state, the Cmax of estradiol following administration of 1.8 milligrams oral estradiol acetate was decreased by 36% when given with food. However, the AUC was comparable between the fed and fasted states [170].

C) Estradiol Cypionate

1) Bioavailability

a) Intramuscular, absorbed over several weeks [55].

1) When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of estradiol cypionate as an oily preparation is slowed. A single intramuscular injection is absorbed over several weeks [55].

D) Estradiol Valerate

1) Bioavailability

a) Intramuscular, absorbed over several weeks [57].

1) When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of estradiol cypionate as an oily preparation is slowed. A single intramuscular injection is absorbed over several weeks [57].

Distribution

A) Distribution Sites

1) Estradiol

a) Protein Binding

1) Estrogens circulate in the blood bound primarily bound to sex hormone binding globulin (SHBG) and to albumin [7][13][38][35][8][92][11][12][36][14][15][94].

2) Estradiol Acetate

a) Protein Binding

1) Estrogens circulate in the blood bound primarily bound to sex hormone binding globulin (SHBG) and to albumin [170][60].

3) Estradiol Cypionate

a) Protein Binding

1) Estrogens circulate in the blood bound primarily to sex hormone binding globulin (SHBG) and to albumin [55].

4) Estradiol Valerate

a) Protein Binding

1) Estrogens circulate in the blood bound primarily to sex hormone binding globulin (SHBG) and to albumin [57].

B) Distribution Kinetics

1) Estradiol

a) Volume of Distribution

1) The distribution of exogenous and endogenous estrogens is similar. Estrogens are widely distributed in the body and are found in higher concentrations in the sex hormone target organs [7][13][38][35][8][92][11][12][36][14][15][94].

2) Estradiol Acetate

a) Volume of Distribution

1) The distribution of exogenous and endogenous estrogens is similar. Estrogens are widely distributed in the body and are found in higher concentrations in the sex hormone target organs [170][60].

3) Estradiol Cypionate

a) Volume of Distribution

1) The distribution of exogenous and endogenous estrogens is similar. Estrogens are widely distributed in the body and are found in higher concentrations in the sex hormone target organs [55].

4) Estradiol Valerate

a) Volume of Distribution

1) The distribution of exogenous and endogenous estrogens is similar. Estrogens are widely distributed in the body and are found in higher concentrations in the sex

hormone target organs [57].

Metabolism

A) Metabolism Sites and Kinetics

1) Estradiol

a) Liver, primary [7][13][38][35][8][92][9][11][12][36][14][15][94]

1) Exogenous estrogens, like endogenous estrogens, are transformed in the liver. Estradiol acetate is hydrolyzed to estradiol. Estradiol is converted reversibly to estrone and both can be converted to estriol, the major urinary metabolite. Additionally, estrogens undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut which is followed by reabsorption. A significant proportion of the circulating estrogens in postmenopausal women exists as sulfate conjugates, especially estrone sulfate [7][13][38][35][8][92][9][11][12][36][14][15][94].

2) Orally administered estradiol is rapidly metabolized in the liver to estrone and its conjugates which contributes to higher circulating levels of estrone than estradiol [8][9][11][12].

3) In vitro and in vivo studies indicate that estrogens are partially metabolized by cytochrome P450 3A4 [7][13][38][35][8][92][9][11][12][36][14][15].

4) Estradiol from the transdermal gel preparations does not undergo first pass metabolism and provides estradiol/estrone ratios at steady state in the range of 0.42 to 0.65 [13][38].

5) Vaginal delivery of estradiol does not undergo first pass metabolism [15][94].

b) Skin, small extent [8][9][11][12]

1) Transdermal estradiol is metabolized by the skin to a small extent. Transdermal administration produces therapeutic plasma levels of estradiol with lower levels of estrone and estrone conjugates. Therefore, smaller total doses are required for transdermal administration of estradiol compared with oral administration of estradiol [8][9][11][12].

2) Estradiol Acetate

a) Liver, primary [170][60]

1) Exogenous estrogens, like endogenous estrogens, are transformed in the liver. Estradiol acetate is hydrolyzed to estradiol. Estradiol is converted reversibly to estrone and both can be converted to estriol, the major urinary metabolite. Additionally, estrogens undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut which is followed by reabsorption. A significant proportion of the circulating estrogens in postmenopausal women exists as sulfate conjugates, especially estrone sulfate [170][60].

2) In vitro and in vivo studies indicate that estrogens are partially metabolized by cytochrome P450 3A4 [170][60].

3) Estradiol Cypionate

a) Liver, primary [55]

1) Exogenous estrogens, like endogenous estrogens, are transformed in the liver. Estradiol acetate is hydrolyzed to estradiol. Estradiol is converted reversibly to estrone and both can be converted to estriol, the major urinary metabolite. Additionally, estrogens undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut which is followed by reabsorption. A significant proportion of the circulating estrogens in postmenopausal women exists as sulfate conjugates, especially estrone sulfate [55].

2) In vitro and in vivo studies indicate that estrogens are partially metabolized by cytochrome P450 3A4 [55].

4) Estradiol Valerate

a) Liver, primary [57]

1) Exogenous estrogens, like endogenous estrogens, are transformed in the liver. Estradiol is converted reversibly to estrone and both can be converted to estriol, the major urinary metabolite. Additionally, estrogens undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut which is followed by reabsorption. A significant proportion of the circulating estrogens in postmenopausal women exists as sulfate conjugates, especially estrone sulfate [57].

2) In vitro and in vivo studies indicate that estrogens are partially metabolized by cytochrome P450 3A4 [57].

B) Metabolites

1) Estradiol

a) Estradiol, active [7][13][38][35][8][92][9][11][12][36][14][15][94]

1) Estradiol is the principal intracellular human estrogen and is substantially more potent at the receptor site than its metabolites, estrone and estriol [7][13][38][35][8][92][9][36][14][15][94].

b) Estrone, active [7][13][38][35][8][92][9][36][14][15][94]

c) Estriol, active[7][13][38][35][8][92][9][36][14][15][94]

2) Estradiol Acetate

a) Estradiol, active [170][60]

1) Estradiol is the principal intracellular human estrogen and is substantially more potent at the receptor site than its metabolites, estrone and estriol [170][60].

b) Estrone, active [170][60]

c) Estriol, active[170][60]

3) Estradiol Cypionate

a) Estrone, active [55]

b) Estriol, active[55]

c) Estradiol is the principal intracellular human estrogen and is substantially more potent at the receptor site than its metabolites, estrone and estriol [55].

4) Estradiol Valerate

a) Estrone, active [57]

b) Estriol, active[57]

c) Estradiol is the principal intracellular human estrogen and is substantially more potent at the receptor site than its metabolites, estrone and estriol [57].

Excretion

A) Kidney

1) Estradiol

a) Renal Clearance (rate)

1) Transdermal

a) Transdermal, patch (Alora(R)): 53 to 69 L/hr [8]

The mean clearance of Alora(R) over an 84-hour dosing interval is presented below [8]:

Dose (milligrams/day)	Application Site	N	Dosing	Clearance (liters/hour)
0.05	Abdomen	20	Multiple	54
0.075	Abdomen	20	Multiple	53
0.1	Abdomen	42	Multiple	61
0.05	Abdomen	31	Single	69
0.05	Buttock	31	Single	66
0.05	Hip*	31	Single	62

b) Renal Excretion (%)

1) 5% to 8% unchanged [15]

a) At 4 and 12 weeks after application of estradiol vaginal ring, the mean percent dose that was excreted in the urine as estradiol was 5% and 8%, respectively [15].

2) Estradiol, estrone, and estriol, as well as their glucuronide and sulfate conjugates, are excreted in urine [7][13][38][35][8][92][9][11][12][36][14][15][94].

2) Estradiol Acetate

a) Renal Excretion (%)

1) Estradiol, estrone, and estriol, as well as their glucuronide and sulfate conjugates, are excreted in urine [170][60].

3) Estradiol Cypionate

a) Renal Excretion (%)

1) Estradiol, estrone, and estriol, as well as their glucuronide and sulfate conjugates, are excreted in urine [55].

4) Estradiol Valerate

a) Renal Excretion (%)

1) Estradiol, estrone, and estriol, as well as their glucuronide and sulfate conjugates, are excreted in urine [57].

B) Bile

1) Estradiol

a) Estrogens undergo biliary secretion of conjugates into the intestine [7][13][38][35][8][92][9][11][12][36][14][15][94][502][503][504][505][114][506][507].

2) Estradiol Acetate

a) Estrogens undergo biliary secretion of conjugates into the intestine [170][60][502][503][504][505][114][506][507].

3) Estradiol Cypionate

a) Estrogens undergo biliary secretion of conjugates into the intestine, hydrolyzed and reabsorbed [55][502][503][504][505][114][506][507].

4) Estradiol Valerate

a) Estrogens undergo biliary secretion of conjugates into the intestine, hydrolyzed and reabsorbed [57][502][503][504][505][114][506][507].

Elimination Half-life

A) Parent Compound

1) Transdermal Gel

a) Estrogel(R): 36 hours [13][38]

1) The apparent terminal half-life for estradiol was 36 hours following administration of 1.25 g of Estrogel(R) and 36 hours [13].

b) Divigel(R): 10 hours [38]

1) The apparent terminal half-life of Divigel(R) was about 10 hours [38].

2) Transdermal Patch

a) Alora(R): 1.75 hours [8]

1) The apparent mean serum half-life of estradiol when administered as the Alora(R) transdermal patch was 1.75 +/- 2.87 hours [8].

b) Vivelle(R): 4.4 hours [11]

c) Vivelle-Dot(R): 5.9 to 7.7 hours [12]

B) Metabolites

1) Estradiol Acetate

a) Oral: estradiol, 21.4 hr to 25.9 hr [170]

b) Oral: baseline adjusted estrone, 15.9 hr to 17.6 hr [170]

1) In 18 healthy postmenopausal women, the mean half-life of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.45 milligrams was 25.9 and 15.9 hours, respectively. The mean half-life of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.9 milligrams was 22.2 and 16.1 hours, respectively. The mean half-life of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 1.8 milligrams was 21.4 and 17.6 hours, respectively [170].

Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: Total serum estradiol concentrations are higher in postmenopausal women with end stage renal disease (ESRD) receiving maintenance hemodialysis at baseline and following oral doses of estradiol. Therefore, the traditional transdermal doses used in patients with normal renal function may be excessive for patients with ESRD who are receiving hemodialysis[92]

PATIENT EDUCATION

Medication Counseling

No results available

Patient Handouts

A) Estradiol (Absorbed through the skin)
Estradiol

Treats hot flashes and other symptoms of menopause or low estrogen.

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 estradiol, or if you have liver disease, breast cancer, or certain other types of cancer. Do not use it if you have a

history of blood clotting problems, or if you had a heart attack or stroke. Do not use this medicine if you may be pregnant, or if you have unusual vaginal bleeding that has not been checked by your doctor.

How to Use This Medicine:

Liquid Mixture, Gel/Jelly, Spray

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you. This medicine is usually applied once a day, at the same time each day.
Use this medicine only on your skin. Rinse it off right away if it gets on a cut or scrape. Do not get the medicine in your eyes, nose, or mouth.
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 you use this medicine.
To use the emulsion:

Apply the emulsion to your legs. The usual daily dose is 2 foil pouches, 1 for each leg.
Cut or tear open the first pouch at the notches near the top. Squeeze out all of the medicine from the pouch onto the top of your left thigh. Rub the medicine thoroughly into your thigh and calf, for about 3 minutes. Repeat these steps to apply the medicine in the second pouch to the right thigh and calf.
Allow the medicine to dry completely before you get dressed. Wait at least 25 minutes before you put on sunscreen.

To use the gel:

Gel pump: You get the correct dose of estradiol each time you press the pump. You may need to prime the pump by pumping 3 times (EstroGel®) or 10 times (Elestrin™) the first time you use it. Follow the patient instructions for the container you use. After you prime the pump, do not press the pump more than 1 time each time you use it.
Apply the gel to clean, dry, and unbroken skin. Spread the gel as thinly as possible over the entire area on the inside and outside of 1 arm from your wrist to your shoulder. Do not apply the medicine directly to your breasts or in or around your vagina.
Do not allow others to come in contact with the area of skin where you applied the gel for at least 1 hour after you use the medicine. Do not allow others to apply the gel for you. Allow the medicine to dry for at least 5 minutes before you get dressed.
Apply sunscreen at least 25 minutes after using Elestrin™ gel. Avoid applying sunscreen on the same application site for 7 days or more.
Gel packet: Cut or tear the Divigel® packet. Squeeze the packet contents onto your upper thigh. Gently spread the gel over your upper thigh, covering a space about the size of 2 palm prints. You do not need to massage or rub in the gel. Allow the gel to dry completely before you put on clothes. Alternate between your right and left upper thigh each day.
Do not allow others to come in contact with the area of skin where you applied the gel for at least 1 to 2 hours after you use the medicine. Do not allow others to apply the gel for you.

To use the spray:

The spray form comes in an applicator that delivers the same amount of estradiol with each spray. You need to prime the pump of a new spray applicator before you use it. Hold the spray upright and pump it 3 times. You only need to prime the pump the first time you use a new spray applicator.
Apply the medicine to clean, dry, and unbroken skin on the inside of your forearm between the elbow and the wrist. Do not apply the medicine directly to your breasts or in or around the vagina.
Allow the medicine to dry for at least 2 minutes before you get dressed. Wait at least 1 hour before you wash your skin.
If your doctor tells you to increase your dose, move the applicator to an area of the skin next to your previous application site before you apply the next dose. Do this for each spray.
Do not rub Evamist® spray into your skin.
Always place the protective cover back on the applicator.
Do not use the applicator for more than 56 sprays.
Apply sunscreen at least 1 hour before you apply Evamist®.

The estradiol gel and spray are flammable. Do not use these medicines near an open flame or while smoking.
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 foods and medicines can affect how estradiol works. Tell your doctor if you are using St John's wort, carbamazepine, clarithromycin, erythromycin, itraconazole, ketoconazole, phenobarbital, rifampin, ritonavir, thyroid medicine, or a blood thinner (such as warfarin).
Do not put cosmetics or skin care products on the treated skin.
Do not eat grapefruit or drink grapefruit juice while you are using this medicine.

Warnings While Using This Medicine:

Pregnancy after menopause is not likely, but if you think you could be pregnant, tell your doctor. This medicine could harm an unborn baby.
Tell your doctor if you are breastfeeding, or if you have kidney disease, asthma, diabetes, edema (body swelling), endometriosis, epilepsy, migraine headaches, porphyria, lupus, thyroid problems, heart disease, high blood pressure, high cholesterol or triglycerides, inherited angioedema, or a history of cancer. Tell your doctor if you had liver problems caused by pregnancy or estrogen.
This medicine may cause the following problems:

Higher risk of heart attack, stroke, or blood clots
Higher risk of endometrial cancer, breast cancer, or uterine cancer
Gallbladder disease
Higher risk of dementia

Tell any doctor or dentist who treats you that you are using this medicine. This medicine may affect certain medical test results. You may need to stop using this medicine before you have surgery or if you need to stay in bed for a long time.
Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments. You should have regular exams and mammograms as directed by your doctor.
Keep all medicine out of the reach of children. Never share your medicine with anyone.
Do not allow children or pets to touch the skin where you applied the medicine. If this happens, wash the child or pet's skin with soap and water.

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
Breast lumps
Chest pain, trouble breathing, or coughing up blood
Loss of vision, double vision, or other vision changes
Numbness or weakness on one side of your body, sudden or severe headache, problems with vision, speech, or walking
Sudden and severe stomach pain, with or without nausea, vomiting, fever, and lightheadedness
Swelling in your hands, ankles, or feet
Unusual vaginal bleeding or heavy bleeding

If you notice these less serious side effects, talk with your doctor:

Changes in weight or hair growth
Headache
Nausea, vomiting, or stomach cramps
Runny or stuffy nose, sore throat, or fever
Skin redness or itching where the medicine is applied
Swollen or tender breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.
B) Estradiol (By injection)
Estradiol

Treats hot flashes and other symptoms of menopause. Also treats prostate cancer in men, and treats lack of estrogen caused by a disorder of the ovaries in women.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to hormone medicines. Do not use this medicine if you are pregnant, or if you have abnormal vaginal bleeding that has not been checked by a doctor. You should not use this medicine if you have a history of cancer of the breast, ovary, or uterus. Do not use if you have liver disease or a history of heart attack, stroke, or blood clots.

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 one of your muscles. You may receive this medicine once a week, once every 2 weeks, or once every 4 weeks.
If you have not had your uterus removed (hysterectomy), you may need to use another hormone medicine together with estradiol. Carefully follow your doctor's instructions about all medicines you are using.
A nurse or other health provider will give you this medicine.
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.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
Use a new needle and syringe each time you inject your medicine.

If a Dose is Missed:
Call your doctor or pharmacist for instructions.

How to Store and Dispose of This Medicine:
If you store this medicine at home, keep it at room temperature, away from heat and direct light. Do not allow the medicine to get cold.
Throw away used needles in a hard, closed container that the needles cannot poke through. Keep this container away from children and pets.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine, containers, and other supplies. Throw away old medicine after the expiration date has passed.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Warnings While Using This Medicine:
It is unlikely that you will become pregnant while you are going through menopause. But, you should know that using this medicine while you are pregnant could harm your unborn baby. If you think you have become pregnant while using the medicine, tell your doctor right away. If you have recently had an infant, tell your doctor if you are breast feeding.
Make sure your doctor knows if you have asthma, epilepsy, migraine headaches, heart disease, or kidney disease. Also tell your doctor if you have endometriosis, gallbladder disease, liver disease, lupus, porphyria, or an underactive thyroid.
This medicine should not be used to treat or prevent heart disease or stroke. In fact, hormone therapy can increase your risk of certain heart or blood vessel problems. Tell your doctor if you have a history of heart attack, stroke, high blood pressure, congestive heart failure, blood clots, or circulation problems.
Your risk of heart disease or stroke from this medicine is higher if you smoke. Your risk is also increased if you have diabetes or high cholesterol, or if you are overweight. Talk with your doctor about ways to stop smoking. If you have diabetes, keep it under control. Ask your doctor about diet and exercise to control your weight and blood cholesterol level.
This medicine may also increase your risk of other medical problems, including certain types of cancer. Talk with your doctor about how these risks might affect you.
Tell any doctor or dentist who treats you that you are using this medicine. You may need to stop using this medicine several days before you have surgery or medical tests. This medicine may also affect the results of certain medical tests.

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
Blistering, peeling, red skin rash.
Breast changes or lumps.
Chest pain, or coughing up blood.
Dark-colored urine or pale stools, yellowing of your skin or the whites of your eyes.
Nausea, vomiting, loss of appetite, pain in your upper stomach.
Numbness or weakness in your arm or leg, or on one side of your body.
Pain in your lower leg (calf).
Shortness of breath, cold sweat, and bluish-colored skin.
Sudden or severe headache, problems with vision, speech, or walking.
Swelling in your hands, ankles, or feet.
Vaginal bleeding or spotting.

If you notice these less serious side effects, talk with your doctor:
Joint pain.
Breast pain or tenderness, discharge from your nipples.
Hair loss, increased hair growth, or skin changes.
Mood changes or depression.
Problems or discomfort when wearing contact lenses.
Vaginal itching or discharge.
Weight gain or loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.
C) Estradiol (By mouth)
Estradiol

Treats symptoms caused by menopause or removal of the ovaries, and treats prostate or breast cancer. Also prevents osteoporosis.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to estrogen medicines, if you are pregnant or breastfeeding, if you have had a blood clot, or if you have vaginal bleeding that has not been checked by a doctor. You should not use this medicine if you have had cancer of the uterus, or in certain cases of breast cancer.

How to Use This Medicine:
Tablet
Your doctor will tell you how much of this medicine to take and how often. Do not take more medicine or take it more often than your doctor tells you to.
You may take your medicine with food or milk to avoid stomach upset.

If a Dose is Missed:
If you miss a dose or forget to take your medicine, take it as soon as you can. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose.
Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.
Keep all medicine out of the reach of children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are also using a blood thinner (Coumadin®).

Warnings While Using This Medicine:
Although it is unlikely that a postmenopausal woman might become pregnant, you should know that using this medicine while you are pregnant could harm the unborn baby. If you think you have become pregnant while using the medicine, tell your doctor right away.
Make sure your doctor knows if you have gallbladder disease, diabetes, heart disease, high blood pressure, high levels of calcium in your blood (hypercalcemia), liver disease, asthma, epilepsy, migraine headaches, kidney disease, high cholesterol, or blood clots.
Taking large doses of estrogens over a long period of time may increase your risk of some kinds of cancer. If you have questions about this risk, talk with your doctor.
Your doctor will need to check your progress at regular visits while you are using this medicine (usually every 6 to 12 months). Be sure to keep all appointments.
Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may affect the results of certain medical tests.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Blistering, peeling, red skin rash
Lumps in breast (women and men)
Numbness or weakness in your arm or leg, pain in your chest or leg (calf)
Severe headache or vomiting, dizziness, slurred speech
Shortness of breath, coughing up blood
Swelling in your hands, ankles, or feet
Vaginal bleeding of unknown cause

If you notice these less serious side effects, talk with your doctor:
Changes in hair growth
Changes in your vision
Nausea, vomiting, stomach cramps, bloated feeling
Swollen and tender breasts (women and men)
Vaginal itching or discharge

If you notice other side effects that you think are caused by this medicine, tell your doctor.
D) Estradiol (Into the vagina)
Estradiol

Treats hot flashes, painful sexual intercourse, and other symptoms of menopause or low estrogen.

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 estradiol, or if

you are pregnant, or have unusual vaginal bleeding that has not been checked by your doctor. Do not use it if you have liver disease, breast or uterine cancer, problems with blood clots, or had a heart attack or stroke.

How to Use This Medicine:

Cream, Insert, Suppository

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.
Vaginal cream:

Measure the cream using the marks on the plastic applicator. Make sure you use the correct mark for your specific dose.

Vaginal ring:

Once the ring is in place, you should not be able to feel it. If you feel uncomfortable, the ring may not be inserted far enough. Gently push the ring farther into your vagina. If you feel pain, talk to your doctor.
The ring may move down accidently. This can happen if you strain to have a bowel movement. Gently push the ring back into place. If the ring comes all the way out, rinse it with warm water and put it back in. Call your doctor if the ring comes out several times.
Remove the ring after 90 days and insert a new one as needed.
Do not flush a used vaginal ring down the toilet. Wrap it with tissue or toilet pair and throw it in the trash.

Vaginal insert:

The insert should be used only in your vagina. Do not swallow the insert.
It is best to use this medicine at the same time each day.
Imvexxy™: Push an insert through the foil of the blister package and hold it with the larger end between your fingers. You may choose to put the insert into your vagina using the lying down or standing up position. Put the insert about 2 inches into your vagina, with the smaller end up, using your finger.
Vagifem®: Do not take the insert out of the applicator. If the insert comes out of the applicator when you open it, carefully put it back in. If the insert falls out of the applicator when you try to insert it, throw it away and use a new applicator and insert.

Store the unopened packages of this medicine 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 estradiol works. Tell your doctor if you are using carbamazepine, clarithromycin, erythromycin, itraconazole, ketoconazole, phenobarbital, rifampin, ritonavir, St John's wort, or thyroid medicines.
Do not eat grapefruit or drink grapefruit juice while you are using this medicine.
Ask your doctor before you use other products or medicines in your vagina. You may need to remove the ring first.

Warnings While Using This Medicine:

Pregnancy after menopause is not likely, but if you think you could be pregnant, tell your doctor. This medicine could harm an unborn baby.
Tell your doctor if you are breastfeeding, or if you have kidney disease, asthma, diabetes, edema, endometriosis, epilepsy, migraine headaches, porphyria, lupus, thyroid problems, heart disease, high blood pressure, high cholesterol, hereditary angioedema, bone problems, or a history of cancer. Tell your doctor if you had liver problems caused by pregnancy or estrogen. Tell your doctor if you have any problems with your vagina or in your pelvic area, including prolapse. Tell your doctor if you are having a surgery that requires inactivity for a long time.
This medicine may cause the following problems:

Increased risk of heart attack, stroke, or blood clots
Increased risk of endometrial, breast, ovarian, or uterine cancer
Possible risk of dementia (especially in women 65 years of age or older)
Gallbladder disease
Eye or vision problems
High blood pressure
High cholesterol or fats in the blood

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 check your progress and the effects of this medicine at regular visits. 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
Breast lumps or tenderness
Chest pain that may spread, coughing up blood, trouble breathing
Fever, diarrhea, muscle pain, dizziness, fainting
Numbness or weakness on one side of your body, sudden or severe headache, problems with speech or walking
Redness, pain, burning, or itching in or near your vagina
Sudden and severe stomach pain, nausea, vomiting
Swelling in your hands, ankles, or feet
Unusual vaginal bleeding, spotting, discharge, or itching
Vision changes

If you notice these less serious side effects, talk with your doctor:

If you notice other side effects that you think are caused by this medicine, tell your doctor.
E) Estradiol Patch (Absorbed through the skin)
Estradiol

Treats symptoms of menopause (including hot flashes and vaginal problems) in women with a uterus. Also treats low estrogen levels and prevent osteoporosis after menopause.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use if you had an allergic reaction to estradiol, or if you have unusual vaginal bleeding that has not been checked by your doctor. Do not use it if you have liver disease, breast cancer, estrogen-dependent tumors, bleeding problems, blood clots, dementia, heart or blood vessel disease, or had a heart attack or stroke.

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.
Place the patch on a clean, dry area of your lower stomach or upper buttock area, where there is no oil, lotion, or powder. Do not apply the patch on or near your breasts, over cut or broken skin, or in a spot where it might rub off (including the waistline).
Press the patch firmly in place with your hand for about 10 seconds.
Change your patch on the same days of each week, to help you remember.
If you have any adhesive left on your skin after you remove the patch, allow it to dry for 15 minutes. Then gently rub the sticky area with oil or lotion to remove the adhesive.
You may take a bath, shower, or swim while wearing a patch.
Fold the used patch in half with the sticky side together. Place it in a sturdy childproof container and throw away, out of the reach of children and pets. Do not flush the patch down the toilet.
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.
If a patch falls off, just put it back on a different area. If the patch does not stick completely, put on a new patch, but continue to follow your original schedule for changing to a new one.
Store the patches at room temperature in a closed container, away from heat, moisture, and direct light. Do not open the pouch until you are ready to use the patch.

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 foods and medicines can affect how estradiol works. Tell your doctor if you are using carbamazepine, clarithromycin, erythromycin, itraconazole, ketoconazole, phenobarbital, rifampin, ritonavir, St John's wort, thyroid medicine, or a blood thinner (including warfarin).
Do not eat grapefruit or drink grapefruit juice while you are using this medicine.

Warnings While Using This Medicine:

Pregnancy after menopause is not likely, but if you think you could be pregnant, tell your doctor. This medicine could harm an unborn baby.
Tell your doctor if you are breastfeeding, or if you have kidney disease, asthma, diabetes, endometriosis, seizures, migraine headaches, porphyria, lupus, thyroid problems, hereditary angioedema, edema (swelling), high blood pressure, high cholesterol or triglycerides, obesity, or a history of cancer. Tell your doctor if you have had your uterus (womb) removed (hysterectomy) or if you are having surgery that will require inactivity for a long time.
This medicine may cause the following problems:

Increased risk of heart attack, stroke, or blood clots
Increased risk of endometrial cancer, breast cancer, or uterine cancer
Possible risk of dementia, especially in women 65 years of age and older
Gallbladder disease
Eye or vision problems
High blood pressure
High cholesterol or fats in the blood
Thyroid problems

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
Blurred or other changes in vision
Breast lumps or tenderness
Chest pain that may spread,, trouble breathing, or coughing up blood
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Fever, diarrhea, muscle pain, dizziness, fainting
Numbness or weakness on one side of your body, sudden or severe headache, problems with vision, speech, or walking
Rapid weight gain, swelling in your hands, ankles, or feet
Redness, pain, burning, or itching in or near your vagina
Unusual vaginal bleeding or heavy bleeding

If you notice these less serious side effects, talk with your doctor:

Headache
Runny or stuffy nose
Skin redness or itching where the patch is placed

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

Estradiol
Estradiol, Micronized
Estradiol Acetate
Estradiol Benzoate
Estradiol Cyp
Estradiol Cypionate
Estradiol Enanthate
Estradiolum
Estradiol Valerate

C) Orphan Drug Status

1) This drug has one or more orphan drug designations, which may include approval or withdrawal of status: Access citation for FDA Orphan Drug Information [54].

D) Physicochemical Properties

1) Estradiol

a) Molecular Weight

1) 272.39 [757]

b) Solubility

1) Soluble in dioxane; slightly soluble in chloroform and ether; sparingly soluble in alcohol and acetone; and practically insoluble in water [758]

2) Estradiol Acetate

a) Molecular Weight

1) 314.42 [759]

3) Estradiol Valerate

a) Molecular Weight

1) 356.50 [57]

Storage & Stability

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].

Trade Names

No results available

Regulatory Status

No results available

References

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