Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

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Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society–appointed task force of nine experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusion: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments—appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health

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Abbreviations: BMD, bone mineral density; DSD, disorder/difference of sex development; DSM, Diagnostic and Statistical Manual of Mental Disorders; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; MHP, mental health professional; VTE, venous thromboembolism.

professional for adults (recommended)—should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment. (***J Clin Endocrinol Metab*** **102: 3869–3903, 2017)**

Summary of Recommendations

1.0 Evaluation of youth and adults

1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

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1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕◯◯)

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕◯)

2.0 Treatment of adolescents

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 |⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 |⊕⊕◯◯)

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 |⊕⊕◯◯)

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 |⊕⊕◯◯).

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕◯◯◯)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 |⊕⊕◯◯)

3.0 Hormonal therapy for transgender adults

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕◯)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 |⊕⊕⊕◯)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕◯◯)

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕◯◯◯)

4.0 Adverse outcome prevention and long-term care

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 |⊕⊕◯◯)

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 |⊕⊕◯◯)

4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 |⊕⊕◯◯)

4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 |⊕⊕◯◯)

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 |⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 |⊕◯◯◯)

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

5.0 Surgery for sex reassignment and gender confirmation

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 |⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 |⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 |⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 |⊕◯◯◯)

Changes Since the Previous Guideline

Both the current guideline and the one published in 2009 contain similar sections. Listed here are the sections contained in the current guideline and the corresponding number of recommendations: Introduction, Evaluation of Youth and Adults (5), Treatment of Adolescents (6), Hormonal Therapy for Transgender Adults (4), Adverse Outcomes Prevention and Long-term Care (7), and Surgery for Sex Reassignment and Gender Confirmation (6). The current introduction updates the diagnostic classification of "gender dysphoria/gender incongruence." It also reviews the development of "gender identity" and summarizes its natural development. The section on clinical evaluation of both youth and adults, defines in detail the professional qualifications required of those who diagnose and treat both adolescents and adults. We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional. We recommend against puberty blocking followed by gender-affirming hormone treatment of prepubertal children. Clinicians should inform pubertal children, adolescents, and adults seeking gender-confirming treatment of their options for fertility preservation. Prior to treatment, clinicians should evaluate the presence of medical conditions that may be worsened by hormone depletion and/or treatment. A multidisciplinary team, preferably composed of medical and mental health professionals, should monitor treatments. Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence. Physicians should educate transgender persons regarding the time course of steroid-induced physical changes. Treatment should include periodic monitoring of hormone levels and metabolic parameters, as well as assessments of bone density and the impact upon prostate, gonads, and uterus. We also make recommendations for transgender persons who plan genital gender-affirming surgery.

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of individuals with GD/gender incongruence a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low–quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the

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values that the task force considered in making the recommendation. In some instances, there are remarks in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision-making, general preventive care measures, and basic principles of the treatment of transgender persons. They labeled these "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to these principles.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society's Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The CGS and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.*, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers' bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Review

The task force commissioned two systematic reviews to support this guideline. The first one aimed to summarize the available evidence on the effect of sex steroid use in transgender individuals on lipids and cardiovascular outcomes. The review identified 29 eligible studies at moderate risk of bias. In transgender males (female to male), sex steroid therapy was associated with a statistically significant increase in serum triglycerides and low-density lipoprotein cholesterol levels. High-density lipoprotein cholesterol levels decreased significantly across all follow-up time periods. In transgender females (male to female), serum triglycerides were significantly higher without any changes in other parameters. Few myocardial infarction, stroke, venous thromboembolism (VTE), and death events were reported. These events were more frequent in transgender females. However, the quality of the evidence was low. The second review summarized the available evidence regarding the effect of sex steroids on bone health in transgender individuals and identified 13 studies. In transgender males, there was no statistically significant difference in the lumbar spine, femoral neck, or total hip BMD at 12 and 24 months compared with baseline values before initiating masculinizing hormone therapy. In transgender females, there was a statistically significant increase in lumbar spine BMD at 12 months and 24 months compared with baseline values before initiation of feminizing hormone therapy. There was minimal information on fracture rates. The quality of evidence was also low.

Introduction

Throughout recorded history (in the absence of an endocrine disorder) some men and women have experienced confusion and anguish resulting from rigid, forced conformity to sexual dimorphism. In modern history, there have been numerous ongoing biological, psychological, cultural, political, and sociological debates over various aspects of gender variance. The 20th century marked the emergence of a social awakening for men and women with the belief that they are "trapped" in the wrong body (3). Magnus Hirschfeld and Harry Benjamin, among others, pioneered the medical responses to those who sought relief from and a resolution to their profound discomfort. Although the term transsexual became widely known after Benjamin wrote "The Transsexual Phenomenon" (4), it was Hirschfeld who coined the term "transsexual" in 1923 to describe people who want to live a life that corresponds with their experienced gender vs their designated gender (5). Magnus Hirschfeld (6) and others (4, 7) have described other types of trans phenomena besides transsexualism. These early researchers proposed that the gender identity of these people was located somewhere along a unidimensional continuum. This continuum ranged from all male through "something in between" to all female. Yet such a classification does not take into account that people may have gender identities outside this continuum. For instance, some experience themselves as having both a male and female gender identity, whereas others completely renounce any gender classification (8, 9). There are also reports of individuals experiencing a continuous and rapid involuntary alternation between a male and female identity (10) or men who do not experience themselves as men but do not want to live as women (11, 12). In some countries, (*e.g.*, Nepal, Bangladesh, and Australia), these nonmale or nonfemale genders are officially recognized (13). Specific treatment protocols, however, have not yet been developed for these groups.

Instead of the term transsexualism, the current classification system of the American Psychiatric Association uses the term gender dysphoria in its diagnosis of persons who are not satisfied with their designated gender (14). The current version of the World Health Organization's ICD-10 still uses the term transsexualism when diagnosing adolescents and adults. However, for the ICD-11, the World Health Organization has proposed using the term "gender incongruence" (15).

Treating persons with GD/gender incongruence (15) was previously limited to relatively ineffective elixirs or creams. However, more effective endocrinology-based treatments became possible with the availability of testosterone in 1935 and diethylstilbestrol in 1938. Reports of individuals with GD/gender incongruence who were treated with hormones and gender-affirming surgery appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association was founded in September 1979 and is now called the World Professional Association for Transgender Health (WPATH). WPATH published its first Standards of Care in 1979. These standards have since been regularly updated, providing guidance for treating persons with GD/gender incongruence (16).

Prior to 1975, few peer-reviewed articles were published concerning endocrine treatment of transgender persons. Since then, more than two thousand articles about various aspects of transgender care have appeared.

It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with GD/gender incongruence.

In the future, we need more rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols. Specifically, endocrine treatment protocols for GD/gender incongruence should include the careful assessment of the following: (1) the effects of prolonged delay of puberty in adolescents on bone health, gonadal function, and the brain (including effects on cognitive, emotional, social, and sexual development); (2) the effects of treatment in adults on sex hormone levels; (3) the requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids during treatment; and (4) the risks and benefits of gender-affirming hormone treatment in older transgender people.

To successfully establish and enact these protocols, a commitment of mental health and endocrine investigators is required to collaborate in long-term, large-scale studies across countries that use the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools (*e.g.*, the European Network for the Investigation of Gender Incongruence) (17, 18).

Terminology and its use vary and continue to evolve. Table 1 contains the definitions of terms as they are used throughout this guideline.

Biological Determinants of Gender Identity Development

One's self-awareness as male or female changes gradually during infant life and childhood. This process of cognitive and affective learning evolves with interactions with parents, peers, and environment. A fairly accurate timetable exists outlining the steps in this process (19). Normative psychological literature, however, does not address if and when gender identity becomes crystallized and what factors contribute to the development of a gender identity that is not congruent with the gender of rearing. Results of studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomic—support the concept that gender identity and/or gender expression (20) likely reflect a complex interplay of biological, environmental, and cultural factors (21, 22).

With respect to endocrine considerations, studies have failed to find differences in circulating levels of sex steroids between transgender and nontransgender individuals (23). However, studies in individuals with a disorder/difference of sex development (DSD) have informed our understanding of the role that hormones may play in gender identity outcome, even though most persons with GD/gender incongruence do not have a DSD. For example, although most 46,XX adult individuals with virilizing congenital adrenal hyperplasia caused by mutations in *CYP21A2* reported a female gender identity, the prevalence of GD/gender incongruence was much greater in this group than in the general population without a DSD. This supports the concept that there is a role for prenatal/postnatal androgens in gender development (24–26), although some studies indicate that prenatal androgens are more likely to affect gender behavior and sexual orientation rather than gender identity *per se* (27, 28).

Researchers have made similar observations regarding the potential role of androgens in the development of gender identity in other individuals with DSD. For example, a review of two groups of 46,XY persons, each with androgen synthesis deficiencies and female raised, reported transgender male (female-to-male) gender role changes in 56% to 63% and 39% to 64% of patients, respectively (29). Also, in 46,XY female-raised individuals with cloacal

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Table 1. Definitions of Terms Used in This Guideline

Biological sex, biological male or female: These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (*e.g.*, a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided.
Cisgender: This means not transgender. An alternative way to describe individuals who are not transgender is "non-transgender people."
Gender-affirming (hormone) treatment: See "gender reassignment"
Gender dysphoria: This is the distress and unease experienced if gender identity and designated gender are not completely congruent (see Table 2). In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced "gender identity disorder" with "gender dysphoria" and changed the criteria for diagnosis.
Gender expression: This refers to external manifestations of gender, expressed through one's name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender.
Gender identity/experienced gender: This refers to one's internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below), gender identity is not visible to others.
Gender identity disorder: This is the term used for GD/gender incongruence in previous versions of DSM (see "gender dysphoria"). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using "gender incongruence of childhood."
Gender incongruence: This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity–related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment.
Gender variance: See "gender incongruence"
Gender reassignment: This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called gender-confirming or gender-affirming treatment.
Gender-reassignment surgery (gender-confirming/gender-affirming surgery): These terms refer only to the surgical part of gender-confirming/gender-affirming treatment.
Gender role: This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women.
Sex designated at birth: This refers to sex assigned at birth, usually based on genital anatomy.
Sex: This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.
Sexual orientation: This term describes an individual's enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer.
Transgender: This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment.
Transgender male (also: trans man, female-to-male, transgender male): This refers to individuals assigned female at birth but who identify and live as men.
Transgender woman (also: trans woman, male-to female, transgender female): This refers to individuals assigned male at birth but who identify and live as women.
Transition: This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.
Transsexual: This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.

exstrophy and penile agenesis, the occurrence of transgender male changes was significantly more prevalent than in the general population (30, 31). However, the fact that a high percentage of individuals with the same conditions did not change gender suggests that cultural factors may play a role as well.

With respect to genetics and gender identity, several studies have suggested heritability of GD/gender incongruence (32, 33). In particular, a study by Heylens *et al.* (33) demonstrated a 39.1% concordance rate for gender identity disorder (based on the DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs. Although numerous investigators have sought to identify specific genes associated with GD/gender incongruence, such studies have been inconsistent and without strong statistical significance (34–38).

Studies focusing on brain structure suggest that the brain phenotypes of people with GD/gender incongruence differ in various ways from control males and females, but that there is not a complete sex reversal in brain structures (39).

In summary, although there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental factors, contribute to this fundamental aspect of human development.

Natural History of Children With GD/Gender Incongruence

With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called "desisters"). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence (20, 40). In adolescence, a significant number of these desisters identify as homosexual or bisexual. It may be that children who only showed some gender nonconforming characteristics have been included in the follow-up studies, because the DSM-IV text revision criteria for a diagnosis were rather broad. However, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (41, 42). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy. Together with an MHP, hormone-prescribing clinicians should examine the psychosocial impact of the potential changes on people's lives, including mental health, friends, family, jobs, and their role in society. Transgender individuals should be encouraged to experience living in the new gender role and assess whether this improves their quality of life. Although the focus of this guideline is gender-affirming hormone therapy, collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome.

Diagnostic assessment and mental health care

GD/gender incongruence may be accompanied with psychological or psychiatric problems (43–51). It is therefore necessary that clinicians who prescribe hormones and are involved in diagnosis and psychosocial assessment meet the following criteria: (1) are competent in using the DSM and/or the ICD for diagnostic purposes, (2) are able to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) are trained in diagnosing psychiatric conditions, (4) undertake or refer for appropriate treatment, (5) are able to do a psychosocial assessment of the patient's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) regularly attend relevant professional meetings.

Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex.

During assessment, the clinician obtains information from the individual seeking gender-affirming treatment. In the case

Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
   1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
   2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
   3. A strong desire for the primary and/or secondary sex characteristics of the other gender
   4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
   5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
   6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:
   1. The condition exists with a disorder of sex development.
   2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (*e.g.*, penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

Reference: American Psychiatric Association (14).

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of adolescents, the clinician also obtains information from the parents or guardians regarding various aspects of the child's general and psychosexual development and current functioning. On the basis of this information, the clinician:

- decides whether the individual fulfills criteria for treatment (see Tables 2 and 3) for GD/gender incongruence (DSM-5) or transsexualism (DSM-5 and/or ICD-10);
- informs the individual about the possibilities and limitations of various kinds of treatment (hormonal/surgical and nonhormonal), and if medical treatment is desired, provides correct information to prevent unrealistically high expectations;
- assesses whether medical interventions may result in unfavorable psychological and social outcomes.

In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with positive outcomes (52–56).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (57) and an assessment of the decision-making capability of the youth. An evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic phase (58).

Social transitioning

A change in gender expression and role (which may involve living part time or full time in another gender role that is consistent with one's gender identity) may test the person's resolve, the capacity to function in the affirmed gender, and the adequacy of social, economic, and psychological supports. It assists both the individual and the clinician in their judgments about how to proceed (16). During social transitioning, the person's feelings about the social transformation (including coping with the responses of others) is a major focus of the counseling. The optimal timing for social transitioning may differ between individuals. Sometimes people wait until they start gender-affirming hormone treatment to make social transitioning easier, but individuals increasingly start social transitioning long before they receive medically supervised, gender-affirming hormone treatment.

Criteria

Adolescents and adults seeking gender-affirming hormone treatment and surgery should satisfy certain criteria before proceeding (16). Criteria for gender-affirming hormone therapy for adults are in Table 4, and criteria for gender-affirming hormone therapy for adolescents are in Table 5. Follow-up studies in adults meeting these criteria indicate a high satisfaction rate with treatment (59). However, the quality of evidence is usually low. A few follow-up studies on adolescents who fulfilled these criteria also indicated good treatment results (60–63).

Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence

1.1. We advise that only trained MHPs who meet the following criteria should diagnose GD/gender incongruence in adults: (1) competence in using the DSM and/or the ICD for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or ICD for diagnostic

Table 3. ICD-10 Criteria for Transsexualism

Transsexualism (F64.0) has three criteria:
1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 y.
3. The disorder is not a symptom of another mental disorder or a genetic, DSD, or chromosomal abnormality.

Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (43–48, 50, 51, 64, 65). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (66), or certain forms of eunuchism (in which a person is preoccupied with or engages in castration and/or penectomy for

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
- the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
- gender dysphoria worsened with the onset of puberty,
- any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
- the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,

2. And the adolescent:
- has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
- agrees with the indication for GnRH agonist treatment,
- has confirmed that puberty has started in the adolescent (Tanner stage ≥G2/B2),
- has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
- the persistence of gender dysphoria,
- any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
- the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,

2. And the adolescent:
- has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
- agrees with the indication for sex hormone treatment,
- has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

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reasons that are not gender identity related) (11). Clinicians should also be able to diagnose psychiatric conditions accurately and ensure that these conditions are treated appropriately, particularly when the conditions may complicate treatment, affect the outcome of gender-affirming treatment, or be affected by hormone use.

Values and preferences

The task force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the good practice statement.

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 |⊕⊕◯◯)

Evidence

In most children diagnosed with GD/gender incongruence, it did not persist into adolescence. The percentages differed among studies, probably dependent on which version of the DSM clinicians used, the patient's age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/gender incongruent in adolescence (20). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (40). Social transition is associated with the persistence of GD/gender incongruence as a child progresses into adolescence. It may be that the presence of GD/gender incongruence in prepubertal children is the earliest sign that a child is destined to be transgender as an adolescent/adult (20). However, social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence.

This recommendation, however, does not imply that children should be discouraged from showing gender-variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the GD/gender-incongruent children to whom this applies. At the present time, clinical experience suggests that persistence of GD/gender incongruence can only be reliably assessed after the first signs of puberty.

Values and preferences

The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence. This justifies the strong recommendation in the face of low-quality evidence.

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 |⊕⊕⊕◯)

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (67, 68). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding the future fertility of adolescents or adults beginning gender-affirming treatment.

Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option. This option is often not preferred, because mature sperm production is associated with later stages of puberty and with the significant development of secondary sex characteristics.

For those designated male at birth with GD/gender incongruence and who are in early puberty, sperm production and the development of the reproductive tract are insufficient for the cryopreservation of sperm. However, prolonged pubertal suppression using GnRH analogs is reversible and clinicians should inform these individuals that sperm production can be initiated following prolonged gonadotropin suppression. This can be accomplished by spontaneous gonadotropin recovery after

cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production, as stated above. Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In males treated for precocious puberty, spermarche was reported 0.7 to 3 years after cessation of GnRH analogs (69). In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6 to 12 months of gonadotropin treatment. However, sperm numbers when partners of these patients conceive are far below the "normal range" (70, 71).

In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (72, 73). Clinicians should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression.

In males with GD/gender incongruence, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis is currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In females with GD/gender incongruence, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender males, both prior to and as a result of androgen treatment (74–77), although these reports were not confirmed by others (78). Pregnancy has been reported in transgender males who have had prolonged androgen treatment and have discontinued testosterone but have not had genital surgery (79, 80). A reproductive endocrine gynecologist can counsel patients before gender-affirming hormone treatment or surgery regarding potential fertility options (81). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve, and oocyte maturation of immature tissue is being studied (82).

2.0 Treatment of Adolescents

During the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. However, for many adolescents with GD/gender incongruence, the pubertal physical changes are unbearable. As early medical intervention may prevent psychological harm, various clinics have decided to start treating young adolescents with GD/gender incongruence with puberty-suppressing medication (a GnRH analog). As compared with starting gender-affirming treatment long after the first phases of puberty, a benefit of pubertal suppression at early puberty may be a better psychological and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche occurs ~2 years later. In boys, the first physical change is testicular growth. A testicular volume ≥4 mL is seen as consistent with the initiation of physical puberty. At the beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early morning with an ultrasensitive assay. From a testicular volume of 10 mL, daytime testosterone levels increase, leading to virilization (83). Note that pubic hair and/or axillary hair/odor may not reflect the onset of gonadarche; instead, it may reflect adrenarche alone.

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment (Table 5), and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 |⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty (Tanner stages G2/B2). (2 |⊕⊕◯◯)

Evidence

Pubertal suppression can expand the diagnostic phase by a long period, giving the subject more time to explore options and to live in the experienced gender before making a decision to proceed with gender-affirming sex hormone treatments and/or surgery, some of which is irreversible (84, 85). Pubertal suppression is fully reversible, enabling full pubertal development in the natal gender, after cessation of treatment, if appropriate. The experience of full endogenous puberty is an undesirable condition for the GD/gender-incongruent individual and may seriously interfere with healthy psychological functioning and well-being. Treating GD/gender-incongruent adolescents entering puberty with GnRH analogs has been shown to improve psychological functioning in several domains (86).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared with initiating physical transition after puberty has been completed (60, 62). Looking like a man or woman when living as the opposite sex creates difficult

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barriers with enormous life-long disadvantages. We therefore advise starting suppression in early puberty to prevent the irreversible development of undesirable secondary sex characteristics. However, adolescents with GD/gender incongruence should experience the first changes of their endogenous spontaneous puberty, because their emotional reaction to these first physical changes has diagnostic value in establishing the persistence of GD/gender incongruence (85). Thus, Tanner stage 2 is the optimal time to start pubertal suppression. However, pubertal suppression treatment in early puberty will limit the growth of the penis and scrotum, which will have a potential effect on future surgical treatments (87).

Clinicians can also use pubertal suppression in adolescents in later pubertal stages to stop menses in transgender males and prevent facial hair growth in transgender females. However, in contrast to the effects in early pubertal adolescents, physical sex characteristics (such as more advanced breast development in transgender boys and lowering of the voice and outgrowth of the jaw and brow in transgender girls) are not reversible.

Values and preferences

These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression.

Remarks

Table 6 lists the Tanner stages of breast and male genital development. Careful documentation of hallmarks of pubertal development will ensure precise timing when initiating pubertal suppression once puberty has started. Clinicians can use pubertal LH and sex steroid levels to confirm that puberty has progressed sufficiently before starting pubertal suppression (88). Reference ranges for sex steroids by Tanner stage may vary depending on the assay used. Ultrasensitive sex steroid and gonadotropin assays will help clinicians document early pubertal changes.

Irreversible and, for GD/gender-incongruent adolescents, undesirable sex characteristics in female puberty are breasts, female body habitus, and, in some cases, relative short stature. In male puberty, they are a prominent Adam's apple; low voice; male bone configuration, such as a large jaw, big feet and hands, and tall stature; and male hair pattern on the face and extremities.

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 l⊕⊕○○)

Evidence

Clinicians can suppress pubertal development and gonadal function most effectively via gonadotropin suppression using GnRH analogs. GnRH analogs are long-acting agonists that suppress gonadotropins by GnRH receptor desensitization after an initial increase of gonadotropins during ~10 days after the first and (to a lesser degree) the second injection (89). Antagonists immediately suppress pituitary gonadotropin secretion (90, 91). Long-acting GnRH analogs are the currently preferred treatment option. Clinicians may consider long-acting GnRH antagonists when evidence on their safety and efficacy in adolescents becomes available.

During GnRH analog treatment, slight development of secondary sex characteristics may regress, and in a later phase of pubertal development, it will stop. In girls, breast tissue will become atrophic, and menses will stop. In boys, virilization will stop, and testicular volume may decrease (92).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploration of his/her transition wish, the individual no longer desires transition, they can discontinue pubertal suppression. In subjects with

Table 6. Tanner Stages of Breast Development and Male External Genitalia

The description of Tanner stages for breast development:
1. Prepubertal
2. Breast and papilla elevated as small mound; areolar diameter increased
3. Breast and areola enlarged, no contour separation
4. Areola and papilla form secondary mound
5. Mature; nipple projects, areola part of general breast contour

For penis and testes:
1. Prepubertal, testicular volume <4 mL
2. Slight enlargement of penis; enlarged scrotum, pink, texture altered, testes 4–6 mL
3. Penis longer, testes larger (8–12 mL)
4. Penis and glans larger, including increase in breadth; testes larger (12–15 mL), scrotum dark
5. Penis adult size; testicular volume > 15 ml

Adapted from Lawrence (56).

precocious puberty, spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH analogs (93).

Recommendations 2.1 to 2.3 are supported by a prospective follow-up study from The Netherlands. This report assessed mental health outcomes in 55 transgender adolescents/young adults (22 transgender females and 33 transgender males) at three time points: (1) before the start of GnRH agonist (average age of 14.8 years at start of treatment), (2) at initiation of gender-affirming hormones (average age of 16.7 years at start of treatment), and (3) 1 year after "gender-reassignment surgery" (average age of 20.7 years) (63). Despite a decrease in depression and an improvement in general mental health functioning, GD/gender incongruence persisted through pubertal suppression, as previously reported (86). However, following sex hormone treatment and gender-reassignment surgery, GD/gender incongruence was resolved and psychological functioning steadily improved (63). Furthermore, well-being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long-term follow-up of individuals managed according to currently existing clinical practice guidelines for transgender youth, and it underscores the benefit of the multidisciplinary approach pioneered in The Netherlands; however, further studies are needed.

Side effects

The primary risks of pubertal suppression in GD/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development. Few data are available on the effect of GnRH analogs on BMD in adolescents with GD/gender incongruence. Initial data in GD/gender-incongruent subjects demonstrated no change of absolute areal BMD during 2 years of GnRH analog therapy but a decrease in BMD *z* scores (85). A recent study also suggested suboptimal bone mineral accrual during GnRH analog treatment. The study reported a decrease in areal BMD *z* scores and of bone mineral apparent density *z* scores (which takes the size of the bone into account) in 19 transgender males treated with GnRH analogs from a mean age of 15.0 years (standard deviation = 2.0 years) for a median duration of 1.5 years (0.3 to 5.2 years) and in 15 transgender females treated from 14.9 (±1.9) years for 1.3 years (0.5 to 3.8 years), although not all changes were statistically significant (94). There was incomplete catch-up at age 22 years after sex hormone treatment from age 16.6 (±1.4) years for a median duration of 5.8 years (3.0 to 8.0 years) in transgender females and from age 16.4 (±2.3) years for 5.4 years (2.8 to 7.8 years) in transgender males. Little is known about more prolonged use of GnRH analogs. Researchers reported normal BMD *z* scores at age 35 years in one individual who used GnRH analogs from age 13.7 years until age 18.6 years before initiating sex hormone treatment (65).

Additional data are available from individuals with late puberty or GnRH analog treatment of other indications. Some studies reported that men with constitutionally delayed puberty have decreased BMD in adulthood (95). However, other studies reported that these men have normal BMD (96, 97). Treating adults with GnRH analogs results in a decrease of BMD (98). In children with central precocious puberty, treatment with GnRH analogs has been found to result in a decrease of BMD during treatment by some (99) but not others (100). Studies have reported normal BMD after discontinuing therapy (69, 72, 73, 101, 102). In adolescents treated with growth hormone who are small for gestational age and have normal pubertal timing, 2-year GnRH analog treatments did not adversely affect BMD (103). Calcium supplementation may be beneficial in optimizing bone health in GnRH analog–treated individuals (104). There are no studies of vitamin D supplementation in this context, but clinicians should offer supplements to vitamin D–deficient adolescents. Physical activity, especially during growth, is important for bone mass in healthy individuals (103) and is therefore likely to be beneficial for bone health in GnRH analog–treated subjects.

GnRH analogs did not induce a change in body mass index standard deviation score in GD/gender-incongruent adolescents (94) but caused an increase in fat mass and decrease in lean body mass percentage (92). Studies in girls treated for precocious puberty also reported a stable body mass index standard deviation score during treatment (72) and body mass index and body composition comparable to controls after treatment (73).

Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRH analogs for precocious/early puberty (105, 106). Blood pressure monitoring before and during treatment is recommended.

Individuals may also experience hot flashes, fatigue, and mood alterations as a consequence of pubertal suppression. There is no consensus on treatment of these side effects in this context.

It is recommended that any use of pubertal blockers (and subsequent use of sex hormones, as detailed below) include a discussion about implications for fertility (see recommendation 1.3). Transgender adolescents may

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want to preserve fertility, which may be otherwise compromised if puberty is suppressed at an early stage and the individual completes phenotypic transition with the use of sex hormones.

Limited data are available regarding the effects of GnRH analogs on brain development. A single cross-sectional study demonstrated no compromise of executive function (107), but animal data suggest there may be an effect of GnRH analogs on cognitive function (108).

Values and preferences

Our recommendation of GnRH analogs places a higher value on the superior efficacy, safety, and reversibility of the pubertal hormone suppression achieved (as compared with the alternatives) and a relatively lower value on limiting the cost of therapy. Of the available alternatives, depot and oral progestin preparations are effective. Experience with this treatment dates back prior to the emergence of GnRH analogs for treating precocious puberty in papers from the 1960s and early 1970s (109–112). These compounds are usually safe, but some side effects have been reported (113–115). Only two recent studies involved transgender youth (116, 117). One of these studies described the use of oral lynestrenol monotherapy followed by the addition of testosterone treatment in transgender boys who were at Tanner stage B4 or further at the start of treatment (117). They found lynestrenol safe, but gonadotropins were not fully suppressed. The study reported metrorrhagia in approximately half of the individuals, mainly in the first 6 months. Acne, headache, hot flashes, and fatigue were other frequent side effects. Another progestin that has been studied in the United States is medroxyprogesterone. This agent is not as effective as GnRH analogs in lowering endogenous sex hormones either and may be associated with other side effects (116). Progestin preparations may be an acceptable treatment for persons without access to GnRH analogs or with a needle phobia. If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see adult section).

Remarks

Measurements of gonadotropin and sex steroid levels give precise information about gonadal axis suppression, although there is insufficient evidence for any specific short-term monitoring scheme in children treated with GnRH analogs (88). If the gonadal axis is not completely suppressed—as evidenced by (for example) menses, erections, or progressive hair growth—the interval of GnRH analog treatment can be shortened or the dose increased. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Table 7 illustrates a suggested clinical protocol.

Anthropometric measurements and X-rays of the left hand to monitor bone age are informative for evaluating growth. To assess BMD, clinicians can perform dual-energy X-ray absorptiometry scans.

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule (see Table 8) after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years (Table 5). (1 |⊕⊕◯◯)

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕◯◯◯)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment (Table 9). (2 |⊕⊕◯◯)

Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

Every 3–6 mo
Anthropometry: height, weight, sitting height, blood pressure, Tanner stages
Every 6–12 mo
Laboratory: LH, FSH, E2/T, 25OH vitamin D
Every 1–2 y
Bone density using DXA
Bone age on X-ray of the left hand (if clinically indicated)

Adapted from Hembree *et al.* (118).

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone;

Table 8. Protocol Induction of Puberty

Induction of female puberty with oral 17β-estradiol, increasing the dose every 6 mo:
- 5 μg/kg/d
- 10 μg/kg/d
- 15 μg/kg/d
- 20 μg/kg/d
- Adult dose = 2–6 mg/d
- *In postpubertal transgender female adolescents, the dose of 17β-estradiol can be increased more rapidly:*
  - 1 mg/d for 6 mo
  - 2 mg/d

Induction of female puberty with transdermal 17β-estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):
- 6.25–12.5 μg/24 h (cut 25-μg patch into quarters, then halves)
- 25 μg/24 h
- 37.5 μg/24 h
- Adult dose = 50–200 μg/24 h
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).*

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):
- 25 mg/m^2/2 wk (or alternatively, half this dose weekly, or double the dose every 4 wk)
- 50 mg/m^2/2 wk
- 75 mg/m^2/2 wk
- 100 mg/m^2/2 wk
- Adult dose = 100–200 mg every 2 wk
- *In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:*
  - 75 mg/2 wk for 6 mo
  - 125 mg/2 wk
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).*

Adapted from Hembree *et al.* (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15 to 16 years (119), and in many countries 16-year-olds are legally competent with regard to medical decision making (120). However, others believe that although some capacities are generally achieved before age 16 years, other abilities (such as good risk assessment) do not develop until well after 18 years (121). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures, such as most surgical procedures (121).

Currently available data from transgender adolescents support treatment with sex hormones starting at age 16 years (63, 122). However, some patients may incur potential risks by waiting until age 16 years. These include the potential risk to bone health if puberty is suppressed

Table 9. Baseline and Follow-up Protocol During Induction of Puberty

Every 3–6 mo
- •Anthropometry: height, weight, sitting height, blood pressure, Tanner stages

Every 6–12 mo
- •In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin D
- •In transgender females: prolactin, estradiol, 25OH vitamin D

Every 1–2 y
- •BMD using DXA
- •Bone age on X-ray of the left hand (if clinically indicated)

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).
For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.

Adapted from Hembree *et al.* (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.

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for 6 to 7 years before initiating sex hormones (*e.g.*, if someone reached Tanner stage 2 at age 9-10 years old). Additionally, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age. However, only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents currently exist (63). Clearly, long-term studies are needed to determine the optimal age of sex hormone treatment in GD/gender-incongruent adolescents.

The MHP who has followed the adolescent during GnRH analog treatment plays an essential role in assessing whether the adolescent is eligible to start sex hormone therapy and capable of consenting to this treatment (Table 5). Support of the family/environment is essential. Prior to the start of sex hormones, clinicians should discuss the implications for fertility (see recommendation 1.5). Throughout pubertal induction, an MHP and a pediatric endocrinologist (or other clinician competent in the evaluation and induction of pubertal development) should monitor the adolescent. In addition to monitoring therapy, it is also important to pay attention to general adolescent health issues, including healthy life style choices, such as not smoking, contraception, and appropriate vaccinations (*e.g.*, human papillomavirus).

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal adolescents with GD/gender incongruence as they use in other individuals with hypogonadism, carefully monitoring for desired and undesired effects (Table 8). In transgender female adolescents, transdermal 17β-estradiol may be an alternative for oral 17β-estradiol. It is increasingly used for pubertal induction in hypogonadal females. However, the absence of low-dose estrogen patches may be a problem. As a result, individuals may need to cut patches to size themselves to achieve appropriate dosing (123). In transgender male adolescents, clinicians can give testosterone injections intramuscularly or subcutaneously (124, 125).

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 "Hormonal Therapy for Transgender Adults").

Values and preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (128).

Remarks

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed. Adult height may be a concern in transgender adolescents. In a transgender female adolescent, clinicians may consider higher doses of estrogen or a more rapid tempo of dose escalation during pubertal induction. There are no established treatments yet to augment adult height in a transgender male adolescent with open epiphyses during pubertal induction. It is not uncommon for transgender adolescents to present for clinical services after having completed or nearly completed puberty. In such cases, induction of puberty with sex hormones can be done more rapidly (see Table 8). Additionally, an adult dose of testosterone in transgender male adolescents may suffice to suppress the gonadal axis without the need to use a separate agent. At the appropriate time, the multidisciplinary team should adequately prepare the adolescent for transition to adult care.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are (1) to reduce endogenous sex hormone levels, and thus reduce

the secondary sex characteristics of the individual's designated gender, and (2) to replace endogenous sex hormone levels consistent with the individual's gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is codetermined in collaboration with both the person pursuing transition and the health care providers. The treatment team should include a medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender incongruence and the mental health concerns of transition, and a primary care provider able to provide care appropriate for transgender individuals. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being (129, 130).

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕◯)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment (Table 10). (1 |⊕⊕⊕◯)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕◯◯)

Evidence

It is the responsibility of the treating clinician to confirm that the person fulfills criteria for treatment. The treating clinician should become familiar with the terms and criteria presented in Tables 1–5 and take a thorough history from the patient in collaboration with the other members of the treatment team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, risks, and benefits of treatment are well understood; and the desire for transition persists. They also need to discuss fertility preservation options (see recommendation 1.3) (67, 68).

Transgender males

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in transgender males (Appendix A) (113, 114, 131–134). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (135). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (this is dependent on the specific assay, but is typically 320 to 1000 ng/dL) (Table 11) (136). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see section 4.0 "Adverse Outcome Prevention and Long-Term Care") and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in transgender males results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness in those genetically predisposed, and increased sexual desire (137).

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen
Very high risk of adverse outcomes:
•Thromboembolic disease
Moderate risk of adverse outcomes:
•Macroprolactinoma
•Breast cancer
•Coronary artery disease
•Cerebrovascular disease
•Cholelithiasis
•Hypertriglyceridemia
Transgender male: testosterone
Very high risk of adverse outcomes:
•Erythrocytosis (hematocrit > 50%)
Moderate risk of adverse outcomes:
•Severe liver dysfunction (transaminases > threefold upper limit of normal)
•Coronary artery disease
•Cerebrovascular disease
•Hypertension
•Breast or uterine cancer

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Table 11. Hormone Regimens in Transgender Persons

Transgender females[a]	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch (New patch placed every 3–5 d)	0.025–0.2 mg/d
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate[b]	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate[c]	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6%[d]	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

[a]Estrogens used with or without antiandrogens or GnRH agonist.

[b]Not available in the United States.

[c]One thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

[d]Avoid cutaneous transfer to other individuals.

In transgender males, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, cessation of menses (usually), and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (138). Clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Transgender females

The hormone regimen for transgender females is more complex than the transgender male regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for females (139). Most published clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range (21, 113, 114, 132–134, 139, 140).

Multiple adjunctive medications are available, such as progestins with antiandrogen activity and GnRH agonists (141). Spironolactone works by directly blocking androgens during their interaction with the androgen receptor (114, 133, 142). It may also have estrogenic activity (143). Cyproterone acetate, a progestational compound with antiandrogenic properties (113, 132, 144), is widely used in Europe. 5α-Reductase inhibitors do not reduce testosterone levels and have adverse effects (145).

Dittrich *et al.* (141) reported that monthly doses of the GnRH agonist goserelin acetate in combination with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 60 transgender females. Leuprolide and transdermal estrogen were as effective as cyproterone and transdermal estrogen in a comparative retrospective study (146).

Patients can take estrogen as oral conjugated estrogens, oral 17β-estradiol, or transdermal 17β-estradiol. Among estrogen options, the increased risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically (134, 140, 141), which is why we specifically suggest that it not be used in any transgender treatment plan. Data distinguishing among other estrogen options are less well established although there is some thought that oral routes of administration are more thrombogenic due to the "first pass effect" than are transdermal and parenteral routes, and that the risk of thromboembolic events is dose-dependent. Injectable estrogen and sublingual

estrogen may benefit from avoiding the first pass effect, but they can result in more rapid peaks with greater overall periodicity and thus are more difficult to monitor (147, 148). However, there are no data demonstrating that increased periodicity is harmful otherwise.

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogen use. Clinicians should measure serum estradiol and serum testosterone and maintain them at the level for premenopausal females (100 to 200 pg/mL and <50 ng/dL, respectively). The transdermal preparations and injectable estradiol cypionate or valerate preparations may confer an advantage in older transgender females who may be at higher risk for thromboembolic disease (149).

Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (150).

Not all individuals with GD/gender incongruence seek treatment as described (*e.g.*, male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (151). We need prospective studies to better understand treatment options for these persons.

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 |⊕○○○)

Evidence

Transgender males

Physical changes that are expected to occur during the first 1 to 6 months of testosterone therapy include cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice (152, 153), clitoromegaly, and male pattern hair loss (in some cases) (114, 144, 154, 155) (Table 12).

Transgender females

Physical changes that may occur in transgender females in the first 3 to 12 months of estrogen and antiandrogen therapy include decreased sexual desire, decreased spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, increased breast tissue growth, and redistribution of fat mass (114, 139, 149, 154, 155, 161) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (114, 139, 149, 155). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in transgender females has been studied (150), precise information about other changes induced by sex hormones is lacking (141). There is a great deal of variability among individuals, as evidenced during pubertal development. We all know that a major concern for transgender females is breast development. If we work with estrogens, the result will be often not what the transgender female expects.

Alternatively, there are transgender females who report an anecdotal improved breast development, mood, or sexual desire with the use of progestogens. However, there have been no well-designed studies of the role of progestogens in feminizing hormone regimens, so the question is still open.

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	—[a]
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	—[b]
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

[a] Prevention and treatment as recommended for biological men.

[b] Menorrhagia requires diagnosis and treatment by a gynecologist.

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Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y[a]
Scalp hair	Variable	—[b]
Voice changes	None	—[c]

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

[a]Complete removal of male sexual hair requires electrolysis or laser treatment or both.

[b]Familial scalp hair loss may occur if estrogens are stopped.

[c]Treatment by speech pathologists for voice training is most effective.

development in transgender females is extremely sparse and based on the low quality of evidence. Current evidence does not indicate that progestogens enhance breast development in transgender females, nor does evidence prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions (162).

Values and preferences

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.*, breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone–induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender males and females confers many of the same risks associated with sex hormone replacement therapy in nontransgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (131, 139).

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 |⊕⊕◯◯)

Evidence

Pretreatment screening and appropriate regular medical monitoring are recommended for both transgender males and females during the endocrine transition and periodically thereafter (26, 155). Clinicians should monitor weight and blood pressure, conduct physical exams, and assess routine health questions, such as tobacco use, symptoms of depression, and risk of adverse events such as deep vein thrombosis/pulmonary embolism and other adverse effects of sex steroids.

Transgender males

Table 14 contains a standard monitoring plan for transgender males on testosterone therapy (154, 159). Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (135).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (163, 164). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (144, 165, 166).

Transgender females

Table 15 contains a standard monitoring plan for transgender females on estrogens, gonadotropin suppression, or antiandrogens (160). Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitor serum estradiol levels using laboratories participating in external quality control, as measurements of estradiol in blood can be very challenging (167).

VTE may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (161). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (149). The incidence decreased when clinicians stopped administering ethinyl estradiol (161). Thus, the use of synthetic estrogens and conjugated estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1 of 60 of transgender females treated with a GnRH analog and oral

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:[a]
   a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
   b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
   c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

[a] Adapted from Lapauw *et al.* (154) and Ott *et al.* (159).

estradiol (141). The patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase gene. In an Austrian gender clinic, administering gender-affirming hormones to 162 transgender females and 89 transgender males was not associated with VTE, despite an 8.0% and 5.6% incidence of thrombophilia (159). A more recent multinational study reported only 10 cases of VTE from a cohort of 1073 subjects (168). Thrombophilia screening of transgender persons initiating hormone treatment should be restricted to those with a personal or family history of VTE (159). Monitoring D-dimer levels during treatment is not recommended (169).

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 l⊕⊕◯◯)

Evidence

Estrogen therapy can increase the growth of pituitary lactrotroph cells. There have been several reports of prolactinomas occurring after long-term, high-dose estrogen therapy (170–173). Up to 20% of transgender females treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (156). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or discontinuation of cyproterone acetate (157, 174, 175).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and every 2 years thereafter. Given that only a few case studies reported prolactinomas, and prolactinomas were not reported in large cohorts of estrogen-treated persons, the risk is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in transgender females, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels (174).

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
   a. Serum testosterone levels should be <50 ng/dL.
   b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

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4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕◯◯)

Evidence

Transgender males

Administering testosterone to transgender males results in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol values (176–179). Studies of the effect of testosterone on insulin sensitivity have mixed results (178, 180). A randomized, open-label uncontrolled safety study of transgender males treated with testosterone undecanoate demonstrated no insulin resistance after 1 year (181, 182). Numerous studies have demonstrated the effects of sex hormone treatment on the cardiovascular system (160, 179, 183, 184). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185). A systematic review of the literature found that data were insufficient (due to very low–quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176). Clinicians should manage cardiovascular risk factors as they emerge according to established guidelines (186).

Transgender females

A prospective study of transgender females found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (178). However, increased weight, blood pressure, and markers of insulin resistance attenuated these favorable lipid changes. In a meta-analysis, only serum triglycerides were higher at ≥24 months without changes in other parameters (187). The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).

Thus, there is limited evidence to determine whether estrogen is protective or detrimental on lipid and glucose metabolism in transgender females (176). With aging, there is usually an increase of body weight. Therefore, as with nontransgender individuals, clinicians should monitor and manage glucose and lipid metabolism and blood pressure regularly according to established guidelines (186).

4.4. We recommend that clinicians obtain BMD measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕◯◯)

Evidence

Transgender males

Baseline bone mineral measurements in transgender males are generally in the expected range for their pretreatment gender (188). However, adequate dosing of testosterone is important to maintain bone mass in transgender males (189, 190). In one study (190), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels in the normal range may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol, both systemically and locally in the bone.

Transgender females

A baseline study of BMD reported T scores less than −2.5 in 16% of transgender females (191). In aging males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (192, 193) and is more important for peak bone mass (194). Estrogen preserves BMD in transgender females who continue on estrogen and antiandrogen therapies (188, 190, 191, 195, 196).

Fracture data in transgender males and females are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss. There have been no studies to determine whether clinicians should use the sex assigned at birth or affirmed gender for assessing osteoporosis (*e.g.*, when using the FRAX tool). Although some researchers use the sex assigned at birth (with the assumption that bone mass has usually peaked for transgender people who initiate hormones in early adulthood), this should be assessed on a case-by-case basis until there are more data available. This assumption will be further complicated by the increasing prevalence of transgender people who undergo hormonal transition at a pubertal age or soon after puberty. Sex for comparison within risk assessment tools may be based on the age at which hormones were initiated and the length of exposure to hormones. In some cases, it may be

reasonable to assess risk using both the male and female calculators and using an intermediate value. Because all subjects underwent normal pubertal development, with known effects on bone size, reference values for birth sex were used for all participants (154).

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for those designated female at birth. (2 |⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 |⊕◯◯◯)

Evidence

Studies have reported a few cases of breast cancer in transgender females (197–200). A Dutch study of 1800 transgender females followed for a mean of 15 years (range of 1 30 years) found one case of breast cancer. The Women's Health Initiative study reported that females taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with females taking placebo (137).

In transgender males, a large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven breast cancers (194). The authors reported that this was not above the expected rate of breast cancers in cisgender females in this cohort. Furthermore, they did report one breast cancer that developed in a transgender male patient after mastectomy, supporting the fact that breast cancer can occur even after mastectomy. Indeed, there have been case reports of breast cancer developing in subareolar tissue in transgender males, which occurred after mastectomy (201, 202).

Women with primary hypogonadism (Turner syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (203, 204). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20 to 30 years). We need long-term studies to determine the actual risk, as well as the role of screening mammograms. Regular examinations and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen deprivation therapy (205). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (206). Although van Kesteren *et al.* (207) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostates of transgender females, studies have reported cases of benign prostatic hyperplasia in transgender females treated with estrogens for 20 to 25 years (208, 209). Studies have also reported a few cases of prostate carcinoma in transgender females (210–214).

Transgender females may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for transgender females who transitioned after age 20 years to have annual screening digital rectal examinations after age 50 years and prostate-specific antigen tests consistent with U.S. Preventive Services Task Force Guidelines (215).

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

Evidence

Although aromatization of testosterone to estradiol in transgender males has been suggested as a risk factor for endometrial cancer (216), no cases have been reported. When transgender males undergo hysterectomy, the uterus is small and there is endometrial atrophy (217, 218). Studies have reported cases of ovarian cancer (219, 220). Although there is limited evidence for increased risk of reproductive tract cancers in transgender males, health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer (221).

Values

Given the discomfort that transgender males experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. Additionally, in certain countries, the approval required to change the sex in a birth certificate for transgender males may be dependent on having a complete hysterectomy. Clinicians should help patients research nonmedical administrative criteria and

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provide counseling. If individuals decide not to undergo hysterectomy, screening for cervical cancer is the same as all other females.

5.0 Surgery for Sex Reassignment and Gender Confirmation

For many transgender adults, genital gender-affirming surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. The type of surgery falls into two main categories: (1) those that directly affect fertility and (2) those that do not. Those that change fertility (previously called sex reassignment surgery) include genital surgery to remove the penis and gonads in the male and removal of the uterus and gonads in the female. The surgeries that effect fertility are often governed by the legal system of the state or country in which they are performed. Other gender-conforming surgeries that do not directly affect fertility are not so tightly governed.

Gender-affirming surgical techniques have improved markedly during the past 10 years. Reconstructive genital surgery that preserves neurologic sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (187). Additionally, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (130, 144) (Table 16).

Surgery that affects fertility is irreversible. The World Professional Association for Transgender Health Standards of Care (222) emphasizes that the "threshold of 18 should not be seen as an indication in itself for active intervention." If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then the individual should not be referred for surgery (223, 224).

Gender-affirming genital surgeries for transgender females that affect fertility include gonadectomy, penectomy, and creation of a neovagina (225, 226). Surgeons often invert the skin of the penis to form the wall of the vagina, and several literatures reviews have reported on outcomes (227). Sometimes there is inadequate tissue to form a full neovagina, so clinicians have revisited using intestine and found it to be successful (87, 228, 229). Some newer vaginoplasty techniques may involve autologuous oral epithelial cells (230, 231).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also creating a sensate pedicled-spot adding a G spot to the neovagina to increase sensation (232). Most recently, plastic surgeons have developed techniques to fashion labia minora. To further complete the feminization, uterine transplants have been proposed and even attempted (233).

Neovaginal prolapse, rectovaginal fistula, delayed healing, vaginal stenosis, and other complications do sometimes occur (234, 235). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsivity and other aspects of sexual function are usually preserved following genital gender-affirming surgery (236, 237).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of transgender males (152, 238). No studies have compared the effectiveness of speech therapy, laryngeal surgery, or combined treatment.

Breast surgery is a good example of gender-confirming surgery that does not affect fertility. In all females, breast size exhibits a very broad spectrum. For transgender females to make the best informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, because the breasts continue to grow during that time (141, 155).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (*e.g.*, cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

laser treatments. Other feminizing surgeries, such as that to feminize the face, are now becoming more popular (239–241).

In transgender males, clinicians usually delay gender-affirming genital surgeries until after a few years of androgen therapy. Those surgeries that affect fertility in this group include oophorectomy, vaginectomy, and complete hysterectomy. Surgeons can safely perform them vaginally with laparoscopy. These are sometimes done in conjunction with the creation of a neopenis. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (242, 243). Radial forearm flap seems to be the most satisfactory procedure (228, 244). Other flaps also exist (245). Surgeons can make neopenile erections possible by reinervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (246, 247), but results are inconsistent (248). Surgeons can also stiffen the penis by imbedding some mechanical device (*e.g.*, a rod or some inflatable apparatus) (249, 250). Because of these limitations, the creation of a neopenis has often been less than satisfactory. Recently, penis transplants are being proposed (233).

In fact, most transgender males do not have any external genital surgery because of the lack of access, high cost, and significant potential complications. Some choose a metaoidioplasty that brings forward the clitoris, thereby allowing them to void in a standing position without wetting themselves (251, 252). Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (253).

The most important masculinizing surgery for the transgender male is mastectomy, and it does not affect fertility. Breast size only partially regresses with androgen therapy (155). In adults, discussions about mastectomy usually take place after androgen therapy has started. Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy 2 years after they begin androgen therapy and before age 18 years. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (254, 255). These often involve chest contouring (256). Mastectomy is often necessary for living comfortably in the new gender (256).

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕◯◯◯)

Evidence

Owing to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. However, one systematic review including a large numbers of studies reported satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (257). For transgender males, the outcomes are less certain. However, the problems are now better understood (258). Several postoperative studies report significant long-term psychological and psychiatric pathology (259–261). One study showed satisfaction with breasts, genitals, and femininity increased significantly and showed the importance of surgical treatment as a key therapeutic option for transgender females (262). Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of

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causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263). Reversal surgery in regretful male-to-female transsexuals after sexual reassignment surgery represents a complex, multistage procedure with satisfactory outcomes. Further insight into the characteristics of persons who regret their decision postoperatively would facilitate better future selection of applicants eligible for sexual reassignment surgery. We need more studies with appropriate controls that examine long-term quality of life, psychosocial outcomes, and psychiatric outcomes to determine the long-term benefits of surgical treatment.

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies criteria for gender-affirming surgery (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (176). For this reason, the surgeon and the hormone-prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery. One study suggests that preoperative factors (such as compliance) are less important for patient satisfaction than are the physical postoperative results (56). However, other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not achieve treatment goals (264) and experience higher rates of postoperative infections and other complications (265, 266). It is also important that the person requesting surgery feels comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (223).

An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.

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Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline

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Objective: The objective of this document is to generate a practice guideline for the management and treatment of symptoms of the menopause.

Participants: The Treatment of Symptoms of the Menopause Task Force included six experts, a methodologist, and a medical writer, all appointed by The Endocrine Society.

Evidence: The Task Force developed this evidenced-based guideline using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned three systematic reviews of published data and considered several other existing meta-analyses and trials.

Consensus Process: Multiple e-mail communications, conference calls, and one face-to-face meeting determined consensus. Committees of The Endocrine Society, representatives from endorsing societies, and members of The Endocrine Society reviewed and commented on the drafts of the guidelines. The Australasian Menopause Society, the British Menopause Society, European Menopause and Andropause Society, the European Society of Endocrinology, and the International Menopause Society (co-sponsors of the guideline) reviewed and commented on the draft.

Conclusions: Menopausal hormone therapy (MHT) is the most effective treatment for vasomotor symptoms and other symptoms of the climacteric. Benefits may exceed risks for the majority of symptomatic postmenopausal women who are under age 60 or under 10 years since the onset of menopause. Health care professionals should individualize therapy based on clinical factors and patient preference. They should screen women before initiating MHT for cardiovascular and breast cancer risk and recommend the most appropriate therapy depending on risk/benefit considerations. Current evidence does not justify the use of MHT to prevent coronary heart disease, breast cancer, or dementia. Other options are available for those with vasomotor symptoms who prefer not to use MHT or who have contraindications because these patients should not use MHT. Low-dose vaginal estrogen and ospemifene provide effective therapy for the genitourinary syndrome of menopause, and vaginal moisturizers and lubricants are available for those not choosing hormonal therapy. All postmenopausal women should embrace appropriate lifestyle measures. **(*J Clin Endocrinol Metab* 100: 3975–4011, 2015)**

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Abbreviations: BZA, bazedoxifene; CEE, conjugated equine estrogens; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DVT, deep vein thrombosis; EPT, estrogen plus progestogen therapy; ET, estrogen therapy; GSM, genitourinary syndrome of menopause; HR, hazard ratio; MetS, metabolic syndrome; MHT, menopausal hormone therapy; MI, myocardial infarction; MPA, medroxyprogesterone acetate; OTC, over the counter; PE, pulmonary embolism; POI, primary ovarian insufficiency; QOL, quality of life; RCT, randomized controlled trial; SERM, selective estrogen receptor modulator; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; VMS, vasomotor symptoms; VTE, venous thromboembolism; VVA, vulvovaginal atrophy.

Summary of Recommendations

1.0 Diagnosis and symptoms of menopause

1.1 We suggest diagnosing menopause based on the clinical criteria of the menstrual cycle. (2|⊕⊕◯◯)

1.2 If establishing a diagnosis of menopause is necessary for patient management in women having undergone a hysterectomy without bilateral oophorectomy or presenting with a menstrual history that is inadequate to ascertain menopausal status, we suggest making a presumptive diagnosis of menopause based on the presence of vasomotor symptoms (VMS) and, when indicated, laboratory testing that includes replicate measures of FSH and serum estradiol. (2|⊕⊕◯◯)

2.0 Health considerations for all menopausal women

2.1 When women present during the menopausal transition, we suggest using this opportunity to address bone health, smoking cessation, alcohol use, cardiovascular risk assessment and management, and cancer screening and prevention. (Ungraded best practice statement)

3.0 Hormone therapy for menopausal symptom relief

3.1 Estrogen and progestogen therapy

3.1a For menopausal women < 60 years of age or < 10 years past menopause with bothersome VMS (with or without additional climacteric symptoms) who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take menopausal hormone therapy (MHT), we suggest initiating estrogen therapy (ET) for those without a uterus and estrogen plus progestogen therapy (EPT) for those with a uterus. (2|⊕⊕◯◯)

Cardiovascular risk

3.1b For women < age 60 or < 10 years past menopause onset considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of cardiovascular disease (CVD) and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2|⊕⊕◯◯)

3.1c For women at high risk of CVD, we suggest initiating nonhormonal therapies to alleviate bothersome VMS (with or without climacteric symptoms) over MHT. (2|⊕⊕◯◯)

3.1d For women with moderate risk of CVD, we suggest transdermal estradiol as first-line treatment, alone for women without a uterus or combined with micronized progesterone (or another progestogen that does not adversely modify metabolic parameters) for women with a uterus, because these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism. (2|⊕⊕◯◯)

Venous thromboembolic events

3.1e For women at increased risk of venous thromboembolism (VTE) who request MHT, we recommend a nonoral route of ET at the lowest effective dose, if not contraindicated (1|⊕⊕◯◯); for women with a uterus, we recommend a progestogen (for example, progesterone and dydrogestone) that is neutral on coagulation parameters. (1|⊕⊕⊕◯)

Breast cancer

3.1f For women considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of breast cancer and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2|⊕⊕◯◯)

3.1g For women at high or intermediate risk of breast cancer considering MHT for menopausal symptom relief, we suggest nonhormonal therapies over MHT to alleviate bothersome VMS. (2|⊕⊕◯◯)

Tailoring MHT

3.1h We suggest a shared decision-making approach to decide about the choice of formulation, starting dose, the route of administration of MHT, and how to tailor MHT to each woman's individual situation, risks, and treatment goals. (Ungraded best practice statement)

Custom-compounded hormones

3.1i We recommend using MHT preparations approved by the US Food and Drug Administration (FDA) and comparable regulating bodies outside the United States and recommend against the use of custom-compounded hormones. (Ungraded best practice statement)

3.2 Conjugated equine estrogens with bazedoxifene

3.2 For symptomatic postmenopausal women with a uterus and without contraindications, we suggest the combination of conjugated equine estrogens (CEE)/bazedoxifene (BZA) (where available) as an option for relief of VMS and prevention of bone loss. (2|⊕⊕⊕◯)

3.3 Tibolone

3.3a For women with bothersome VMS and climacteric symptoms and without contraindications, we suggest tibolone (in countries where available) as an alternative to MHT. (2|⊕⊕◯◯)

3.3b We recommend against adding tibolone to other forms of MHT. (1|⊕⊕◯◯)

3.3c We recommend against using tibolone in women with a history of breast cancer. (1|⊕⊕◯◯)

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3.4 Clinical management of patients taking hormone therapies

Monitoring during therapy

3.4a For women with persistent unscheduled bleeding while taking MHT, we recommend evaluation to rule out pelvic pathology, most importantly, endometrial hyperplasia and cancer. (1|⊕⊕⊕◯)

3.4b We recommend informing women about the possible increased risk of breast cancer during and after discontinuing EPT and emphasizing the importance of adhering to age-appropriate breast cancer screening. (1|⊕⊕⊕◯)

3.4c We suggest that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman. (Ungraded best practice statement)

3.4d For young women with primary ovarian insufficiency (POI), premature or early menopause, without contraindications, we suggest taking MHT until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed. (2|⊕⊕◯◯)

Stopping considerations

3.4e For women preparing to discontinue MHT, we suggest a shared decision-making approach to elicit individual preference about adopting a gradual taper vs abrupt discontinuation. (2|⊕⊕◯◯)

4.0 Nonhormonal therapies for VMS

4.0 For postmenopausal women with mild or less bothersome hot flashes, we suggest a series of steps that do not involve medication, such as turning down the thermostat, dressing in layers, avoiding alcohol and spicy foods, and reducing obesity and stress. (2|⊕⊕◯◯)

4.1 Nonhormonal prescription therapies for VMS

4.1a For women seeking pharmacological management for moderate to severe VMS for whom MHT is contraindicated, or who choose not to take MHT, we recommend selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) or gabapentin or pregabalin (if there are no contraindications). (1|⊕⊕⊕◯)

4.1b For those women seeking relief of moderate to severe VMS who are not responding to or tolerating the nonhormonal prescription therapies, SSRIs/SNRIs or gabapentin or pregabalin, we suggest a trial of clonidine (if there are no contraindications). (2|⊕⊕◯◯)

4.2 Over-the-counter and alternative nonhormonal therapies for VMS

4.2 For women seeking relief of VMS with over-the-counter (OTC) or complementary medicine therapies, we suggest counseling regarding the lack of consistent evidence for benefit for botanicals, black cohosh, omega-3-fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis. (2|⊕⊕◯◯)

5.0 Treatment of genitourinary syndrome of menopause

5.1 Vaginal moisturizers and lubricants

5.1a For postmenopausal women with symptoms of vulvovaginal atrophy (VVA), we suggest a trial of vaginal moisturizers to be used at least twice weekly. (2|⊕⊕◯◯)

5.1b For women who do not produce sufficient vaginal secretions for comfortable sexual activity, we suggest vaginal lubricants. (2|⊕⊕◯◯)

5.2 Vaginal estrogen therapies

5.2a For women without a history of hormone- (estrogen) dependent cancers who are seeking relief from symptoms of genitourinary syndrome of menopause (GSM) (including VVA) that persist despite using vaginal lubricants and moisturizers, we recommend low-dose vaginal ET. (1|⊕⊕⊕◯)

Practice statement

5.2b In women with a history of breast or endometrial cancer, who present with symptomatic GSM (including VVA), that does not respond to nonhormonal therapies, we suggest a shared decision-making approach that includes the treating oncologist to discuss using low-dose vaginal ET. (Ungraded best practice statement)

5.2c For women taking raloxifene, without a history of hormone- (estrogen) dependent cancers, who develop symptoms of GSM (including VVA) that do not respond to nonhormonal therapies, we suggest adding low-dose vaginal ET. (2|⊕⊕◯◯)

5.2d For women using low-dose vaginal ET, we suggest against adding a progestogen (ie, no need for adding progestogen to prevent endometrial hyperplasia). (2|⊕◯◯◯)

5.2e For women using vaginal ET who report postmenopausal bleeding or spotting, we recommend prompt evaluation for endometrial pathology. (1|⊕⊕◯◯)

5.3 Ospemifene

5.3a For treatment of moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women without contraindications, we suggest a trial of ospemifene. (2|⊕⊕⊕◯)

5.3b For women with a history of breast cancer presenting with dyspareunia, we recommend against ospemifene. (1|⊕◯◯◯)

Method of Development of Evidence-based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of The Endocrine Society deemed management of menopause a priority area in need of a practice guideline and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop the recommendations. The Task Force commissioned three systematic reviews of the literature to inform its key recommendations. The Task Force used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence using the recommendations of the GRADE system. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" or "we recommend against" and the number 1, and weak recommendations use the phrase "we suggest" or "we suggest against" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the values the panelists considered when making the recommendation. In some instances, there are remarks, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions. In this guideline, the Task Force made several statements to emphasize the importance of shared decision making, general preventive care measures, and basic principles of women's health. These were labeled as ungraded best practice statements. Direct evidence for these statements was either unavailable or not systematically appraised and was considered out of the scope of this guideline. The intention of these statements is to draw attention and remind providers of these principles, and these statements should not be considered as graded recommendations (3).

The 2013 Appraisal of Guidelines for Research and Evaluation II (AGREEII) criteria (23 items) were satisfied, with three exceptions. Item 5 stipulates that the views and preferences of the target population (patients, public, etc) have been sought. The Task Force did not conduct specific polling/outreach to the public in anticipation of this guideline. Item 14 states that a procedure for updating the guideline is provided. This process has not been formalized. Item 20 suggests that the potential resource implications of applying the recommendations have been considered. The Task Force did not include cost analysis of risk assessment tools or prescription drug therapies.

The Endocrine Society maintains a rigorous conflict-of-interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before the members are approved to serve on the Task Force and periodically during the development of the guideline. The conflict-of-interest forms are vetted by the CGS before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through the Endocrine Society office.

Funding for this guideline was derived solely from the Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

Commissioned systematic reviews

The Task Force formulated three questions for systematic reviews to provide evidence supporting this guideline. The first compared the effect of oral vs transdermal es-

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trogens on the risk of venous and arterial thrombotic events. Low-quality evidence derived from 15 observational studies suggested that, compared with transdermal MHT, oral MHT was associated with increased risk of VTE, deep vein thrombosis (DVT), and possibly stroke, but not myocardial infarction (MI) (4). The second question evaluated the effect of MHT on mortality. Data from 43 randomized controlled trials (RCTs) demonstrated no association between all-cause mortality, regardless of hormone type, the presence of pre-existing heart disease, or length of follow-up (5). Meta-analysis of 2 RCTs in which MHT was started at a *mean* age less than 60 and 3 RCTs in which MHT was started less than10 years after menopause suggested possible reduction of mortality with MHT. The third question compared the effect of MHT with natural progesterone vs synthetic progestins on breast cancer risk. Low-quality evidence from two observational studies suggested that natural progesterone may be associated with a reduced risk for breast cancer compared with synthetic progestins, but data were insufficient to draw a firm conclusion.

Introduction and background

VMS, hot flashes, and night sweats, are the hallmarks of menopause, although not all women experience these symptoms. Other climacteric symptoms include sleep disturbance (6, 7), arthralgia (7–9), and vaginal dryness and dyspareunia (7, 10, 11). It is less clear whether anxiety, irritability, depression, palpitations, skin dryness, loss of libido, and fatigue can be attributed to menopause (7, 9, 12). Symptoms frequently start in the years before the final menstrual period and can last, with unpredictable duration, from a few years to more than 13 years (13–16).

ET has long been recognized as the most effective treatment for the relief of bothersome vasomotor and vaginal symptoms associated with menopause. However, prescriptions for MHT declined considerably after the 2002 publication of the Women's Health Initiative (WHI) RCT. This study determined that for postmenopausal women (average age, 63 y), oral CEE alone after hysterectomy (17), or coupled with daily medroxyprogesterone acetate (MPA) in women with a uterus (18), was associated with risks disproportionate to preventive benefits (17, 18). During ensuing years, a consensus arose that most healthy symptomatic women, without contraindications and closer to the time of menopause (<10 y after menopause onset or age <60 y), were appropriate candidates for MHT for symptom relief (19, 20). Post hoc WHI analyses and observational data suggest that benefits exceed risks in most of these women. At this juncture, women in the United States and some other countries have a broader range of therapeutic choices than ever before, including: MHT dose, type, and route of administration; new selective estrogen receptor modulators (SERMs) as solo or combination therapies; and expanded choices of nonhormonal prescription medications. In this guideline, we emphasize safety in identifying which late perimenopausal and recently postmenopausal women are candidates for various therapeutic agents. Considerations include the risks and benefits of each available therapy, the expected duration of treatment, the intensity of monitoring during therapy, and most importantly, individualizing the course of therapy to reflect the specific characteristics of the patient who is making decisions regarding symptom management.

This guideline covers the full spectrum of therapies for relief of the most common and bothersome menopausal symptoms (Figure 1). (The detailed management of early menopause transition, primary ovarian insufficiency, and prevention of osteoporosis and fracture are considered beyond the current scope.) Choice of therapy is ideally based on available evidence regarding safety and efficacy and is generally a shared decision including both patient and provider. The treatment selected should be tailored to the individual patient and will vary according to each woman's symptom severity, age, medical profile, personal preference, and estimated benefit/risk ratio. The impact of severe menopausal symptoms on quality of life (QOL) can be substantial, and there are instances in which a woman with a history of coronary heart disease (CHD) or breast cancer, for example, will choose to accept a degree of risk that might otherwise be considered to outweigh the benefits of MHT. An accepted philosophy is that a fully informed patient should be empowered to make a decision that best balances individual QOL benefits against potential health risks (21).

1.0 Diagnosis and symptoms of menopause

1.1 We suggest diagnosing menopause based on the clinical criteria of the menstrual cycle. (2⊕⊕○○)

1.2 If establishing a diagnosis of menopause is necessary for patient management in women having undergone a hysterectomy without bilateral oophorectomy or presenting with a menstrual history that is inadequate to ascertain menopausal status, we suggest making a presumptive diagnosis of menopause based on the presence of VMS and, when indicated, laboratory testing that includes replicate measures of FSH and serum estradiol. (2⊕⊕○○)

Technical remark

Table 1 summarizes other etiologies of secondary amenorrhea to be considered in the differential diagnosis.

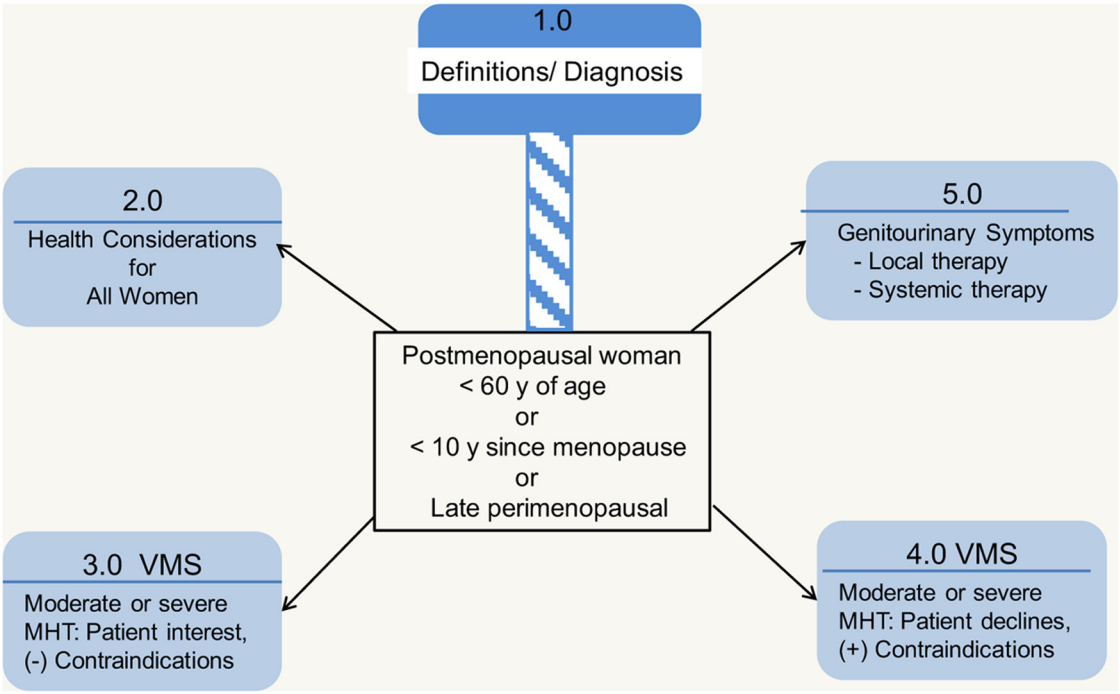

Figure 1. Approach to menopause guideline. Numbers correspond to section of text addressing selected clinical issue.

Diagnosis

Table 1 lists definitions of the clinical spectrum of menopause. In a woman with an intact uterus, menopause is a clinical diagnosis based upon cessation of menses for at least 12 months. Sex steroids, gonadotropins, inhibin B, or anti-Mullerian hormone measurements do not further inform the diagnosis, do not indicate precisely when the final menstrual period will occur, and will not influence management unless a woman is seeking fertility. In women having undergone a hysterectomy but not bilateral oophorectomy, elevated FSH levels and estradiol concentrations < 20 pg/mL on several occasions support but do not

Table 1. Definitions of Spectrum of Menopause

Menopause	Clinical status after the final menstrual period, diagnosed retrospectively after cessation of menses for 12 mo in a previously cycling woman and reflecting complete or nearly complete permanent cessation of ovarian function and fertility.
Spontaneous menopause	Cessation of menses that occurs at an average age of 51 y in the absence of surgery or medication (316–318).
Menopausal transition (or perimenopause)	An interval preceding the menopause characterized by variations in menstrual cycle length and bleeding pattern, mood shifts, vasomotor, and vaginal symptoms and with rising FSH levels and falling anti-Mullerian hormone and inhibin B levels, which starts during the late reproductive stage and progresses during the menopause transition (15, 319).
Climacteric	The phase in the aging of women marking the transition from the reproductive phase to the nonreproductive state. This phase incorporates the perimenopause by extending for a longer variable period before and after the perimenopause.
Climacteric syndrome	When the climacteric is associated with symptomatology.
Menopause after hysterectomy without oophorectomy	Spontaneous cessation of ovarian function without the clinical signal of cessation of menses.
Induced menopause	Cessation of ovarian function induced by chemotherapy, radiotherapy, or bilateral oophorectomy.
Early menopause	Cessation of ovarian function occurring between ages 40 and 45 in the absence of other etiologies for secondary amenorrhea (pregnancy, hyperprolactinemia, and thyroid disorders).
POI	Loss of ovarian function before the age of 40 y with waxing and waning course and potential resumption of menses, conception, and pregnancy (320). The prevalence of POI is approximately 1% (321) and is differentiated into idiopathic, autoimmune (associated with polyglandular autoimmune syndromes), metabolic disorders, and genetic abnormalities (including fragile X premutation).

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confirm the diagnosis. A distinction between the late perimenopause transition, marked by episodes of > 60 days of amenorrhea and increasing severity of VMS (15), and early postmenopause cannot be made on the sole basis of hormone measurements. With radiotherapy- or chemotherapy-induced menopause, it is important to recognize that ovarian function may resume after 12 months of amenorrhea (22), depending on the age of the woman and the dose and duration of treatment (22). For POI, persistent FSH elevation in women < age 40 provides a tentative diagnosis (Table 1).

Signs and symptoms

Vasomotor symptoms

Prevalence. Hot flashes (also called hot flushes) occur in approximately 75% of postmenopausal women in the United States (23). In the Study of Women Across the Nation (SWAN), after controlling for age, education, health, and economic strain, researchers found that US Caucasian women report more psychosomatic symptoms, African American and Hispanic women report more VMS, and Asian women report more somatic complaints (16, 24). Notably, across countries and ethnic backgrounds, the percentage of women reporting hot flashes varies (25–27). In a cross-sectional study of premenopausal women (mean age, 48 y), one-third reported "ever" experiencing hot flashes (28). A comparison between VMS experienced during the premenopause vs the postmenopause may be informative when counseling a postmenopausal woman regarding symptom relief, although to our knowledge, the presence and frequency of premenopausal hot flashes have not been studied as being predictive of response to therapy in the postmenopause. Persistence of hot flashes may also vary depending upon when in the menopausal transition VMS were first noted. In SWAN, earlier onset of VMS was associated with longer postmenopausal duration (16).

Clinical manifestations. Hot flashes typically begin as the sudden sensation of heat centered on the upper chest and face. When moderate or severe, the hot flash rapidly becomes generalized, lasts from 2 to 4 minutes, and can be associated with profuse perspiration, palpitations, or anxiety. Triggers include spicy food or alcohol. At night, vasomotor instability manifests as hot flashes or night sweats, which may represent different physiological mechanisms. The differential diagnosis includes several entities distinguishable by clinical features (Table 2). New-onset VMS in older (age, ≥ 65 y) postmenopausal women may be associated with, but not necessarily causally related to, increased risk of major CHD and all-cause mortality (29).

Table 2. Conditions That May Cause or Mimic Vasomotor Events and That Can Be Distinguished From Menopausal Symptoms by History, Examination, and Investigations, as Indicated

Hormone excess
Thyroid hormone excess
Carcinoid syndrome (flushing without sweating)
Pheochromocytoma (hypertension, flushing, and profuse sweating)
Dietary factors
Alcohol
Spicy food
Food additives (eg, monosodium glutamate, sulfites)
Pharmaceuticals
Chronic opioid use
Opiate withdrawal
SSRIs (may cause sweats)
Nicotinic acid (intense warmth, itching lasting up to 30 min)
Calcium channel blockers
Medications that block estrogen action or biosynthesis
Chronic infection (increased body temperature)
Other medical conditions
Postgastric surgery dumping syndrome
Mastocytosis and mast cell disorders (usually with gastrointestinal symptoms)
Some cancers: medullary carcinoma of the thyroid, pancreatic islet-cell tumors, renal cell carcinoma, lymphoma
Anxiety disorders

Association with sleep. In polysomnography studies, nocturnal hot flashes are more common during the first 4 hours of sleep, whereas subsequent rapid eye movement sleep suppresses hot flashes, arousals, and awakenings (30). A recent study that induced estrogen deficiency in healthy premenopausal women with a GnRH agonist directly demonstrated that hot flashes are associated with three factors: 1) an increase in episodes of waking after sleep-onset; 2) a decrease in perceived sleep efficiency; and 3) a statistically significant correlation between nocturnal VMS and sleep disruption (31). Although these data are informative, it has not been substantiated whether they apply in naturally postmenopausal women with continuously high gonadotropins. An important contributing factor is aging, which likely is also involved in sleep disturbances in menopausal women.

Mechanisms. VMS appear to involve the central nervous system (32) because: 1) hot flashes occur simultaneously with, but are not caused by, LH pulses (33, 34); and 2) research has shown an association with the neuroregulators kisspeptin, neurokinin B, and dynorphin (35). Alterations of thermoregulatory systems are mechanistically involved because women with hot flashes exhibit a narrowing of the thermoregulatory-neutral zone (32). Whereas premenopausal women initiate mechanisms to dissipate heat when the core body temperature increases

by 0.4°C, this happens with much lower increases in temperature in menopausal women (36). Core body temperature is usually still within the normal range at the onset of the flash, but inappropriate peripheral vasodilatation with increased digital and cutaneous blood flow and perspiration results in rapid heat loss and a fall in core body temperature (32). Shivering may occur to restore the core temperature (36).

Genitourinary syndrome of menopause

This new term "genitourinary syndrome of menopause" (GSM) combines the conditions of VVA and urinary tract dysfunction (Table 3) (37). VVA most often presents in the late postmenopausal stage, when VMS may have abated (15). When VVA is severe, women may have discomfort wearing tight-fitting clothing or while sitting or exercising. Sexual activity is not required for patients to experience vaginal or genital discomfort. Urinary symptoms— dysuria, urinary frequency, and recurrent urinary tract infections—increase in severity with time since menopause.

Other signs and symptoms

The menopausal decline of estradiol increases bone resorption and contributes to fractures (38).

Possible related signs and symptoms

Research has suggested (but not proven) a direct relationship between menopause and mood changes, mild depressive symptoms, anxiety, irritability, arthralgias, loss of libido, palpitations, skin dryness, fatigue, and reduction in QOL (38, 39). As opposed to the conclusions in the 2005 National Institutes of Health State of the Science consensus regarding the uncertain relationship between mood and menopause, more recent longitudinal studies now support an association of the menopause transition with depressed mood, major depressive episodes, and anxiety.

Table 3. Genitourinary Syndrome of Menopause

Symptoms
Vulvar pain, burning, or itching
Vaginal dryness
Vaginal discharge
Dyspareunia
Spotting or bleeding after intercourse
Dysuria, urinary frequency, urgency
Recurrent urinary tract infections
Signs, external genitalia
Decreased labial size
Loss of vulvar fat pads
Vulvar fissures
Receded or phimotic clitoris
Prominent urethra with mucosal eversion or prolapse
Signs, vagina
Introital narrowing
Loss of elasticity with constriction
Thin vaginal epithelial lining
Loss of mature squamous epithelium
Pale or erythematous appearance
Petechiae, ulcerations, or tears
Alkaline pH (>5.5)
Infection (yellow or greenish discharge)

Derived from D. J. Portman et al: Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Menopause*. 2014;21:1063–1068 (37), with permission.

2.0 Health considerations for all menopausal women

2.1 When women present during the menopausal transition, we suggest using this opportunity to address bone health, smoking cessation, alcohol use, cardiovascular risk assessment and management, and cancer screening and prevention. (Ungraded best practice statement)

Evidence

The menopause transition, a portal to the second half of life, is a critical window to reassess lifestyle, recognize ongoing and potential health concerns, and encourage a proactive approach to future well-being, regardless of menopausal symptoms. To decrease morbidity and mortality from CVD and cancer and maintain QOL, optimizing diet and exercise to maintain healthy weight are important measures, as are counseling regarding alcohol use and smoking cessation and identifying and treating hypertension, glucose intolerance, and dyslipidemias (40, 41).

Adequate intake of calcium and vitamin D, along with limiting alcohol consumption will minimize bone loss and reduce the risk of falls and fractures (42). For postmenopausal women < 65 years of age and at high risk of osteoporosis, dual-energy x-ray absorptiometry assessment of bone mineral density contributes to risk assessment. ET for the relief of menopausal symptoms prevents bone loss and reduces fracture risk (43). Women without VMS and at significant risk of osteoporosis can discuss the merits of ET for bone preservation. Recent guidelines address bone-specific therapies (43).

3.0 Hormone therapy for menopausal symptom relief

3.1 Estrogen and progestogen therapy

3.1a For menopausal women < 60 years of age or < 10 years past menopause with bothersome VMS (with or without additional climacteric symptoms) who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take MHT, we suggest initiating ET for those without a uterus and EPT for those with a uterus. (2⊕⊕◯◯)

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Evidence

In postmenopausal women, ET improves menopause-associated (climacteric) symptoms (eg, VMS, genitourinary symptoms, sleep disturbance, menopause-associated anxiety and depressive symptoms, and arthralgias). ET also reduces menopause-related bone loss, lowers the risk of fragility fractures in older women, and reduces the incidence of self-reported diabetes. In addition, combined EPT reduced the risk of colorectal cancer and, in cumulative follow-up of the WHI, endometrial cancer (38, 44).

MHT is not appropriate for all symptomatic menopausal women (Figure 2). There are no commonly recognized lists of absolute or relative contraindications to MHT as published in professional society guidelines. And whereas US product labeling (regulated by the FDA) does include contraindications to MHT (Table 4), caution is also advised for women with certain additional medical conditions (Table 4). Risk/benefit assessment is the most important consideration, and QOL may be an important issue in a decision to recommend MHT. Women with conditions precluding MHT (Table 4) who are unwilling to take MHT, or at substantial risk for breast cancer or CVD, can consider nonhormonal options for symptom relief (*Section 4.0*).

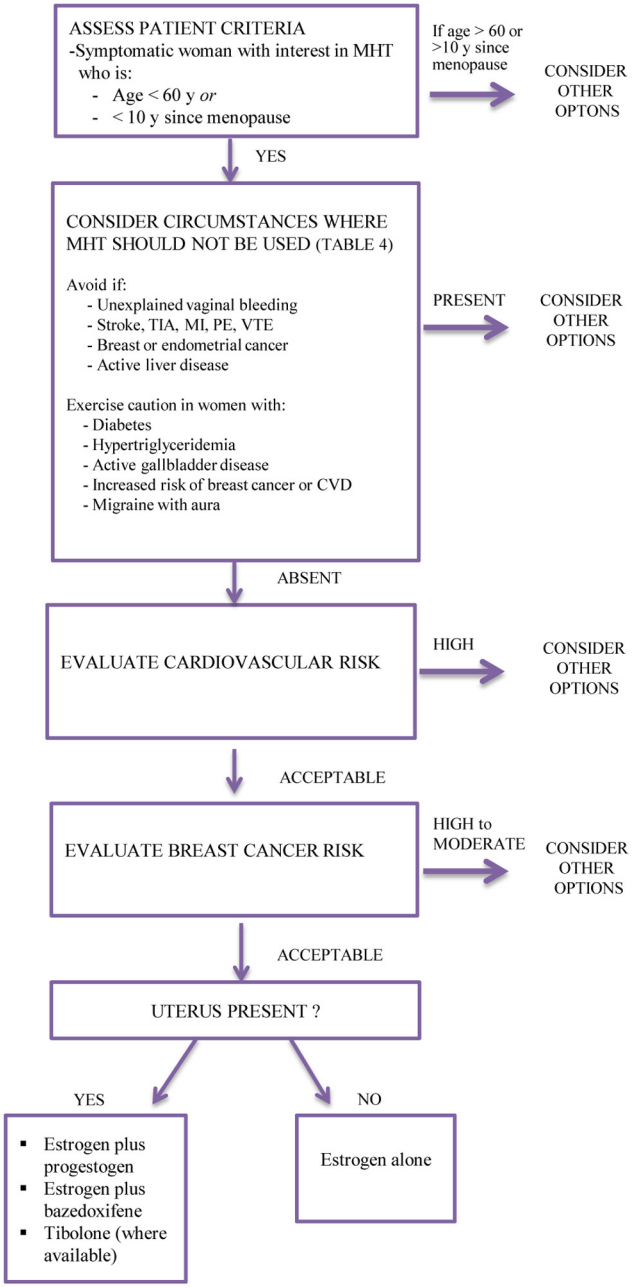

Figure 2. Approach to the patient with VMS contemplating MHT. TIA, transient ischemic attack.

Risks and benefit overview

Healthcare providers and patients should choose MHT based on individual risks and benefits utilizing a shared

Table 4. Specific Cautions to Use of Systemic MHT or SERMs[a,b] for Treatment of Menopausal Symptoms

In general, ET should not be used in women with any of the following conditions:
Undiagnosed abnormal genital bleeding
Known, suspected, or history of cancer of the breast
Known or suspected estrogen-dependent neoplasia including endometrial cancer
Active DVT, pulmonary embolism, or history of these conditions
Active arterial thromboembolic disease (for example, stroke, MI) or a history of these conditions
Known anaphylactic reaction or angioedema in response to any ingredient in the medication[c]
Known liver impairment or disease
Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders[c]
Known or suspected pregnancy
Caution should also be exercised in women with:
Gallbladder disease (oral ET)
Hypertriglyceridemia (>400 mg/d) (oral ET)
Diabetes
Hypoparathyroidism (risk of hypocalcemia)
Benign meningioma
Intermediate or high risk of breast cancer
High risk of heart disease
Migraine with aura (oral ET)
Other conditions[d]

[a] Also apply to conjugated estrogens/BZA, ospemifene, and tibolone therapies.

[b] Advice not to use estrogens in the specific conditions listed is based on FDA recommendations and package labeling in the United States. The advice to exercise caution is based on a review of the literature (including package labeling) and not dictums generally included in various Menopause Society guidelines. Because these guidelines are meant to be used internationally, it should be noted that these considerations may vary from country to country.

[c] Specific to CEE ± combination with BZA.

[d] Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

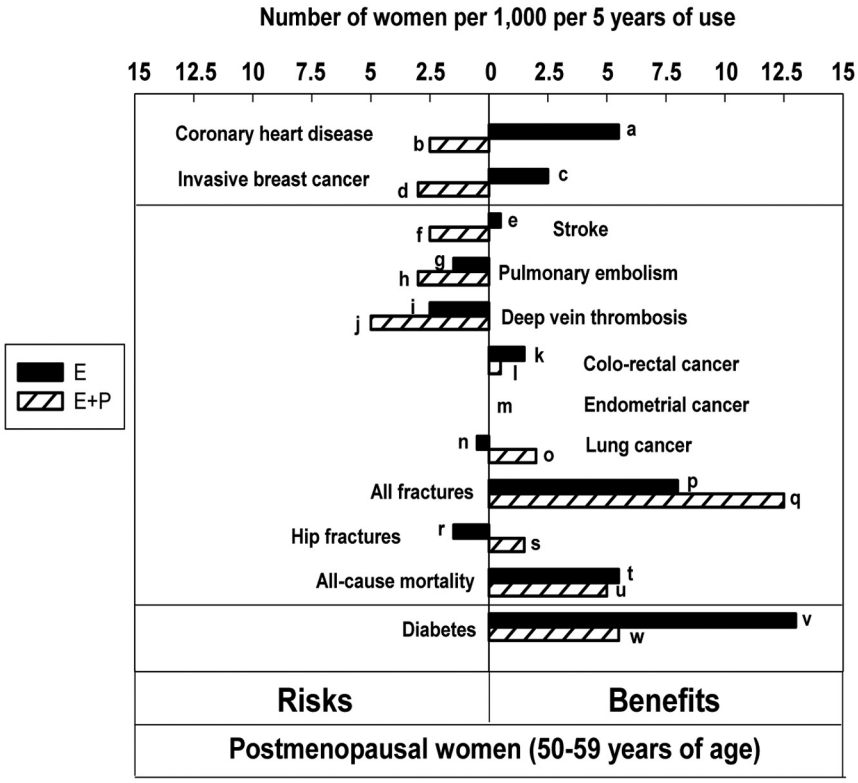

Figure 3. Updated summary of the effects of orally administered CEE alone or combined with MPA in women ages 50–59 years during intervention phase of WHI. One set of analyses examined the risks and benefits of these agents in women ages 50–59 years. This figure plots these data, which are expressed here as excess risks and benefits per 1000 women using MHT for 5 years. Because women deciding to use MHT are more likely to continue this for a period of years rather than 1 year, this figure is constructed according to that assumption. WHI studies were not powered for age-related subset analyses, and none of the data presented in the figure are statistically significant. Nonetheless, this figure represents the best estimates that are available at the present time and are likely more reliable than similar estimates based on observational studies as reported previously in The Endocrine Society Scientific Statement (38). The HR (95% CI) values for the bars in the figure are listed here with reference to the alphabetical designations shown next to the bars: a, HR, 0.60 (0.35–1.04); b, HR, 1.34 (0.82–2.19); c, HR, 0.82 (0.50–1.34); d, HR, 1.21 (0.81–1.80); e, HR, 0.99 (0.53–1.85); f, HR, 1.51 (0.81–2.82); g, HR, 1.53 (0.63–3.75); h, HR, 2.05 (0.89–4.71); i, HR, 1.66 (0.76–3.67); j, HR, 3.01 (1.36–6.66); k, HR, 0.71 (0.30–1.67); l, HR, 0.79 (0.29–2.18); m, HR, 1.00 (ns-ns); n, HR, 1.12 (0.45–2.75); o, HR, 0.62 (0.30–1.29); p, HR, 0.90 (0.72–1.11); q, HR, 0.82 (0.68–1.00); r, HR, 5.01 (0.59–42.9); s, HR, 0.17 (0.02–1.45); t, HR, 0.70 (0.46–1.09); u, HR, 0.67 (0.43–1.04); v, HR, 0.83 (0.67–1.04); and w, HR, 0.85 (0.66–1.09). [RJ Santen, et al: Competency in menopause management: whither goest the internist? *J Womens Health (Larchmt)*. 2014;23(4): 281–285, courtesy of Mary Ann Liebert, Inc].

decision-making approach. Current recommendations suggest that the initiation of MHT should generally be limited to women < 60 years of age or < 10 years after menopause onset. Accordingly, data are needed to estimate risks and benefits in this specific population. No adequately powered RCTs with clinical outcomes have been specifically conducted with younger, symptomatic women, however, and data for women < 50 years old are limited. The best available evidence comes from subgroup analyses of WHI data, which provide information specifically in women 50 to 59 years of age or < 10 years since menopause onset. Because of the number of women participants ages 50 to 59 (5520 in the combined therapy arm and 3313 in the estrogen-alone arm), and the low event rate for MI and stroke in this age group, such data provide trends but few statistically significant differences. Findings from observational studies, case reports, and clinical expertise, both from the United States and other countries, provide additional sources of evidence regarding younger postmenopausal women.

Estimations of risks and benefits previously published in The Endocrine Society's 2010 Scientific Statement utilized both observational and RCT data. However, updated outcomes from the WHI are now available. Accordingly, the updated reanalysis of the WHI (44) is considered by many to provide the best available data on risks and benefits in women ages 50 to 59, but not in those younger than age 50. The 2010 Statement expresses attributable (excess) benefits and risks as the number of affected women/1000 users/5 years of therapy, assuming that most women initiating MHT will consider therapy for 5 years. Maintaining this format, the risks and benefits (as reported in the WHI and reflecting the specific oral therapies studied) are presented in Figure 3 and are not repeated in the text of this guideline. These data, representing the effects of CEE with or without MPA, cannot be extrapolated to other MHT regimens. However, in the absence of RCTs with other specific agents, they provide the most conservative estimates. Notably, the baseline risk of most adverse events is lower in younger vs older women and results in lower attributable risk although relative risks may be similar among various age groups. The converse is also true for benefits, such as fracture reduction.

Benefits of MHT

Vasomotor symptoms

ET is the most effective treatment for VMS and improving QOL in symptomatic women (38). In a dose-dependent manner, MHT reduces hot flash frequency by approximately 75% and severity by 87%, compared with 50% with placebo (38, 45, 46).

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Genitourinary syndrome of menopause

Systemic estrogen administration effectively treats VVA and improves symptoms of overactive bladder and recurrent urinary tract infections (47, 48). With lower doses of systemic MHT, vaginal symptoms may persist and local therapy may be needed (*Section 5*).

Sleep disruption

Large placebo-controlled trials reported significantly fewer sleep disturbances with MHT use (44), but additional data are required for definitive conclusions.

Anxiety and depressive symptoms

Anxiety symptoms increase during the menopause transition and are associated with an increased likelihood of a major depressive disorder (49). ET may improve mild-to-moderate depressive symptoms during or shortly after the menopause transition, whereas antidepressant therapy remains appropriate treatment for major depression (50, 51).

Arthralgia

Joint pain or stiffness and general aches or pains were improved in women receiving EPT (38, 44, 52). Joint pain increased slightly after discontinuation of treatment (44).

Potential preventive benefits of menopausal hormone therapy

Although studies have suggested certain preventive benefits, the U.S. Preventive Services Task Force (53) and many expert groups (40, 54–56) recommend against MHT for primary or secondary disease prevention, whereas other experts disagree (57).

Bone loss and fracture. RCTs, observational studies, and meta-analyses consistently report reduction in bone loss with ET (38). The updated WHI analysis reports a significant reduction in vertebral fractures and a borderline significant reduction for all fractures with EPT in women ages 50 to 59 years (Figure 3); this effect was greater than with ET (44). Benefit may also be dose-related (38).

Type 2 diabetes. RCTs (58–60) and large observational studies (61, 62) reported that MHT reduced the prevalence of self-reported diabetes by 14 to 19% (44), an effect that did not persist after therapy was discontinued (44).

Colorectal cancer. In clinical trials, EPT was associated with a nonsignificant lower incidence of colorectal cancer in women ages 50 to 59 (44). Cancers that did occur in women receiving EPT, however, were diagnosed at a more advanced stage when all age groups were considered (64). The reduction in cancer during active therapy did not persist after discontinuation (44).

Endometrial cancer. During 13 years of cumulative follow-up of the WHI, combined CEE and MPA was associated with a 35% reduction in endometrial cancer in women ages 50 to 59 years (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.37–1.12) (44). This finding may be unique to the specific type, dose, and regimen utilized.

Risks of MHT

Endometrial cancer

Unopposed ET increases the risk of endometrial hyperplasia and cancer (38, 65, 66), whereas concurrent progestogen therapy (Table 5) for at least 12 days per month reduces this risk (18, 44, 67) and is recommended for all women with a uterus. Continuous combined CEE and MPA was associated with a reduced risk of endometrial cancer over 13 years of cumulative follow-up (44). After 6 to 10 years, sequential regimens may be associated with a 2-fold increased risk of endometrial cancer, particularly in thin women (38). Micronized progesterone and dydrogesterone, in combination with estrogen, have been associated with an approximate 2-fold increase in endometrial cancer when continued beyond 5 years in a large observational study (68). In contrast, one RCT comparing micronized progesterone with MPA (3 y) (69), a second RCT comparing micronized progesterone with chlormadinone acetate (18 mo) (70), and a third trial of single-tablet formulation of cyclical estradiol-dydrogesterone (2 y) (71) each demonstrated endometrial safety. The difference in outcome may reflect enhanced patient compliance with progestogen therapies when formulated in combination. Limited information is available about the safety of long cycle intermittent use of progestogens, but concern has been raised about increased risk of endometrial cancer (72, 73).

The levonorgestrel intrauterine device (not approved for a postmenopausal indication in the United States, but widely used in other countries and, increasingly, off-label in United States) appears effective at minimizing hyperplasia and endometrial cancer risk, especially in obese women (74–76).

Breast cancer

Estrogen therapy. Most, but not all, observational studies report an increased breast cancer risk with oral or transdermal estradiol when initiated in recently menopausal women (77–79). This increase occurs as a function of duration of ET (38, 80–82) with a linear trend in the largest study (83). Insufficient numbers of patients may confound

Table 5. Commonly Prescribed Hormone Therapies

Preparation	Doses	Comments
Systemic estrogen therapies[a]		
Oral estrogen tablets		
Micronized E2	0.5, 1.0, 2.0 mg/d	
Estradiol valerate[b]	1.5 mg/d	
CEE	0.3, 0.45, 0.625 mg/d	Higher doses available Preparation used in WHI
Transdermal estrogens		
Estradiol patch	0.025 to 0.1 mg once or twice weekly depending on preparation 0.014 mg/wk	Corresponds to 0.5 to 2.0 mg estradiol tablets Diffusion can be different from one patch to another Preserved bone in women >60 y old
Estradiol percutaneous gel	0.25–1.5 mg qd	Corresponds to 0.5 to 2.0 mg estradiol tablets Can be transferred to persons and pets by skin contact
Estradiol transdermal spray	1.5 mg qd	Estradiol via spray Can be transferred to persons and pets by skin contact
Vaginal ring		
Estradiol acetate	0.05–0.10 mg/d	Systemic levels of estradiol provide relief of VMS; 90-d duration/ring
Progestogen therapies		
Oral progestin tablets		
Medroxyprogesterone acetate	2.5, 5, 10 mg/d	Utilized in WHI
Norethindrone	0.35 mg/d	
Neta	5.0 mg/d	
Megestrol acetate	20, 40 mg/d	
Dydrogesterone[b]	10 mg/d	
Chlormadinone acetate[b]	5, 10 mg/d	
Medrogestone[b]	5 mg/d	
Nomegestrol acetate[b]	3.75, 5 mg/d	
Promegestone[b]	0.125, 0.25, 0.5 mg/d	
Oral progesterone capsule		
Micronized progesterone	100, 200 mg/d	In peanut oil; avoid if peanut allergy. May cause drowsiness and should be taken at bedtime
Intrauterine system progestin[c]		
LNorg	20 μg released/d 6 μg/d	IUD for 5-y use IUD for 3-y use
Vaginal gel progesterone[c]	4%, 8%	45- or 90-mg applicator
Combination hormone therapies		
Oral		
CEE + MPA	0.3–0.625 mg/1.5–5 mg/d	Cyclic or continuous
E2 + Neta	0.5–1 mg/0.1–0.5 mg/d	Continuous
E2 + drospirenone	0.5–1 mg/0.25–1 mg/d	Continuous
E2 + norgestimate	1 mg/0.09 mg/d	Cycle 3 d E alone, 3 d E + progesterone
E2 + dydrogesterone[b]	1–2 mg/5–10 mg/d	Cyclic and continuous
E2 + cyproterone acetate[b]	2 mg/1 mg/d	Continuous
E2 + MPA[b]	1–2 mg/2–10 mg/d	Continuous
CEE + BZA[d]	0.45 mg/20 mg/d	Continuous
Transdermal		
E2 + Neta	50 μg/0.14–0.25 mg/patch	Twice weekly
E2 + LNorg	45 μg/0.015 mg/patch	Once weekly

Abbreviations: IUD, intrauterine device; E, estrogen; E2, 17-β estradiol; LNorg, levonorgestrel; Neta, norethindrone acetate or norethisterone acetate; qd, once daily.

[a] Not all preparations and doses are available in all countries.

[b] Only available outside the United States.

[c] Not approved in the United States for endometrial protection when administered with postmenopausal estrogen.

[d] Approved indications in the United States include treatment of moderate to severe VMS associated with menopause and prevention of postmenopausal osteoporosis. In the European Union, the indications state: treatment of estrogen deficiency symptoms in postmenopausal women with a uterus (with at least 12 mo since the last menses) for whom treatment with progestin-containing therapy is not appropriate. The experience treating women older than 65 years is limited.

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the interpretation of these data on ET alone (ie, type II statistical error). It is possible that in observational studies mammographic surveillance differed between users and nonusers of MHT. The finding of increased risk in recently menopausal women is controversial, however. In women in the WHI ages 50 to 59 or < 10 years after menopause onset, CEE did not increase risk (44, 84). The statistically significant 21% reduction of invasive breast cancer in the 13-year cumulative follow-up of all women in the estrogen-alone arm of the WHI was of similar magnitude in each age group (44), but some analyses have suggested less reduction or an increase in risk among women starting ET close to menopause (77, 85).

The presence or absence of obesity confounds the interpretation of existing data. The aromatase enzyme, which increases with obesity, results in enhanced endogenous estrogen production, which may minimize the additional effects of exogenous ET. The insulin resistance associated with obesity also confounds the relationship between obesity and breast cancer risk (86). Therefore, increased breast cancer risk with ET in non-US studies might reflect differing levels of obesity between US and European populations. CEE and estradiol may also have differential effects as suggested by in vitro (87) and primate (88) studies. In summary, the risk of breast cancer from estrogen alone, taken for 5 years, appears to be small.

Combined EPT. Studies examining the effects of combined therapy report a consistent increase in breast cancer risk (38, 89, 90). It should be noted that the original WHI study did not report any increase overall in women who had not previously used MHT (hormone naive), but data on this issue are not available for women ages 50 to 59 or < 10 years postmenopausal (18, 91), and there are no reported follow-up data for the hormone-naive women. In women ages 50 to 59 in the WHI, the excess risk of invasive breast cancer during the intervention phase persisted 7 years after the cessation of EPT, with 4.5 excess cases/1000 over 5 years (HR, 1.34; 95% CI, 1.03–1.75) (44). Studies have reported similar findings with most other estrogen/progestogen combinations (38, 89, 92). However, observational data suggest that progesterone or dydrogesterone (5, 89) may be associated with a lower risk, but further studies are required to confirm this. Observational studies also report a greater risk when EPT is started close to menopause (79, 85, 93) and with continuous rather than with cyclic regimens (78, 82, 94).

Lung cancer

In the 50- to 59-year age group in the WHI study, the incidence of lung cancer was not significantly increased or decreased in either treatment arm (44).

Ovarian cancer

In the 50- to 59-year age group of the WHI, the HR of ovarian cancer with EPT was 0.30 (two vs six cases; 95% CI, 0.06–1.47), with 1.5 fewer cases/1000 per 5 years of treatment (44). No data have been reported for ET. A controversial meta-analysis of 52 observational studies (95–97) showed an increase of 0.52 cases/1000 in women starting MHT (no difference in risk between ET and EPT) at age 50 and continuing therapy for 5 years. Risk persisted 5 years after stopping MHT, with 0.37 cases/1000 in the same women when ages 55 to 59 (95). Of note, the overall risk of ovarian cancer with EPT in the WHI (HR, 1.41), although not statistically significant, was comparable to findings in the meta-analysis, as was the rate in the cumulative follow-up (HR, 1.24). Based on current data, adequately powered RCTs are needed to fully ascertain ovarian cancer risk in symptomatic, recently postmenopausal women.

Coronary heart disease

Estrogen therapy. The age at initiation of ET influences risk. In the WHI, there was a trend toward a reduction in CHD and total MI in women aged 50 to 59 years at trial enrollment (44). Composite outcomes, including revascularization (98) and coronary artery calcium scores (99), were lower with ET than with placebo.

Observational studies of ET suggest the potential for CHD benefit in some women, although a number of biases might have contributed to those conclusions (100). In summary, ET does not increase CHD risk in women starting therapy at ages < 60 years and may possibly reduce this risk.

Although observational studies suggest that a dermal route of ET may carry a lower risk of MI (101, 102), a meta-analysis reported no significant difference in CHD outcomes between oral and transdermal MHT (4). No associations with estrogen dose were reported (101, 102).

Combined EPT. Age at initiation of EPT does not appear to influence the relative risk of CHD, based on the most recent WHI data (44) and a meta-analysis (4). In women in the WHI aged 50 to 59, there was a trend toward excess risk of CHD, but no increased risk was apparent in women < 10 years since menopause onset (44). These findings and those of several recent studies have been controversial. A randomized osteoporosis trial that did not have CHD as a predefined primary endpoint reported that 10 years of MHT treatment in women < 50 years old at study onset was associated with the reduction of a composite safety endpoint (death, hospital admission for MI, or heart failure) (103). This study has been criticized for its composite index and nonblinded nature. A primary pre-

vention RCT of recently (< 3 y) postmenopausal women ages 42 to 58 failed to detect a difference in progression of atherosclerosis (as assessed by carotid intima-medial thickness and coronary artery calcium determinations) after 4 years of therapy (104) but may have been underpowered to detect significant differences (ie, type II error). In summary, EPT does not appear to be associated with an increased risk of CHD among women close to the onset of menopause, and if any risk elevation is present in women younger than 60 years, its magnitude is small. A definitive conclusion regarding CHD risk requires an appropriately powered RCT.

Stroke

Researchers reported a nonsignificant trend toward an increase in stroke risk with EPT in women ages 50 to 59 in the WHI (44) but did not report an adverse effect with ET. When examined by years since menopause, ET increased stroke risk in women < 10 years since menopause (6.5 women/1000 over 5 y) (44). The differences between these two groups might reflect the difficulty in establishing time of menopause in women with a hysterectomy.

No RCTs have evaluated stroke risk according to estrogen type, dose, or route of administration. Some observational studies suggest that transdermal estradiol in doses ≤ 50 μg may confer a lower risk compared with higher dose transdermal or oral therapies (4, 105). Other studies are conflicting regarding effects of estrogen type (102, 106) and dose (101, 105, 107). In summary, MHT may confer a small risk of stroke.

Venous thromboembolic events

Estrogen therapy. RCTs demonstrate that oral ET increases VTE risk in women ages 50 to 59 (44). These data are supported by observational studies (106, 108, 109). Risk declined after discontinuing therapy (44). Observational studies (108–112) and meta-analyses (4, 113) suggest that transdermal ET does not increase VTE risk, even in women with thrombophilia or obesity (114–117). In an observational study, oral CEE was associated with a 2-fold increase in VTE compared with oral estradiol (106).

Combined EPT. The WHI trial found an association between EPT and both DVT and pulmonary embolism (PE) in women ages 50 to 59 (44). Risks resolved when therapy was discontinued. Observational studies suggest that formulations containing MPA and normethytestosterone derivatives appear to be associated with greater risk than other progestogens (108, 109, 111). A recent meta-analysis comparing ET and EPT did not report any statistically significant differences in risk (4).

Gallbladder disease

No data are available specifically for women ages 50 to 59; conclusions regarding gallbladder disease rely on overall findings of the WHI. ET resulted in 29 excess cases/1000 women over 5 years (44). This risk did not persist after discontinuation (44, 118). With EPT, the excess risk was 23 women/1000 (44), similar to another trial (119). Risk persisted at least 5 years after cessation of EPT (44, 120). Observational studies report increased risk with oral, but not transdermal, estradiol (121, 122) and increased dose and duration (120, 123).

Incontinence

Stress urinary incontinence, urge urinary incontinence, and mixed urinary incontinence increase in women taking oral ET and EPT (124, 125). An increased risk may persist after discontinuation (44).

Uncertain benefits of hormone therapy

Mortality

A meta-analysis of RCTs demonstrated no significant effect on all-cause mortality with MHT use, but these data included women < and > 60 years of age (5). A recent Cochrane collaboration review reported a 30% relative risk reduction (HR, 0.70; 95% CI, 0.52–0.95) of all-cause mortality in women starting MHT < 10 years since menopause (or < age 60) (127). Comparison of the ET and EPT groups in the WHI suggested a stronger trend by age group among those on ET, with a statistically significant trend by age in the ET trial but not in the EPT trial (44). Observational studies (128–130) reported a reduction in mortality with MHT, as did one small RCT with composite endpoints (103). This is consistent with meta-analyses that reported a 30–40% mortality reduction (131, 132). In summary, further data are required for definitive conclusions about mortality in younger women.

Dementia

Observational studies suggest a possible benefit of MHT if started in younger women closer to menopause (133), as opposed to the detrimental effects reported in clinical trials when MHT is initiated in women > 65 years old (134). Some studies of postmenopausal women treated with estradiol reported an improvement in verbal memory and executive function (135–138), whereas other studies did not associate CEE therapy with cognitive improvement (139, 140). Definitive conclusions about MHT in women < age 60, therefore, are lacking.

Individual baseline risk assessment and therapeutic decisions

Evaluating risk facilitates individual counseling and decisions regarding MHT for symptom relief (Figure 2).

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However, no clinical trial evidence is available to support the practice of incorporating risk assessment instruments for quantifying cardiovascular (CHD, stroke, and VTE) and breast cancer risks among women considering MHT. Nevertheless, we feel that risk assessment instruments are useful to facilitate decision-making regarding MHT.

Cardiovascular risk

3.1b For women < age 60 or < 10 years past menopause onset considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of CVD and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2⊕⊕◯◯)

3.1c For women at high risk of CVD, we suggest initiating nonhormonal therapies to alleviate bothersome VMS (with or without climacteric symptoms) over MHT. (2⊕⊕◯◯)

Technical remarks

High risk includes known MI, cerebrovascular disease, and peripheral arterial disease, abdominal aortic aneurysm, diabetes mellitus, chronic kidney disease, and 10-year CVD risk > 10% (40).

3.1d For women with moderate risk of CVD, we suggest transdermal estradiol as first-line treatment, alone for women without a uterus or combined with micronized progesterone (or another progestogen that does not adversely modify metabolic parameters) for women with a uterus because these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism. (2⊕⊕◯◯)

Evidence

Cardiovascular risk

Results showing fewer excess CHD and stroke events when MHT was initiated in younger rather than older study participants in the WHI (141) provide the foundation for the widely accepted consensus that MHT should be initiated primarily in younger women (age < 60 y) close in time (< 10 y) to menopause onset, when women likely have less baseline atherosclerosis (19, 20). The population prevalence of obesity, hypertension, dyslipidemia, and diabetes continues to increase. Accordingly, baseline CVD risk evaluation is important in women considering MHT. As reviewed in recent statements, CHD and stroke are associated with a wide range of risk factors, many unique to women (40, 41). Notably, a prior history of CHD conveys the highest risk of subsequent MI and stroke (142). We feel that methods to integrate these factors to categorize individual risk as minimal, moderate, and high are useful and can be accomplished qualitatively by clinical judgment or quantitatively by risk assessment tools.

Country- and population-specific CVD risk calculators are available to quantify individual risk per local guidelines (143). However, specific cutoffs for the safe use of MHT have not been formally validated, and practice differs from country to country.

The Menopause Decision-Support Algorithm (63) starts with calculating the American College of Cardiology (ACC)/American Heart Association (AHA) 10-year CVD risk (144), then stratifies by years since menopause to suggest appropriateness of MHT (Table 6) (63). For a woman at intermediate risk, family history, coronary artery calcium score, C-reactive protein, and ankle-brachial index can further stratify risk (144); inflammatory markers and lipid ratios predict treatment-related CHD events (145).

Metabolic syndrome. The metabolic syndrome (MetS) is associated with higher risk of cardiovascular events and breast and colon cancers (146). In a nested case-control study in the WHI, women with MetS at baseline were twice as likely to have CHD events while taking oral MHT as with placebo (147). In contrast, women without MetS had no increase in CHD risk on MHT. Transdermal estradiol with micronized progesterone might have less deleterious metabolic effects than oral therapies, but there are no RCTs that have evaluated the safety of these preparations in women with MetS.

Diabetes. Diabetes is considered by the AHA to be a CHD risk equivalent (40), which would suggest that women with diabetes should not take MHT. However, clinical trial evidence of CVD outcomes associated with MHT in women with diabetes is mostly lacking. Some diabetic women were included in RCTs (Heart and Estrogen/Progestin Replacement Study [19%]; WHI [4.4–7.7%]), but these trials were not powered to assess differences in CVD

Table 6. Evaluating CVD Risk in Women Contemplating MHT

	Years Since Menopause Onset	
10-y CVD Risk	**<5 y**	**6 to 10 y**
Low (<5%)	MHT ok	MHT ok
Moderate (5–10%)	MHT ok (choose transdermal)	MHT ok (choose transdermal)
High (>10%)[a]	Avoid MHT	Avoid MHT

CVD risk calculated by ACC/AHA Cardiovascular Risk Calculator (144). Methods to calculate risk and risk stratification vary among countries. Derived from J. E. Manson: Current recommendations: what is the clinician to do? *Fertil Steril.* 2014;101:916–921 (63), with permission. © Elsevier Inc.

[a] High risk includes known MI, stroke, peripheral artery disease, etc.

outcomes. A few short-term RCTs have evaluated glucose control in diabetic women taking a variety of MHT preparations and showed either no effect or improved control (148). The evidence at this time is inadequate to make firm recommendations. An individualized approach to treating menopausal symptoms could be considered, with a low threshold to recommend nonhormonal therapies, particularly in women with concurrent CVD. However, some diabetic women, after careful evaluation of cardiovascular risk, may be candidates for MHT, preferably transdermal estrogen and micronized progesterone or another less metabolically active progestogen.

Venous thromboembolic events

3.1e For women at increased risk of VTE who request MHT, we recommend a nonoral route of ET at the lowest effective dose, if not contraindicated (1|⊕⊕◯◯); for women with a uterus, we recommend a progestogen (for example, progesterone and dydrogestone) that is neutral on coagulation parameters. (1|⊕⊕⊕◯)

Evidence

Obesity, age, and thrombophilia are associated with increased risk of VTE. An approximately 2-fold increased risk of VTE (both DVT and PE) with oral MHT is similar among women at low, intermediate, or high risk (149, 150). Accordingly, the attributable risk of MHT will be higher in those at high or intermediate baseline risk.

A prior history of VTE confers the highest risk. If the patient has a known inherited coagulation defect, such as Factor V Leiden, oral ET or EPT should be avoided because research has shown a high risk of VTE recurrence (114). A history of VTE due to pregnancy, oral contraceptives, unknown etiology, or blood clotting disorders poses a contraindication to any ET, whereas VTE due to past immobility, surgery, or bone fracture would be a contraindication to oral but not necessarily transdermal MHT (151). In some countries, a history of any VTE is a contraindication to oral but not low-dose transdermal ET.

Breast cancer

3.1f For women considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of breast cancer and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. (2|⊕⊕◯◯)

3.1g For women at high or intermediate risk of breast cancer considering MHT for menopausal symptom relief, we suggest nonhormonal therapies over MHT to alleviate bothersome VMS. (2|⊕⊕◯◯)

Technical remarks

High or intermediate risk includes calculated level of risk that would qualify for risk-reducing medications.

Evidence

There are no established clear criteria for recommending (or avoiding) MHT based on a woman's risk of breast cancer. Nonsignificant trends from the WHI suggest that the relative risk of breast cancer in association with MHT remains stable or increases in the 5-year Gail model breast risk categories of < 1.25 vs ≥ 1.75. On this basis, the excess or attributable risk should increase in women at higher categories of risk (90, 152). As another consideration, it seems prudent not to recommend MHT for women whose risk meets the criteria for breast cancer prevention with SERMs or aromatase inhibitors. The U.S. Preventive Services 2013 Task Force recommends that women with a 5-year risk of $\geq 3\%$ should be considered for preventive therapy with tamoxifen or raloxifene (126), whereas the American Society of Clinical Oncology guidelines suggest discussing such therapy in women with a risk of $\geq 1.67\%$ (153), consistent with enrollment criteria of breast cancer prevention trials. Prevention recommendations differ outside the United States. Another consideration is to take into account the data suggesting that breast cancer risk is associated with combined estrogen/progestogen use, but less so, if at all, with CEE alone.

We suggest one potential algorithm for MHT counseling, extrapolated from breast cancer prevention trial enrollment criteria (Table 7); however, it is not validated in clinical trials or widely utilized. This algorithm requires the assessment of breast cancer risk, which can be accomplished by qualitative methods or preferably with readily available quantitative risk assessment tools. The National Cancer Institute Breast Cancer Risk Assessment Tool pro-

Table 7. Breast Cancer Risk Cutoffs for Counseling Before Recommending MHT[a]

Risk Category[a]	5-y NCI or IBIS Breast Cancer Risk Assessment, %	Suggested Approach
Low	<1.67	MHT ok
Intermediate	1.67–5	Caution[b]
High	>5	Avoid

Abbreviations: IBIS, International Breast Intervention Study; NCI, National Cancer Institute.

[a] Categories here are newly defined for these guidelines and based on recommendations published for use of antiestrogens for breast cancer prevention (126, 153, 322, 323). The assumption is that candidates for breast cancer prevention with antiestrogens should not be candidates for initiating MHT. Method to calculate risk varies among countries.

[b] Caution indicates need for detailed counseling regarding anticipated benefits and risks of MHT with strong consideration of nonhormonal therapies for symptom relief, and possible consideration of chemopreventive strategies for women who meet suggested criteria.

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vides a standardized online risk calculator for 5-year risk of invasive breast cancer (154). The International Breast Intervention Study calculator predicts 10-year and lifetime risk (155, 156). For women with strong family histories of breast cancer, several other methods are available (155). Although these provide useful predictive information, all are limited by only moderate discriminatory accuracy (155). Mammographic breast density, when added to these methods, may emerge as an important objective risk for women contemplating MHT (157–159).

Although a history of breast cancer is considered by most to be a contraindication to MHT, the severity of menopausal symptoms, the compromise in QOL experienced by breast cancer survivors, and limitations of nonhormonal therapies for relief of VMS present a persistent clinical challenge. As recently summarized, it is not possible from currently available studies to draw firm conclusions regarding the risks of MHT in this population (38), but adding estrogen seems counterintuitive when current breast cancer therapies interrupt or decrease estrogen levels. Future studies taking into account estrogen receptor status, time since diagnosis and therapy, mastectomy status, and risks for breast cancer recurrence might better inform decision-making.

Tailoring menopausal hormone therapy

3.1h We suggest a shared decision-making approach to decide about the choice of formulation, starting dose, the route of administration of MHT, and how to tailor MHT to each woman's individual situation, risks, and treatment goals. (Ungraded best practice statement)

Clinicians prescribe estrogen alone for women without a uterus. Starting dosages are generally lower than those in the WHI (Table 5), and the overarching principle is to use the lowest effective dose with upward titration based on clinical response. Clinicians usually do not measure estradiol levels to monitor therapy except when symptoms do not improve with escalating doses, particularly after changing the mode of administration from oral to transdermal. For younger women with surgical menopause or those with POI who are accustomed to higher baseline endogenous estradiol levels, clinicians often prescribe higher starting doses of ET (eg, transdermal estradiol, 100 μg), and then slowly lower the dose as tolerated. When women with premature menopause approach the age of natural menopause, the reassessment and tapering of MHT dose seems reasonable.

Estrogen preparations

Oral estrogens. Estradiol tablets or conjugated estrogens (synthetic or equine) are convenient, are studied most extensively, and alleviate climacteric symptoms in a dose-dependent fashion. CEE, derived from pregnant mares' urine and used for decades, contain more than 200 compounds with varying estrogenic potency (160). Oral micronized estradiol and other oral estrogen preparations may result in up to 5-fold higher levels of circulating estrone and 10- to 20-fold higher estrone sulfate than transdermally administered estradiol at comparable or even higher doses. The biological effects of these estrone and estrone-sulfate increments are unknown (161–163).

Cutaneous and transdermal estradiol. Cutaneous and transdermal estradiol, administered via percutaneous gels, sprays, emulsions, or transdermal patches, have a similar efficacy as oral ET in reducing climacteric symptoms and are easily tailored to the individual (164, 165). The primary advantage of transdermal ET is to alleviate the first-pass hepatic metabolic effect (166) of oral estrogens resulting in a procoagulant effect and increases in SHBG, thyroid-binding globulin, cortisol-binding globulin (167, 168), triglycerides, and markers of inflammation such as C-reactive protein (167, 169).

Transdermal therapies, at low doses, are preferable for women with a VTE risk, as evidenced by a recent meta-analysis commissioned for these guidelines (4), and they may also be preferable in patients with hypertension, hypertriglyceridemia, obesity, MetS, diabetes, or a history of gallbladder disease. Clinicians should keep in mind that there are no existing head-to-head RCTs with clinical outcomes that compare transdermal with oral therapies.

Vaginal delivery of systemic estrogens. Estradiol acetate vaginal rings, delivering 50 or 100 μg of estradiol daily (Table 5), provide consistent systemic estradiol levels for 3 months per ring insertion. They are indicated for treatment of moderate to severe VMS and VVA due to menopause (170, 171). High-dose vaginal creams containing estradiol or CEE (ie, 1–2 g) also result in systemic estrogen levels. Concomitant progestogen is needed with these preparations to abrogate endometrial stimulation. We discuss low-dose vaginal ETs for the specific treatment of GSM in *Section 5.0*.

Progestogen administration

In women with a uterus, a progestogen must be added to prevent endometrial hyperplasia and cancer. The various formulations (Table 5) are administered in two regimens. The combined sequential regimen includes estrogen for 20 to 25 days and a progestogen for 12 to 15 days each month. This approach is preferred for recently menopausal woman who are prone to breakthrough bleeding during the first year or two of therapy. The combined continuous regimen utilizes both an estrogen and pro-

gestogen daily on a continuous basis. Clinicians can administer progestogen orally, transdermally by patch, vaginally, or by intrauterine administration (172). The levonorgestrel intrauterine device minimizes systemic progestogen absorption, but increased blood levels do occur, and one observational study reported higher breast cancer incidence (173).

Progestogen alone. For those who do not tolerate ET, progestogens can relieve VMS. In RCTs, oral synthetic progestogens (Table 5) (174, 175) and micronized progesterone (176) were effective. Clinical outcome trials are lacking in women with breast cancer; thus, progestogen therapy is best avoided, except under limited circumstances in these patients, because the effect on recurrence is unclear (80).

Custom-compounded hormones

3.1i We recommend using MHT preparations approved by the FDA and comparable regulating bodies outside the United States and recommend against the use of custom-compounded hormones. (Ungraded best practice statement)

Evidence

A number of FDA-approved hormonal therapies are "biochemically identical" to endogenous estradiol and progesterone and are preferred to custom-compounded options. Custom-compounded hormone therapies have become increasingly popular but are not recommended because the manufacturing process lacks FDA oversight (177). Clinical trials documenting the efficacy and safety of compounded progesterone for endometrial protection are lacking. Proponents of custom-compounded hormone therapies often advise measuring salivary hormone levels to monitor therapy. However, scientific evidence is lacking to justify salivary measurements due to inter- and intra-assay variability, variable salivary flow rates dependent upon hydration, food intake, and other factors, and the inability to predict the pharmacokinetics of a custom-compounded hormone dose in a manner that would allow for valid salivary sampling.

3.2 Conjugated equine estrogens with bazedoxifene

3.2 For symptomatic postmenopausal women with a uterus and without contraindications, we suggest the combination of CEE/BZA (where available) as an option for relief of VMS and prevention of bone loss. (2⊕⊕⊕○)

Evidence

The combination of CEE with the SERM/BZA (available in the United States and licensed in the European Union) relieves VMS and vaginal atrophy and reduces bone resorption in women with a uterus; it provides an alternative to progestogen therapy for women averse to vaginal bleeding, breast tenderness, or altered mood. A series of RCTs up to 2 years in duration evaluated effects of CEE/BZA (0.45 mg/20 mg, the approved dose) compared with MHT (CEE 0.45 mg/MPA 1.5 mg) (178–180).

Benefits

Vasomotor symptoms. The number and severity of moderate-to-severe VMS were significantly decreased at 12 weeks; hot flash frequency was reduced by 74% compared with 51% for placebo, and hot flash severity was reduced up to 54%. Hot flash reduction was sustained at 12 months ($P < .05$) (181).

Bone loss. Bone loss at the lumbar spine and hip was prevented in postmenopausal women at risk for osteoporosis (182), as reflected by reduction of serum bone turnover markers and enhancement of bone mineral density vs placebo (180, 181). At 12 months, CEE/BZA was less effective at the lumbar spine than CEE/MPA (180). Fracture data are lacking.

Vaginal effects. Treating postmenopausal women ages 40 to 65 with VVA at baseline (183) improved vaginal maturation at 12 weeks (181). Women reported a lower incidence of dyspareunia.

Quality of life. Secondary endpoints included improvements in sleep, health-related QOL, and improved treatment satisfaction (184, 185). In RCTs, both CEE/BZA and CEE/MPA improved sleep disturbance and time to fall asleep (185).

Safety considerations

Breast. The incidence of breast pain and tenderness was similar for CEE/BZA and placebo (185–187) and was less than with CEE/MPA. After 1 year of therapy with CEE/BZA, mammographic breast density was not appreciably different than with placebo, whereas it increased with CEE/MPA (184). In trials up to 2 years, the rates of breast cancer (reported as adverse events, not clinical outcomes) were not sufficient to assess risk or benefit (186, 187).

Endometrium. Cumulative amenorrhea rates for CEE/BZA were comparable with placebo and greater than for CEE/MPA (188). At 2 years, the incidence of neither endometrial hyperplasia nor endometrial cancer was increased (180, 189).

Potential risks

Adverse events. Although an osteoporosis trial found a 2-fold risk of VTE with BZA 20-mg therapy alone (190),

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there was no additive effect on VTE when BZA was combined with CEE, although adequately powered studies are necessary (181). In trials of up to 2 years in women ages 40 to 65, rates of cardiovascular events, cancers (breast, endometrial, ovarian), and mortality were similar to placebo (191), but studies were underpowered to draw firm conclusions regarding these endpoints.

3.3 Tibolone

3.3a For women with bothersome VMS and climacteric symptoms and without contraindications, we suggest tibolone (in countries where available) as an alternative to MHT. (2|⊕⊕◯◯)

3.3b We recommend against adding tibolone to other forms of MHT. (1|⊕⊕◯◯)

3.3c We recommend against using tibolone in women with a history of breast cancer. (1|⊕⊕◯◯)

Evidence

Tibolone belongs to the group of normethyltestosterone progestogen derivatives and has metabolites that exhibit estrogenic, progestogenic, and androgenic effects (192). This agent (193) is available in many countries outside of the United States at doses of 1.25–2.5 mg/d.

Benefits

Menopausal symptoms. Tibolone alleviates VMS with equivalent or lesser potency than conventional MHT. Tibolone also improves sleep, mood, and urogenital atrophy and may improve libido (194–197).

Bone loss and fracture. Tibolone prevents postmenopausal bone loss and osteoporotic fractures in women with osteoporosis (198, 199), but is not approved for this purpose because of the increased risk of stroke in older women with osteoporosis initiating therapy at ages ≥ 60 years (199).

Possible risks

Endometrium. There is no endometrial thickening (197) or increase in myoma with tibolone (200). A Cochrane analysis concluded that there was no clear evidence of endometrial cancer with tibolone therapy (seven RCTs, n = 8152; odds ratio, 1.98; 95% CI, 0.73–5.32) (194).

Thrombosis and CVD. In an observational study (110), tibolone did not increase the risk of thrombosis. In an RCT of older women with osteoporosis, tibolone increased stroke (199).

Breast and colon cancers. The incidence of breast tenderness is low (around 3%), (201, 202), and neither mammographic density nor invasive breast cancer was increased; however, the risk of colon cancer was decreased (199, 201). An RCT of women with a history of breast cancer, after a median follow-up of 3.1 years, reported a higher rate of breast cancer recurrence with tibolone (HR, 1.40; 95% CI, 1.14–1.70) (203). The study reported the greatest increase for women taking an aromatase inhibitor (HR, 2.42; 95% CI, 1.01–5.79).

3.4 Clinical management of patients taking hormone therapies

Monitoring during therapy

3.4a For women with persistent unscheduled bleeding while taking MHT, we recommend evaluation to rule out pelvic pathology, most importantly, endometrial hyperplasia and cancer. (1|⊕⊕⊕◯)

3.4b We recommend informing women about the possible increased risk of breast cancer during and after discontinuing EPT and emphasizing the importance of adhering to age-appropriate breast cancer screening. (1|⊕⊕⊕◯)

Technical remarks

Regular clinical follow-up, initially, within 1 to 3 months after starting MHT, and then every 6 to 12 months, depending upon the individual (and health care system), allows for monitoring efficacy and side effects (abdominal/pelvic pain, mastalgia, metrorrhagia, weight gain, mood changes, blood pressure), and if necessary, making treatment adjustments (Table 8).

Duration of therapy

3.4c We suggest that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman. (Ungraded best practice statement)

Technical remarks

Most published recommendations suggest using MHT for the shortest duration possible, but strong evidence is lacking to support this recommendation. Current proposed limits on duration of therapy are informed by large intervention trials (5 to 7 y) with extended follow-up for 13 years (44). Regarding duration of use, these data suggest that risk rates for breast cancer and CVD increase with age and time since menopause, although the risks with ET appear to be less than with EPT. Ovarian cancer risk may also increase relative to duration of MHT (95). We conclude, and guidelines from other societies concur, that clinicians and patients should reassess MHT continuation yearly and discuss the risks (and individual benefits) beyond 5 years (55, 56). Patients likely to consider

Table 8. Clinical Caveats During Treatment With MHT

Symptom/Condition When MHT Started	Approach to Resolution
Persistent, intolerable VMS	Switch mode of administration or adjust dose of estrogen and/or progestogen.
Hot flashes that persist after treatment adjustment	Consider another etiology of flashes (Table 2). Ensure absorption: if transdermal, consider serum estradiol determination.
Bleeding: approach depends on time since menopause, MHT regimen, duration of therapy, duration and character of bleeding	Sequential regimen may be more appropriate for recently menopausal (<2 y), because unscheduled bleeding with continuous combined MHT can be problematic. Persistent irregular bleeding (>6 mo) should be evaluated for endometrial pathology; if obese, diabetic, or having family history for endometrial cancer, evaluate sooner. Atrophic endometrium in women more remote from menopause may respond to increased estrogen dose if otherwise appropriate.
Breast tenderness	Usually responds to a reduction in estrogen dose or change in progestogen preparation. CEE/BZA may improve symptoms. Changing to tibolone may be helpful in women who develop mastalgia on conventional MHT.
Baseline TG level >200 mg/dL	Review family history and seek contributing factors. Transdermal ET is preferred. If oral estrogen is selected, monitor serum TG levels 2 wk after starting therapy.
Hypothyroid on thyroid replacement	Monitor TSH 6 to 12 wk after starting oral MHT; T_4 dose may need to be increased (209).

Abbreviation: TG, triglycerides.

continuing therapy include those who fail an attempt to stop EPT, who are at high risk for fracture, or for whom alternative therapies are not appropriate.

3.4d For young women with POI, premature, or early menopause, without contraindications, we suggest taking MHT until the time of anticipated natural menopause, when the advisability of continuing MHT can be reassessed. (2⊕⊕◯◯)

Stopping considerations

3.4e For women preparing to discontinue MHT, we suggest a shared decision-making approach to elicit individual preference about adopting a gradual taper vs abrupt discontinuation. (2⊕⊕◯◯)

Evidence

A number of studies have compared methods (ie, taper protocols vs abrupt cessation) to facilitate the discontinuation of MHT (204–207) and have detected no differences. Therefore, the approach to discontinuation is an individual choice. Anecdotally, some women find that a very low dose of ET maintains adequate symptom relief and well-being and prefer that to complete discontinuation.

Menopausal symptoms and joint pain can recur when MHT is discontinued (44). Depending on the severity of the symptoms, women may elect to restart MHT, perhaps at a lower dose, or seek relief with nonhormonal therapies. Accelerated bone loss was reported after the discontinuation of MHT, whereas in contrast, bone density is stable for some years after discontinuing bisphosphonate therapy. Bisphosphonates, however, remain in bone indefinitely, and most expert groups do not recommend initiating bisphosphonate therapy for osteoporosis prevention in women aged 50 to 59. Adverse effects such as osteonecrosis of the jaw and atypical femur fractures, while rare, increase with the duration of therapy. Furthermore, as opposed to reports from observational studies (208), in the long-term follow-up of the WHI, hip fracture rates did not increase during 5 to 7 years of observation after MHT was discontinued (44). Breast cancer risk after 5 years of EPT in the WHI persisted 7 years after discontinuation. A large meta-analysis of observational studies found a persistent risk of ovarian cancer up to a decade after discontinuing MHT (95). Urinary incontinence persisted after oral MHT was discontinued; however, the percentage of affected women was approximately one-third less than during active treatment (44). MHT discontinuation may result in symptoms of VVA (*Section 5.0*), and when oral therapy is discontinued, glucose, cholesterol, triglycerides, calcium, and TSH (209) levels may change.

4.0 Nonhormonal therapies for VMS

4.0 For postmenopausal women with mild or less bothersome hot flashes, we suggest a series of steps that do not involve medication, such as turning down the thermostat, dressing in layers, avoiding alcohol and spicy foods, and reducing obesity and stress. (2⊕⊕◯◯)

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Evidence

As hot flashes result from alterations of the thermoregulatory neutral zone, shedding layers of clothing, using fans, keeping the bedroom cool (30), avoiding alcohol and spicy foods, and reducing stress may be effective. Being overweight or obese is a risk factor for VMS (26, 210, 211), and weight loss may reduce hot flash frequency (212, 214).

4.1 Nonhormonal prescription therapies for VMS

4.1a For women seeking pharmacological management for moderate to severe VMS for whom MHT is contraindicated, or who choose not to take MHT, we recommend SSRIs/SNRIs or gabapentin or pregabalin (if there are no contraindications). (1|⊕⊕⊕◯)

Evidence

The interpretation of hot flash efficacy studies requires an appreciation of an important confounding factor. There is a strong, consistently reported placebo effect, which averages 30% (range, 4–57%; Figure 4) and occurs more often in women with high anxiety and stress scores (215–220). Clinical trials of paroxetine, venlafaxine, desvenlafaxine, citalopram, and escitalopram demonstrate statistically significant efficacy with a reduction of frequency of hot flashes ranging from 25 to 69% (Figure 4). The composite score of hot flash frequency and severity is reduced by 27–61%. Other agents such as sertraline and fluoxetine are associated with non-statistically significant trends toward the reduction of hot flashes and inconsistent results (221–223).

Meta-analyses and a Cochrane review concluded that SSRIs and SNRIs exert mild-to-moderate effects to reduce hot flashes in women with a history of breast cancer (217, 224–227). Each of these agents appears to have similar efficacy in breast cancer survivors as in healthy menopausal women, although studies are small (213, 217, 228–234). Caution is advised in the use of paroxetine in patients taking tamoxifen because paroxetine markedly interferes with the metabolism of tamoxifen to its metabolite, endoxifen (221, 222, 224, 235–237).

The only FDA-approved agent in this class is low-dose paroxetine mesylate, but others have been used off-label in the United States. No direct trials are available to determine the relative efficacy of one over another. We describe suggested daily doses, efficacy, side effects, and contraindications in Figure 4. In general, the evidence suggests that these agents are effective and well tolerated.

Gabapentin

Four RCTs confirmed moderate efficacy in relieving hot flashes (238–241). On the basis of clinical experience, women whose hot flashes occur primarily at night respond well to a single bedtime dose. Individual dose requirements vary widely, as determined by empiric dose escalation, and range from 300 to 1200 mg. Gabapentin effects as a sedative and a reducer of vasomotor instability work well together when used at bedtime because sedating side effects dissipate by morning. However, when used during the day, gabapentin may result in a level of lethargy that is not tolerable.

Pregabalin

In one 6-week RCT, pregabalin (75–150 mg twice daily) decreased mean hot flash scores by 65 and 71%, compared with 50% by placebo (242), and was reasonably well tolerated.

Choice of SSRI/SNRI vs gabapentin/pregabalin

A randomized, crossover, multicenter trial that compared recommended doses of venlafaxine vs gabapentin, 300 mg three times a day (243), reported that both agents reduced hot flash scores by 66%, but two-thirds of patients preferred venlafaxine over gabapentin. The quality of this comparative evidence is low due to imprecision.

Relative efficacy of nonhormonal prescription therapies vs estrogens

A limited number of head-to-head RCTs have compared varying estrogen doses, preparations, and routes of administration with nonhormonal agents (213, 240, 244). None of the RCTs established statistically significant superiority of one treatment regimen over another. However, when these and other published data are taken into account (213, 217, 236, 245), the limited evidence available suggests that standard-dose MHT is more effective than nonhormonal agents.

4.1b For those women seeking relief of moderate to severe VMS who are not responding to or tolerating the nonhormonal prescription therapies SSRIs/SNRIs or gabapentin or pregabalin, we suggest a trial of clonidine (if there are no contraindications). (2|⊕⊕◯◯)

Evidence

Clonidine

Several RCTs demonstrated that this α-2-adrenergic receptor agonist reduced hot flashes, but less effectively than the SSRI/SNRIs, gabapentin, and pregabalin, and with more side effects (Figure 4) (217, 236). Clonidine transdermal patches are preferred over tablets because of more stable blood levels.

4.2 OTC and alternative nonhormonal therapies for VMS

4.2 For women seeking relief of VMS with OTC or complementary medicine therapies, we suggest counseling re-

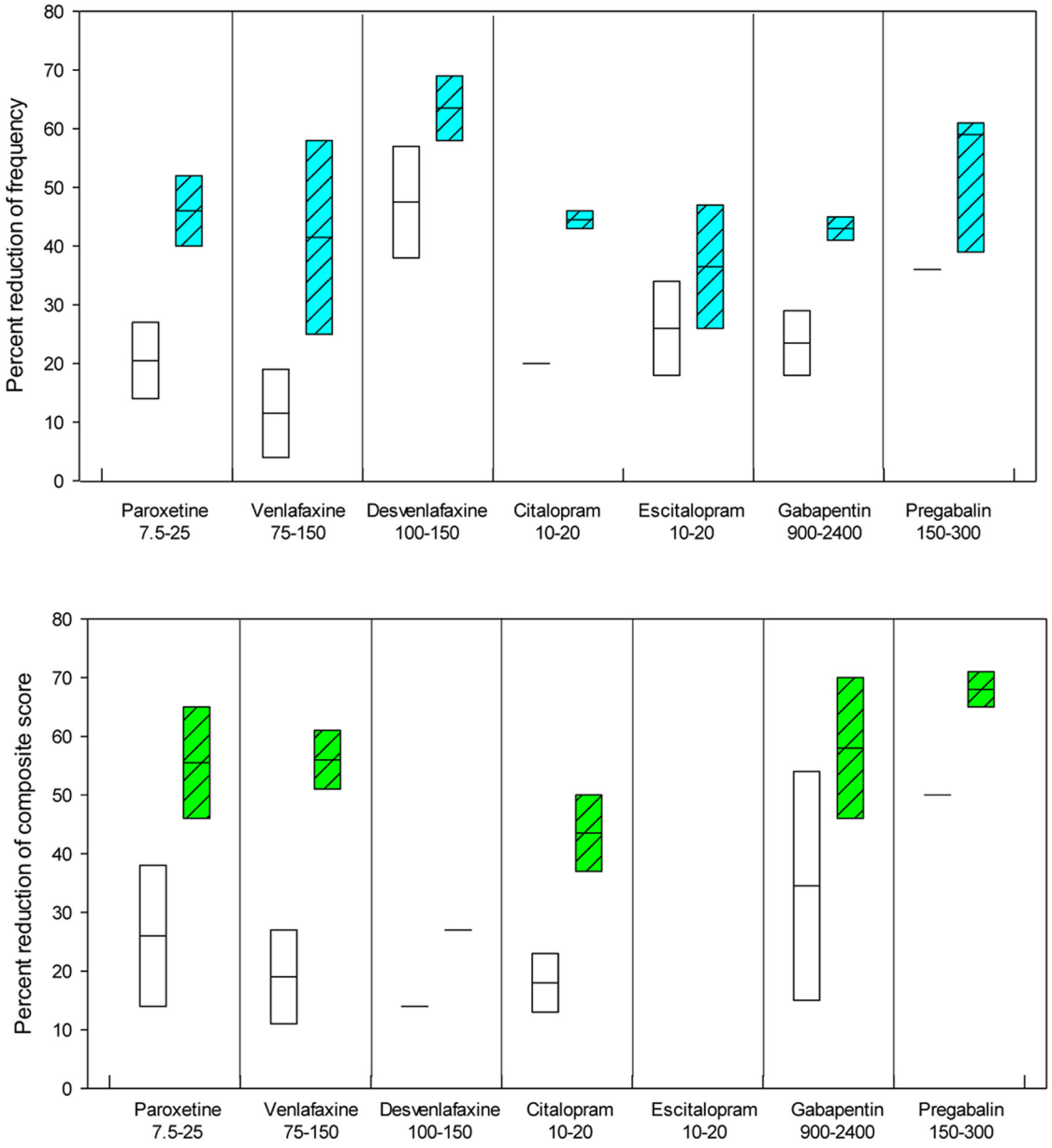

Figure 4. Hot flash frequency and composite score with nonhormonal prescription therapies for relief of VMS. Upper panel, Effect on frequency of VMS; lower panel, effect on composite score (severity times frequency; best representation of effect); open bars, placebo; colored bars, therapies; length of bars, ranges in studies; horizontal bar, means. All of these agents are generally well tolerated (226). Hypersensitivity or prior adverse drug reactions to each of these agents represent contraindications. For the SSRI/SNRIs, prior neuroleptic syndrome, serotonin syndrome, and concurrent use of monoamine oxidase inhibitors are also contraindications. SSRI/SNRIs should be used with caution in patients with bipolar disease, uncontrolled seizures, hepatic or renal insufficiency, uncontrolled hyponatremia, concurrent use of other SSRI/SNRIs, or poorly controlled hypertension. These agents uncommonly induce suicidal thoughts within the first few months of treatment. Preliminary evidence suggests a possible increase in risk of bone fracture. Gabapentin and pregabalin may increase suicidal thoughts and behaviors, cause drowsiness or dizziness, and impair balance and coordination. Pregabalin may impair memory and concentration. Clonidine is contraindicated in patients with low blood pressure and may cause lightheadedness, hypotension, headache, and constipation; sudden cessation of treatment can be associated with significant increments in blood pressure (63).

garding the lack of consistent evidence for benefit for botanicals, black cohosh, omega-3 fatty acids, red clover, vitamin E, and mind/body alternatives including anxiety control, acupuncture, paced breathing, and hypnosis. (2|⊕⊕◯◯)

Evidence

Clinical trials with these agents have reported inconsistent efficacy over placebo, but individual patients may experience benefit (Table 9). The MSFLASH trial showed that omega-3 fatty acids do not improve VMS (246). In a randomized trial of 187 symptomatic menopausal women, clinical hypnosis was associated with a 74.2% reduction in hot flashes compared with a 17.1% reduction in women randomized to structured attention control ($P < .001$) (247). The phytoestrogens are nonsteroidal compounds that have both estrogenic and anti-

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Table 9. Alternative Therapies for Treatment of VMS

Agents	Comments	Refs.
Agents with inconsistent reports of benefit		
Genistein	Purified isoflavone ±Estrogenically active Breast safety not established	324–336
Daidzein	Purified isoflavone ±Estrogenically active Breast safety not established	324–336
S-equol	Metabolite of daidzein	337
Nonpurified isoflavones	Breast safety not established	338
Flaxseed		225, 236, 328, 339–341
Red clover	Breast safety not established	225, 236, 328, 339–341
High-dose extracted or synthesized phytoestrogen		225, 236, 328, 339–341
Dietary soy	Agreement about breast safety	248
Vitamin E	10% benefit in some studies	217, 342, 343
Reports with predominantly no benefit		
Black cohosh	Some short-term trials report benefit, most report no benefit Breast safety not established Reports of liver toxicity	225, 344–352
Omega-3 fatty acids	No benefit in MSFLASH trial	246
Acupuncture	Not effective when compared to "sham acupuncture" controls	353–356
Exercise	Exercise with sweating may increase hot flashes	357
Other complementary approaches	Ginseng, dong quai, wild yam, progesterone creams, traditional Chinese herbs, reflexology, magnetic devices	225, 332
Agents requiring further study		
Stellate ganglion block	Need further RCTs to establish lack of complications	358
Guided relaxation	Stress management, deep breathing, paced respiration, guided imagery, mindfulness training	217, 225, 247, 359–365
Hypnosis	Recent studies suggest efficacy	247
Cognitive behavior modification	Recent studies suggest efficacy with trained practitioners	366, 367

estrogenic properties. Caution is advised because some of these agents, when consumed as supplements, can exert estrogenic effects, a concern in breast cancer survivors although dietary soy appears to have no adverse effects on breast cancer prognosis (248).

5.0 Treatment of genitourinary syndrome of menopause

5.1 Vaginal moisturizers and lubricants

5.1a For postmenopausal women with symptoms of VVA, we suggest a trial of vaginal moisturizers to be used at least twice weekly. (2⊕⊕◯◯)

Evidence

Vaginal moisturizers (eg, polycarbophil-based moisturizer, hyaluronic acid-based preparations, and a pectin-based preparation), when used regularly (at least twice weekly), may provide an effective nonhormonal approach to alleviating symptoms of vaginal atrophy. However, studies have been small, mostly open-labeled, and limited to 12 weeks (249–257). Although helpful, these approaches are not likely as effective as vaginal ET. Vaginal moisturizers have not been shown to reduce urinary tract symptoms or asymptomatic bacteriuria. Use of a vaginal moisturizer may not eliminate the need for a vaginal lubricant during intercourse.

5.1b For women who do not produce sufficient vaginal secretions for comfortable sexual activity, we suggest vaginal lubricants. (2⊕⊕◯◯)

Evidence

Vaginal lubricants are used to enhance the sexual experience in women with symptoms of VVA by alleviating vaginal dryness and preventing dyspareunia (258). Lubricants do not treat the underlying problem and only briefly alleviate symptoms. Several OTC options are available. Because data do not demonstrate the superiority of one to another, women can experiment with these products. Olive oil is also effective (259). Petroleum jelly has been associated with an increased rate of bacterial vaginosis (260).

5.2 Vaginal estrogen therapies

5.2a For women without a history of hormone- (estrogen) dependent cancers who are seeking relief from symptoms of GSM (including VVA) that persist despite using

vaginal lubricants and moisturizers, we recommend low-dose vaginal ET. (1|⊕⊕⊕○)

Evidence

A 2006 Cochrane meta-analysis of vaginal estrogens (261) compared 19 efficacy trials and found that all products effectively alleviated symptoms, but study differences limited comparisons among agents. As a guiding principle, we recommend using the lowest effective dose.

RCTs of low-dose vaginal estrogen products (262–267) report rapid improvement of vaginal symptoms (vaginal dryness or dyspareunia) and urinary symptoms (dysuria and urge incontinence) within 2 to 3 weeks. Objective improvements continue at 12 weeks and are maintained to 1 year. Limited evidence suggests that vaginal ET may prevent recurrent urinary tract infections (268, 269) and overactive bladder (270, 271). No clear proof exists that vaginal ET prevents or improves pelvic prolapse (272), but it may be advantageous preoperatively (273). Adverse effects include potential transfer to partner via penile or oral absorption and, with vaginal creams, residue on undergarments.

Vaginal estrogens

Vaginal estrogen preparations have been categorized as: 1) low, 2) intermediate, and 3) systemic doses (274) (Table 10). By using the lowest effective doses, systemic absorption is minimized. During the initiation of therapy, vaginal atrophy may enhance systemic absorption, although not all studies demonstrate this effect (267, 275). When vaginal epithelium is restored (after several weeks of ET), systemic absorption may decrease (276, 277).

Low-dose therapies

Low-dose vaginal ring. Low-dose vaginal rings result in estradiol levels that remain within the normal postmenopausal range; however, bone resorption and lipid levels decrease, suggesting possible systemic effects (278, 279). Insertion and removal at 3-month intervals may be difficult, the ring can be sensed during intercourse, and it can be expelled, particularly in women who have undergone a hysterectomy (265).

Vaginal estradiol tablets. The 10-μg tablet provides standard twice weekly dosing, relieves vaginal symptoms by 8 weeks, and is effective for at least 52 weeks (263, 275, 280, 281). Therapy is initiated with daily administration for 2 weeks, and then twice weekly thereafter. Vaginal placement of the tablet may provide less introital benefit than creams.

Promestriene (estradiol diether). This is a low-dose estrogen used outside the United States. Evidence is limited to studies of poor quality and very few RCTs (282).

Intermediate-dose vaginal estrogen

The 25-μg estradiol tablets increase plasma estradiol from 3.1 ± 0.83 to 19.8 ± 6.1 pg/mL by 7 days (283). An RCT of CEE vaginal cream ≥ 0.3 mg applied daily or twice weekly reported an improvement in VVA by 12 weeks that was sustained for 52 weeks without reports of endometrial effects (266). Intermediate-dose estradiol and CEE creams provide flexibility of dosing, allow treatment from the introitus to the vaginal apex, and provide the emollient effect of vehicle. Some systemic absorption exists (284, 285).

Table 10. Classification of Government-Approved Vaginal Estrogens

Type	Dose	Serum Estradiol Level
Low dose		<20 pg/mL
Silastic estradiol vaginal ring	7.5 μg	
Estradiol vaginal tablet	10 μg	
Promestriene (estradiol diether) ovule[a]	10 mg	
Estriol ovule[a]	0.5 mg	
Estriol + progesterone + *Lactobacillus Doderleini* ovule[a]	0.2 mg + 2 mg + 341 mg	
Promestriene cream[a]	3 mg	
Estriol cream[a]	0.015–0.03 mg	
Intermediate dose		>20 pg/mL
CEE vaginal cream >0.3-mg dose		5–50 pg/mL
Estradiol vaginal tablet 25 μg[b]		Some >20 pg/mL
High dose (systemic)		35–200 pg/mL
Estradiol vaginal ring	50 and 100 μg	
Vaginal estradiol	>0.5 mg	
Vaginal CEE	>0.5 mg[c]	

[a] Not approved or recommended in United States.

[b] No longer available in United States.

[c] Predominantly estrone sulfate; LH suppression reflects systemic absorption.

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Systemic-dose vaginal estrogen

CEE 0.625- to 2.5-mg vaginal cream, administered daily, results in systemic effects as evidenced by LH and FSH suppression (285). No RCT data are available regarding the FDA-approved dosing of estradiol 2- to 4-g vaginal cream, administered daily for 1 to 2 weeks, followed by a maintenance dosage of 1 g, one to three times a week.

Other hormonal agents

Estriol vaginal preparations (gels and suppositories) are manufactured and government regulated in a number of countries outside the United States. Estriol is considered a low-affinity estrogen and, despite increased plasma concentration after repeated vaginal administration, is not considered to have substantial systemic effects (286, 287).

Adverse events

Because serum estradiol levels during therapy usually fall within the normal postmenopausal range, the risk profile with low-dose vaginal ET is expected to be lower than with systemic ET (288). However, long-term endometrial safety data are lacking, and 1 year is the maximum duration of RCTs of vaginal ET (261). Side effects include vulvovaginal candidiasis (289, 290) and, with higher dosing and systemic absorption, vaginal bleeding and breast pain (289). Increased CVD or VTE risk has not been reported (261). This may reflect an actual neutral effect due to the absence of a first-pass hepatic effect by vaginal estrogens, or that studies of women at high CVD or VTE risk are lacking (281). Available evidence does not support the boxed warning on low-dose vaginal estrogen regarding an increased risk of CHD, stroke, VTE, dementia, and breast cancer, and efforts to modify the labeling of these products are in progress (288).

Practice statement

5.2b In women with a history of breast or endometrial cancer, who present with symptomatic GSM (including VVA), that does not respond to nonhormonal therapies, we suggest a shared decision-making approach that includes the treating oncologist to discuss using low-dose vaginal ET. (Ungraded best practice statement)

Evidence

Breast cancer

Whether small increases in circulating estrogens from low-dose vaginal estrogen can stimulate the growth of residual breast cancer cells (280, 291–293) remains an unanswered question. However, for women taking aromatase inhibitors, the effectiveness of which depends upon blocking up to 95% of estrogen synthesis and reducing circulating estradiol levels to < 1 pg/mL (250), caution is raised because minimal amounts of estrogen can be absorbed with low-dose vaginal ET. In a cohort case-control study of 13 479 breast cancer survivors taking adjuvant tamoxifen or aromatase inhibitor therapy for at least 1 year, after 3.5 years of concurrent administration of the low-dose estrogen ring or 10-μg vaginal tablet, breast cancer recurrence did not increase (relative risk, 0.78; 95% CI, 0.48–1.25) (294). These data are insufficient, however, to conclude safety and to recommend this approach.

Endometrial cancer

The effect of low-dose vaginal ET on endometrial cancer recurrence is unknown. The only RCT attempting to evaluate the effect of systemic ET on recurrence rate and survival in women after surgery for stage I or II endometrial cancer was closed prematurely without complete enrollment (295). In the absence of RCT findings to guide practice recommendations, the decision to use ET remains controversial and involves assessing the severity of postmenopausal symptoms and tumor characteristics (296, 297).

5.2c For women taking raloxifene, without a history of hormone- (estrogen) dependent cancers, who develop symptoms of GSM (including VVA) that do not respond to nonhormonal therapies, we suggest adding low-dose vaginal ET. (2⊕⊕◯◯)

Evidence

Raloxifene has neutral vaginal effects (298–300). In two clinical trials, vaginal, but not oral (301) ET, was safely used to treat vaginal symptoms in women taking raloxifene without untoward endometrial effects (302, 303).

5.2d For women using low-dose vaginal ET, we suggest against adding a progestogen (ie, no need for adding progestogen to prevent endometrial hyperplasia). (2⊕◯◯◯)

5.2e For women using vaginal ET who report postmenopausal bleeding or spotting, we recommend prompt evaluation for endometrial pathology. (1⊕⊕◯◯)

Evidence

Bleeding or spotting in a woman using only vaginal estrogens is uncommon in the absence of endometrial pathology. The 2006 Cochrane review of 19 studies found no significant difference among vaginal creams, tablets, or rings in terms of endometrial thickness or hyperplasia or in the proportion of women with adverse events (261). Recent 1-year-long studies of vaginal CEE cream and low-dose vaginal estradiol tablets revealed no cases of endometrial hyperplasia or cancer as determined by endometrial biopsy (263, 266, 304). Vaginal administration of

estradiol tablets, when placed in the upper third of the vagina, may result in a uterine first-pass effect resulting in a higher degree of uterine stimulation (305–309). It is unknown whether endometrial proliferation, hyperplasia, or cancer can occur after long-duration treatment (> 1 y) or in women with risk factors (late menopause, higher body mass index, higher dosing). For women at higher risk of endometrial cancer, surveillance using transvaginal ultrasound, followed by endometrial biopsy if endometrial thickening is present, may be prudent. Intermittent (possibly annual) progestogen withdrawal may be considered to assess endometrial status (261, 280).

5.3 Ospemifene

5.3a For treatment of moderate to severe dyspareunia associated with vaginal atrophy in postmenopausal women without contraindications, we suggest a trial of ospemifene. (2|⊕⊕⊕◯)

5.3b For women with a history of breast cancer presenting with dyspareunia, we recommend against ospemifene. (1|⊕◯◯◯)

Evidence

Benefits

Not all women are comfortable using vaginal ET, and women may prefer an oral medication specifically indicated for dyspareunia.

Vaginal symptoms and sexual function. Two 12-week RCTs of ospemifene reported improvements in pH and vaginal maturation index, severity of dyspareunia (310, 311), and standardized measures of sexual function (including desire, arousal, orgasm, and satisfaction) (312). Two year-long studies (313, 314) demonstrated sustained vaginal benefits.

Risks

Vasomotor symptoms. The most common adverse effect was VMS (7.2% of women taking ospemifene compared with 2% taking placebo) (314).

Cardiovascular. Ospemifene involves risk of VTE (315) and is contraindicated in women at risk for venous or arterial thrombosis or stroke. In safety studies, incidence rates for thromboembolic stroke, hemorrhagic stroke, and DVT were 0.72, 1.45, and 1.45/1000, respectively, in women receiving ospemifene 60 mg vs 1.04, 0, and 1.04/1000, respectively, in women assigned to placebo (310).

Endometrium. No cases of endometrial carcinoma have been reported. Studies reported endometrial thickening of ≥ 5 mm at a rate of 60.1/1000 women per year of therapy with ospemifene vs 21.2/1000 women per year of therapy with placebo. The incidence of proliferative endometrium (weakly plus active plus disordered) was 86.1/1000 women with ospemifene vs 13.3/1000 with placebo (315). The incidence of uterine polyps was 5.9 cases/1000 women with ospemifene vs 1.8/1000 women with placebo (315).

Breast. Data on breast density or breast cancer risk are lacking. Estrogen-dependent neoplasia is a contraindication.

Future research

There are numerous gaps in our knowledge regarding menopause symptoms. Some of these include a lack of the most basic understanding of what causes hot flashes, questions regarding the potential link between VMS and CVD in older vs younger postmenopausal women, and a poor understanding of the relationships between menopause and sleep and hormonal transitions and mood, which have significant social and economic implications. Given the uncertainties regarding the precise neuroendocrine events that cause VMS, developing specific targeted therapies is challenging. Establishing appropriate animal models and expanding recent research involving the neuroregulators kisspeptin, neurokinin B, and dynorphin may help develop new effective treatments (35).

Management of the transition to menopause remains uncharted territory. The SWAN and the Melbourne Women's Midlife Health Project provide extensive epidemiological, physiological, and descriptive data characterizing reproductive changes that occur during the transition to menopause. However, clinical management decisions are often based on the extrapolation of observational data collected from studies conducted in younger, reproductive age women. RCTs of frequently prescribed therapies, such as oral contraceptives, MHT, and measures to control mood, with clinical outcomes relevant to women of relatively advanced age are sorely needed to confidently advise patients regarding the safest and most effective therapies to use during this transition.

Managing the loss of ovarian function in premenopausal women due to surgery, the range of disorders manifesting as POI, or the sequelae of treatment for breast cancer and other malignancies remains challenging. This is due to a dearth of quality data assessing the long-term risks and benefits of MHT or other options for symptom relief and prevention of chronic diseases in these groups. Fertility issues can be managed with modern assisted reproductive technology, but we fall short on adequately managing estrogen deficiency. Pressing questions remain

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regarding optimal treatment preparation, dosing and regimens, and the merits of long-term MHT, even in women without menopausal symptoms. International registries and clinical trials are overdue to address the long-reaching implications of these important issues.

The most persistent question for naturally postmenopausal women is how to balance menopausal symptom relief with the prevention of chronic diseases of aging such as CHD, osteoporotic fractures, and dementia. ET has long been hypothesized to meet this goal, although conclusive evidence remains elusive, and questions persist regarding the interaction between EPT and these outcomes, as well as breast cancer. Observational data suggesting differences in VTE risk and other CVD outcomes continue to accumulate, suggesting a significant need for adequately powered clinical trials comparing the safety and efficacy of oral with transdermal therapies in younger, recently postmenopausal women.

Finally, new SERM therapies (alone and partnered with estrogens) are promising, but larger, longer trials are needed to fully characterize the benefit/risk profiles of these new treatments and inform the clinician as to which patients stand to benefit the most from their use.

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SPECIAL ARTICLE

The *Physicians' Desk Reference*

Problems and Possible Improvements

Jay S. Cohen, MD; Paul A. Insel, MD

The *Physicians' Desk Reference* (*PDR*) is a widely used source of drug information by American physicians and patients, but as we shall discuss, it suffers from numerous shortcomings.[1] The *PDR* is a collection of written and pictorial information that is provided and paid for by pharmaceutical manufacturers. The written material for a given drug is a compilation of data and recommendations that are identical to those in the drug's package insert. The wording and directives that are included in these package inserts (and thus in the *PDR*) represent information that the pharmaceutical companies are permitted to present following discussion and approval by the Food and Drug Administration (FDA), Rockville, Md. The *PDR* is thus a negotiated effort of commercial enterprises and governmental regulators.

Family physicians rely on the *PDR* more than any other drug information resource.[2] According to the Medical Economics Data Production Company, Montvale, NJ, which publishes the *PDR*: "Nine out of ten doctors consider the PDR to be their most used drug reference book . . . 97% of physicians say that the PDR is the book they go to when they're prescribing a drug they're not completely familiar with" (Mr Cy Caine, PDR Electronics, Medical Economics Data Production Co, oral communication, September 12, 1994). Moreover, each year, approximately 500 000 *PDR*s are sent to physicians, and about 500 000 more are sold to other professionals and to the general public.

Even so, the *PDR* has received little objective scrutiny with regard to the quality of its data. We will address the following questions: Is the information provided by the *PDR* comprehensive, current, and accurate? Does the cost-free mailing of annual editions of the *PDR*, underwritten by the drug industry, constitute a conflict of interest? Does physicians' reliance on the *PDR* influence the quality and objectivity of their knowledge of drugs, and by extension, the quality of care given to patients?

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THE BASIS OF THE POPULARITY OF THE *PDR*

The popularity of the *PDR* among physicians is probably not a coincidence. First and perhaps foremost, for physicians, the *PDR* is delivered by mail free of charge. Unlike textbooks that can become quickly outdated, the *PDR* is updated by both periodic supplements during a given year and new annual editions.

The *PDR* enters the lives of physicians when they are young. The first free copy arrives during medical school. It is a powerful gift not only because it is free, but also, we believe, because receipt of the *PDR* has symbolic power, implying that a medical student is almost a physician. The result is that from the start, the *PDR* becomes identified as a natural part of being a physician. Medical students who begin clinical clerkships are often urged to consult the *PDR* to learn the brand names of drugs that preclinical pharmacology classes generally avoid teaching; yet, clinicians often favor brand names of drugs when they discuss and prescribe therapeutic agents. Moreover, the *PDR* pro-

vides information about doses—a topic that is typically ignored in preclinical teaching.

Beyond cost and convenience, there are other reasons for the popularity of the *PDR*. The format of the *PDR* is superior to many other drug information resources. The organization of the *PDR* is simplified by 3 color-coded, easily identified indexes: (1) an alphabetical list of drugs that contains both the brand and generic names, (2) a listing of drugs by therapeutic category and symptoms, and (3) an index that provides the drug manufacturers' 1-800 telephone numbers for professional support. The "Product Identification Section" (ie, glossy pages of color pictures of drug formulations) is an excellent visual-identification section. Thus, its organization and presentation make the *PDR* very "user-friendly." Package insert information in the *PDR* can thus be readily used to complement information that is provided by other sources of drug advertising.

As the *PDR* is well indexed, regularly updated, easy to use, and free, all these factors contribute to the popularity of the *PDR*. Moreover, because the *PDR* represents a compilation of package inserts that have been evaluated by the FDA, the *PDR* is perceived as government-approved information about drugs. Thus, it is commonly used to answer questions with regard to the "standard of care" of drug administration.

DEFICIENCIES IN THE *PDR*

The substance of the *PDR* lies in its "Product Information" section (ie, the manufacturer-written package inserts). It is in this largest and most important part of the book that we believe multiple problems exist: (1) In the *PDR*, dosage information and guidelines are inadequate and do not always account for interindividual variation. (2) Dosage methods that are recommended in the *PDR* are likely to be based on clinical studies that are skewed toward accelerated and higher dosing. (3) Clinically relevant low-dose information, when present, tends to be lost amid the lengthy write-ups in the *PDR*. (4) Many drug descriptions in the *PDR* provide no dosing adjustments for elderly patients. (5) Specific dosages for specific diagnoses are sometimes omitted. (6) Data with regard to side effects in the *PDR* tend to be unfocused, inaccurate, and inadequately updated. (7) The *PDR* sometimes contains outdated information.

Inadequate Dosage Information and Guidelines

It is a fundamental pharmacologic observation that normal subjects who are administered the same dose of a medication show variations in response. Depending on the drug, the range of interindividual variation in pharmacokinetics can be large, sometimes varying up to 40-fold.[3-5] If we add the factor of intraindividual variation, the implications become even greater. For this reason, textbooks of clinical pharmacology advise (and clinical experience dictates) individualization of drug dosages according to the requirements of each patient. Yet, in the guidelines in the *PDR*, many drugs are recommended in only 1 or 2 dosages and information with regard to dosing in relation to meals is not generally provided.

For example, terfenadine (Seldane) is recommended at 60 mg twice each day for all patients, regardless of factors such as age, size, gender, state of health, concomitant medications, or a history of medication intolerance. This one-size-fits-all approach might be appropriate if terfenadine were entirely benign, but substantial evidence implicates its role in life-threatening cardiac arrhythmias.[6] This side effect appears to be, in part, dose-related.[6,7] Moreover, data that preceded the marketing of terfenadine and that demonstrated effectiveness of the drug at dosages 50% lower than those recommended[8,9] are not mentioned in its *PDR* description.

Product descriptions in the *PDR* often contain brief summaries of findings from selected clinical studies that support the dosages recommended by the manufacturer. In part, this is a consequence of the regulatory environment that demands agreement between a manufacturer and the FDA with regard to the content of these descriptions. Studies that demonstrate effectiveness of lower than recommended dosages may be omitted from the *PDR*. Examples include flurazepam hydrochloride (Dalmane),[10,11] zolpidem tartrate (Ambien),[12-14] ibuprofen (Motrin),[15,16] diclofenac sodium (Voltaren),[17-20] fluoxetine hydrochloride (Prozac),[21,22] ranitidine hydrochloride (Zantac),[23-25] and omeprazole (Prilosec).[26]

Similarly, most *PDR* drug descriptions provide pharmacokinetic data on certain factors (eg, peak plasma drug levels, mean elimination half-lives); however, in many cases, these data are expressed as statistical means without confidence limits. We believe that the absence of such data may inhibit the ability of physicians to understand unusual and idiosyncratic reactions in some patients.

Guidelines for administration of medications at only 1 or 2 doses are sometimes medically irrational; yet, new drugs often are recommended in the *PDR* with this type of guideline. Perhaps this has more to do with economics than science. Drug manufacturers understand that penetrating an established market is difficult; thus, nonscientific issues may take precedence in carving out a niche for a new drug.[27]

A drug for which the formulation and dosage are easy for physicians to remember (and for patients to use) will presumably have a better chance of being prescribed than will a drug with complex dosage guidelines that may better match the range of individual variation. Although flexible dosing schedules may be more medically sound, complicated dosing schedules are harder to remember, take more time to explain to patients, and may contribute to noncompliance. Thus, flexible dosing may be a liability in a competitive market for drug prescriptions.

Basis of *PDR*-Recommended Dosage Methods

Because of economic and time considerations, Phase 1 and 2 studies may be relatively brief. For example, in the case of fluoxetine, stud-

ies were sometimes ended before this long-acting drug reached its peak blood levels.[28] Studies that have been designed to define dosage may have been conducted with subjects who are younger, healthier, and thus potentially more tolerant of pharmacologic effects than are patients. All of these factors favor higher dosages.

Recent efforts by the FDA to achieve a more balanced gender and racial representation in Phase 1, 2, and 3 studies will improve but may not completely remedy this situation. Even under the best of circumstances, studies that are conducted on a small sample are limited in their ability to determine side effects and optimal dosages in the larger population. Information about adverse drug reactions and the full range of dosing regimens are sometimes only learned after a drug is made available for prescribing[29,30]; yet, the dosing recommendations in the *PDR* that are based almost entirely on data from Phase 1, 2, and 3 studies do not incorporate information obtained during Phase 4 (after drug release) unless a manufacturer applies to the FDA to change the package insert.

Clinically Relevant Low-Dose Information Amid Lengthy Write-ups in the *PDR*

The *PDR* sometimes offers efficacy and toxicity data associated with lower drug dosages, but these data can be difficult to find or recognize. In the description of cimetidine (Tagamet), one reads: "800 mg h.s. [at bedtime] is the dose of choice for most [acute duodenal ulcer] patients . . . "[31(p2403)]; yet, who these "most patients" are is not precisely defined. Elsewhere in the write-up, one finds results of a study in which cimetidine (400 mg at bedtime) healed 66% of patients with duodenal ulcers after 4 weeks of treatment; other data indicate that treatment with 800 and 1600 mg of cimetidine given at bedtime healed 75% and 81% of patients, respectively. Thus, most patients healed in response to 400 mg of cimetidine that was taken at bedtime, but the recommendation ignores these results. A more prominent mention of the effectiveness of the lower dose in the dosage guidelines for cimetidine would offer physicians an alternative for use with patients who are prone to side effects.

Ondansetron hydrochloride (Zofran) provides another example. If one reviews a detailed table that is published in the *PDR* and that summarizes the efficacy of the recommended dosage (8 mg 3 times daily) of ondansetron hydrochloride, one is likely to miss the effectiveness of another dosage (4 mg 3 times daily), unless one reads a footnote to the table.[31(p862)] In addition, the effectiveness of a dosage of 1 mg 3 times daily[32-34] in some subjects is not mentioned at all.

With ranitidine hydrochloride, the *PDR* acknowledges the effectiveness of treating a duodenal ulcer with a dosage of 100 mg twice daily, which is 33% lower than the recommended dosage of 150 mg twice daily[31(p1110)]; yet, a preparation is not marketed for treatment with the lower dosage.

Absence of Dosing Adjustments for Elderly Patients in Drug Descriptions

Many drugs demonstrate altered pharmacokinetics in elderly patients, owing sometimes to hepatic, but more commonly, to decreased renal excretion as a consequence of a decreased glomerular filtration rate and renal blood flow. As a result, elderly patients should receive lower doses of certain drugs than do other adult subjects to achieve equivalent efficacy and to prevent unnecessary toxic effects. Lower doses may be safer, too, because the responses of older patients to drugs can be more unpredictable than for other patient populations.[35] This unpredictability, coupled with a higher drug use than in other age groups, has resulted in a higher incidence of side effects in the elderly compared with that in the younger adult population.[30,36,37]

Until recently, the FDA did not require package inserts to include dosage adjustments for elderly patients. In 1989, for 425 drugs that are often used by elderly patients, only about half had information in the *PDR* about use in this population.[38] Thus, information in the *PDR* may be misleading with regard to the safety of "standard adult" dosages in elderly patients. Given the growing number of elderly patients in the United States, and the possibility that interindividual variation in these patients may be even broader than among the general population, the *PDR* should provide dosage guidelines for elderly patients for all drugs that are used in this population.

Omission of Specific Dosages for Specific Diagnoses

Drug manufacturers are not required to study every possible use of a new drug. Approval by the FDA requires proof of effectiveness in the treatment of 1 definable disorder. Yet, once a drug is approved, physicians can (and often do) use it for any condition that they choose. In some cases, these "new" uses prove to be helpful to patients; thus, medical practice is not necessarily reflected by what is contained in the *PDR*. For a manufacturer to add a new indication to the *PDR* would require the filing of a New Drug Application with the FDA. As a result, guidelines for use and dosage in the *PDR* may not be accurate for certain conditions. Examples include drugs such as diclofenac for pain or tendinitis,[39-42] propranolol hydrochloride (Inderal) for mitral valve prolapse syndrome,[43] trazodone hydrochloride (Desyrel) for insomnia,[44-46] and topical tretinoin (Retin-A).[47]

This may be a particular problem for certain classes of therapeutic agents. One example relates to antidepressant drugs, for which most dosage guidelines in the *PDR* make no reference to specific diagnoses. Although fluoxetine, paroxetine hydrochloride (Paxil), sertraline hydrochloride (Zoloft), venlafaxine hydrochloride (Effexor), amitriptyline hydrochloride (Elavil), imipramine hydrochloride (Tofranil), and other antidepressants were initially approved for treating major depression, the guidelines do not indicate that the recommended dosages are specific for this condition. This is important because these drugs are commonly utilized in treating milder conditions (ie, dysthymic panic, and obsessive-compulsive disorders, pain

and premenstrual syndromes, insomnia, and other types of depression) that may respond to lower dosages than those recommended for major depression. The result is that physicians tend to prescribe the *PDR*-recommended dosages that befit major depression to patients with milder conditions; this practice may play a role in the high incidence of side effects that are seen with antidepressant drugs.

Unfocused, Inaccurate, and Inadequately Updated Data for Side Effects in the *PDR*

The range and rate of side effects listed in the *PDR* are derived from findings from both preclinical and clinical studies, which are, by necessity, limited in the number of subjects and duration of treatment. Thus, previously unrecognized side effects and varying incidences of already recognized side effects may be discovered during Phase 4,[48] as drugs are administered to a larger number of patients with a wide variety of diseases and conditions and for longer terms than when those drugs were used in Phase 2 and 3 trials.[3] Typically, though, a package insert (*PDR* description) for a new drug is written before the drug is able to be prescribed. The result is that the *PDR* tends to present potentially inaccurate, imprecise, and incomplete data with regard to side effects.

Moreover, a review of the profile of side effects of a given drug in the *PDR* can often be so extensive that clinically important side effects may be difficult for the physician to discern from those that are less frequent and less severe. This is particularly the case with older medications, for which the frequency of side effects is generally not provided in the *PDR*. Because this information is lacking in the *PDR*, physicians may not appropriately warn patients of side effects that are most serious and most likely to occur, and when a side effect occurs, physicians may overlook the drug as the culprit.[30]

For example, since 1990, the *PDR* has listed the rate of fluoxetine-induced sexual impairments (reduced libido, impaired ability for ejaculation, or orgasm) at about 2% each,[31(p946)] whereas studies have reported the combined incidences as high as 34%.[49] Physicians who have prescribed fluoxetine may not have been aware of these facts, in part because the *PDR* was not updated to reflect this information. Interestingly, because the manufacturer sought FDA approval for this drug in treating obsessive-compulsive disorders, a new side-effect table offers rates of 11% for decreased libido plus 7% for abnormal ejaculation in males; the lower incidences listed in the table regarding use in depression remain the same.

Outdated Information in the *PDR*

Even though a new edition of the *PDR* is published annually, the information contained therein is not necessarily up-to-date. If one compares the drug descriptions in the 1995 *PDR* with versions published a decade (or, in some cases, 2 decades) earlier, many of the descriptions are virtually identical in the 2 versions. Examples include the descriptions of Benadryl (diphenhydramine hydrochloride), Esidrix (hydrochlorthiazide), Dalmane (flurazepam hydrochloride), and Elavil (amitriptyline).

With most medications, postmarketing studies and clinical experience reveal unanticipated changes in uses and dosing patterns. These discoveries are reported in journals and some textbooks, but physicians may not consult these sources as often as they consult the *PDR*. Consequently, the *PDR* does not keep physicians informed about new uses and new concerns. This issue is related to the general lack of incorporation of information obtained from postmarketing (Phase 4) studies into the *PDR*.

AN INHERENT CONFLICT OF INTEREST?

The poor prescribing habits of physicians and the relationship between these habits and iatrogenic illness have been documented.[30,48] We believe that such habits in part relate to the information on which physicians base therapeutic decisions. Where do physicians turn for this information? Ideally, this information would be objective and would derive from medical school course work, textbooks, journals, postgraduate training, and continuing education courses. The reality, though, is that a substantial portion derives from the *PDR*. In essence, the industry that develops medications is a principal source of information for physicians who prescribe and choose among these products, thus presenting a problematic conflict of interest.

Although it is expected that physicians should play an independent role in the evaluation and utilization of the medications that they prescribe, reliance on the *PDR* (and other pharmaceutical company–derived sources of information) will almost certainly compromise independent judgments. In addition, as a company-derived collection of package inserts, the *PDR* provides neither adequate comparative analyses among drugs in similar or different classes nor information about cost, which is an issue of immense importance in the current era of health care provision.

THE ROLE OF THE FDA IN THE CONTENT OF THE *PDR*

Although the information contained in the *PDR* is generated by the pharmaceutical manufacturers, the individual drug descriptions must be approved by the FDA. Generally, the approval process is negotiated by representatives of the manufacturers and by FDA officials, often with input from external advisers to the FDA. This helps to provide a consensus for what is included in the package insert, but it may limit the information that manufacturers can include in their drug descriptions. For example, FDA regulations that require manufacturers to establish the safety and efficacy of a given drug and dosage may preclude a manufacturer's ability to include information about lower doses that have been shown to be effective in premarketing studies but have not been shown conclusively enough or in enough subjects to meet FDA standards. Similarly, requirements by the FDA may make it difficult for manu-

facturers to add information about previously unproved uses for their drugs despite findings during Phase 4 studies. Thus, procedural features and statutory rules probably contribute to shortcomings in the *PDR*.

ASSURANCE OF A RELIABLE SOURCE OF DRUG INFORMATION FOR PHYSICIANS

The ultimate responsibility for therapeutic decisions lies with the medical community, but physicians rely on the data that are made available to them. Without the *PDR* or a similar equivalent, where would physicians derive drug information, and would it be an improvement?

One possibility for ensuring a more objective source of drug information might be the dissemination to all physicians on an annual basis of 1 or more monograph, that would provide such information. The principal impediment to the dissemination of this type of monograph to all practicing physicians is financial, since the cost and preparation of an annual mailing would be large. Although the advent of computer-based technology should allow development of online, readily updated, objective, and inexpensive guides for the prescribing of drugs that include comparative information about the pharmacology and cost of different drugs, it is not clear that an interest group is committed to the development of such a guide. Nevertheless, this alternative deserves further consideration. We believe that a more feasible alternative is to improve the *PDR*, thereby maintaining the benefit of its already established system of annual dissemination and its long history of acceptance by physicians. Improvement of the *PDR* could be accomplished by having it meet well-defined medical and pharmacologic standards including (1) regular updating of drug descriptions to incorporate new data, in particular, data obtained in Phase 4 studies with regard to clinical uses, side effects, and doses; (2) recommendations about adjustments in dosing required for both younger adult and elderly patients and, to the extent possible, for pediatric patients as well; (3) highlighted sections to illustrate changes in annual editions; (4) more precise information with regard to the frequency of side effects and results of studies with lower than "standard" doses; and (5) the current wholesale cost of a drug.

Are these changes realistic? Could pharmaceutical manufacturers, the medical profession, and the FDA work cooperatively to fashion such a *PDR*? In fact, this potential has already been met in isolated cases. For example, the pharmacokinetic data on desipramine hydrochloride (Norpramin) mentions that a 36-fold difference in plasma levels has been seen in individuals who take identical oral doses of this drug, thus alerting physicians to the wide range of clinical responses that may occur.

The oral anticoagulant warfarin sodium (Coumadin) demonstrates that dosage guidelines can be updated. For 2 decades, warfarin has sometimes been prescribed in unnecessarily high dosages, as reflected by a high incidence of side effects.[50,51] In response to this problem, in 1990, the manufacturer updated the dosage recommendations for this drug. The new dosages are lower, the range is wider, and the recommendations include the need to individualize dosages, in particular with lower dosages for elderly and debilitated patients.[31(pp950-951)]

The *PDR* dosage recommendations can be changed when it has been deemed worthwhile or necessary. For example, triazolam (Halcion) and temazepam (Restoril) have had a lowering of dosages recommended in the *PDR*.

Indeed, if the potential of a "new" *PDR* is to be maximized, a reevaluation of the role of the FDA must also be part of the process. A requirement of more information about clinical responses at different dosing levels for different diseases, an assessment of drugs so as to define appropriate dosages for geriatric patients, and a regular updating of dosage guidelines and of prevalence rates of side effects would seem to be appropriate stipulations. In addition, a revision of regulations by the FDA so that manufacturers would add newly discovered uses and results of efficacy and toxicity in postmarketing studies. By requiring that manufacturers add dates to all drug descriptions, the FDA would alert readers to the timeliness of the data in the *PDR*.

CONCLUSIONS

The *PDR* is a mainstay of drug information for American physicians and probably the profession's leading source of drug data and prescribing guidelines. Despite this key role as a source of drug information, we believe that a number of aspects of the *PDR* require reappraisal in light of the evolving demography of the American population, pharmacokinetic and pharmacodynamic discoveries, clinical experiences with marketed drugs, and the reality of cost containment in medicine today.

Because physicians, as well as informed patients, need a source of drug information in 1 form or another, there is a role for a "*PDR*"—an objective, comprehensive, carefully conceived collection of descriptions of available drugs that can provide guidance about prescribing and utilizing medications. Although ultimately we believe that computer-based, online sources will become the standard for drug information to physicians (and, indeed, one of these sources may well be the *PDR*), at the present time we propose that appropriate revisions of what is in part an imprecise and outdated *PDR* could prove to be beneficial to the prescribing of drugs and, thus, to patient care.

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Discriminatory experiences associated with posttraumatic stress disorder symptoms among transgender adults

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Abstract

Discrimination has been shown to disproportionately burden transgender people; however, there has been a lack of clinical attention to the mental health sequelae of discrimination, including posttraumatic stress disorder (PTSD) symptoms. Additionally, few studies contextualize discrimination alongside other traumatic stressors in predicting PTSD symptomatology. The current study sought to fill these gaps. A community-based sample of 412 transgender adults (mean age 33, SD=13; 63% female-to-male spectrum; 19% people of color; 88% sampled online) completed a cross-sectional self-report survey of everyday discrimination experiences and PTSD symptoms. Multivariable linear regression models examined the association between self-reported everyday discrimination experiences, number of attributed domains of discrimination, and PTSD symptoms, adjusting for prior trauma, sociodemographics, and psychosocial co-morbidity. The mean number of discrimination attributions endorsed was 4.8 (SD=2.4) and the five most frequently reported reasons for discrimination were: gender identity and/or expression (83%), masculine and feminine appearance (79%), sexual orientation (68%), sex (57%), and age (44%). Higher everyday discrimination scores (β=0.25; 95% CL=0.21–0.30) and greater number of attributed reasons for discrimination experiences (β=0.05; 95% CL=0.01–0.10) were independently associated with PTSD symptoms, even after adjusting for prior trauma experiences. Everyday discrimination experiences from multiple sources necessitate clinical consideration in treatment for PTSD symptoms in transgender people.

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Keywords

PTSD; discrimination; stigma; transgender

Transgender people, who have a gender identity that differs from their assigned sex at birth, experience high levels of prejudice, discrimination, and violence (Bockting, Miner, Romine, Hamilton, & Coleman, 2013; Grant, 2011; Lombardi, Wilchins, Priesing, & Malouf, 2002; Mizock & Lewis, 2008; Shipherd, Maguen, Skidmore, & Abramovitz, 2011). A national study of more than 6,000 U.S. transgender respondents found that 63% reported an emotionally- or life-impairing experience of discrimination (Grant, 2011). Discrimination toward transgender people occurs across settings (e.g., employment, healthcare) and can be both chronic (e.g., interpersonal rejection) and acute (e.g., victimization) (Lombardi, 2009; Mizock & Lewis, 2008; Mizock & Mueser, 2014). Physical violence and sexual assault due to transgender identity are also highly prevalent across the life course (Clements-Nolle, Marx, & Katz, 2006; Grant, 2011; Stotzer, 2009). Consistent with minority stress theory (Hendricks & Testa, 2012; Meyer, 2003b), both violent and non-violent forms of discrimination are associated with adverse mental health outcomes in transgender people, including depression, anxiety, psychological distress, and substance abuse (Grant, 2011; Lombardi, et al., 2002).

Posttraumatic stress disorder (PTSD), a stress-sensitive disorder associated with significant morbidity and impairment (Kessler, 2000), represents one of the most common mental health conditions to arise from direct or vicarious exposure to life-threatening events, serious injury, or sexual assault (APA, 2013). PTSD is characterized by four key symptoms: (1) persistent intrusive thoughts or re-experiencing of the event; (2) avoidance of stimuli associated with the event; (3) negative cognitions and mood such as emotional numbing and detachment from others; and (4) changes in arousal or reactivity such as hypervigilance, irritability, exaggerated startle response, or self-destructive reckless behavior (APA, 2013). While PTSD affects an estimated 6.8% of the U.S. general adult population (Kessler et al., 2005), prevalence estimates in transgender samples range from 18 to 61% (Rowe, Santos, McFarland, & Wilson, 2015; Shipherd, et al., 2011; Valera, Sawyer, & Schiraldi, 2001; Wharton, 2007) and greater severity and frequency of emotional numbing, behavioral avoidance, and physiological arousal relative to non-transgender people have been reported (Wilson, 2013).

Despite the high prevalence of discrimination and PTSD in transgender people, the relationship between these phenomena remains understudied. A possible explanation for the dearth of research in this area is that exposure to non-violent forms of discrimination may not meet *DSM* criteria for a traumatic event (e.g., Criterion A). However, like acute traumatic stress, chronic and persistent threats to one's identity in the form of everyday discrimination threaten a person's core human needs for trust, understanding, control and belonging, with harmful mental health effects (Swim & Thomas, 2006). Further, trauma and discrimination, whether acute or chronic, produce similar stress responses, including avoidance of stimuli associated with the traumatic or discriminatory event (Bockting, et al., 2013; Carter & Forsyth, 2010; Meyer, 2003b; Pascoe & Richman, 2009) and hypervigilance

(e.g., anticipatory stress) about the possibility of future trauma or discrimination (Bockting, et al., 2013; Carter & Forsyth, 2010; Meyer, 2013; Pachankis, Goldfried, & Ramrattan, 2008), as well as similar physiological responses in reaction to acute laboratory-based stressors (Hatzenbuehler & McLaughlin, 2014). Despite evidence that traumatic stress exposure and stigma-related stress operate through similar minority stress processes (Meyer, 2003b), no studies have explored the relationship between discrimination and PTSD symptoms in transgender people, a highly stigmatized and underserved group.

In addition to known traumatic stressors such as childhood physical and/or sexual abuse and intimate partner violence, which increase probability of PTSD symptoms (Brewin, Andrews, & Valentine, 2000; Golding, 1999), a potential source of additional traumatic stress responses for transgender people is exposure to acts of discrimination based on gender identity or gender presentation. In addition, qualitative studies have illustrated that transgender individuals experience discrimination and oppression based on their gender identity and intersecting stigmatized identities (e.g., race/ethnicity, age, social class, and citizenship status) (Daley, Solomon, Newman, & Mishna, 2008; de Vries, 2014; Gamarel, Walker, Rivera, & Golub, 2014; Sevelius, 2013).

While research indicates that individuals with multiple identities often incorporate these identities into a single unified sense of self (McAdams, 1997; Meyer, 2010; Singer, 2004), multiple identities can provoke different forms of discrimination in diverse contexts. Indeed, multiple minority statuses can lead to greater discrimination exposure and result in greater erosion of core needs, as well as hypervigilance, avoidance, and physiological stress responses (e.g. Pascoe & Richman, 2009). For example, a study of 873 Latino and Black adults in New York City found that participants who experienced multiple domains of discrimination related to age, race, gender, weight, income, religion, mental or physical illness, immigration status, or sexual orientation, had a greater probability of reporting poor mental health than those who experienced no discrimination or discrimination in only one domain (Stuber, Galea, Ahern, Blaney, & Fuller, 2003). Similarly, a national study of 1,052 youth found that multiply disadvantaged youth faced greater exposure to multiple forms of discrimination than their more advantaged counterparts, and experiencing numerous forms of discrimination was more strongly associated with adverse mental and physical health outcomes than experiencing only one form of disadvantage (Grollman, 2012). Given that many transgender people may possess multiple stigmatized identities or characteristics (e.g., minority race/ethnicity, older age, low SES) and report discrimination and distress (Bockting, et al., 2013; Daley, et al., 2008; de Vries, 2014; Gamarel, Walker, et al., 2014; Golub & Gamarel, 2013; Reisner, Bailey, & Sevelius, 2014; Sevelius, 2013; Witten, 2009), the additive stress associated with experiencing discrimination based on multiple minority stigmas represents an important area for research.

Appearance-related stigma represents a possible mechanism through which transgender people experience discrimination. Appearance-related stigma refers to the extent to which one's appearance produces a negative reaction in others (Jones, Farina, Hastorf, & French, 1984). Transgender individuals who do not conform to the socially sanctioned expression of their assigned sex at birth often experience mistreatment by others who view their self-expression as non-normative (Bockting, et al., 2013). Conversely, transgender individuals

with high visual conformity are said to have "passing privilege" in that their stigma (i.e., being transgender) is concealable (Jones, et al., 1984) and they are therefore able to hide their transgender status and avoid mistreatment (Sevelius, 2013; Xavier, 1999). Social (i.e., living full-time in one's gender) and medical gender affirmation (i.e., hormones/surgery to masculinize/feminize) processes may impact the extent to which a transgender person appears more or less visually gender nonconforming, in turn impacting exposure to experiences of discrimination; however, the relationship between gender affirmation processes and experiences of discrimination are understudied.

Despite accumulating evidence that transgender people evince high prevalence of discrimination and PTSD symptoms, critical questions remain unanswered as to whether experiencing discrimination, as well as discrimination based on multiple stigmatized identities, is associated with PTSD symptoms. The purpose of this study was to: (1) examine discrimination experiences in a sample of transgender adults and explore reasons attributed to discrimination; (2) explore whether endorsing a higher number of attributed reasons for discrimination is associated with more PTSD symptoms; (3) identify whether gender affirmation processes are associated with discrimination experiences, including whether higher visible gender nonconformity is a risk factor and whether social transition or medical gender affirmation are protective factors for PTSD symptoms; and (4) evaluate whether discrimination experiences and the number of attributed domains are independently associated with elevated PTSD symptoms, after adjustment for some known traumatic stressors (e.g., childhood abuse and intimate partner violence).

Method

Participants and Procedures

A community-based sample of 452 transgender and gender nonconforming Massachusetts residents, ages 18 to 75 years, were purposively sampled from August-December 2013 for Project VOICE (Voicing Our Individual and Community Experiences), a study designed to examine the association between social stress and health. Participants were recruited via transgender-specific online and in-person venues. The majority (88%) were sampled online (via transgender electronic listservs, emails, web postings at local community-based websites, and social networking sites); 12% were sampled in-person (completed the survey via electronic tablets provided by the research team onsite at transgender community events, local social programming, and other gatherings). Eligible respondents were ages 18 years or older, self-identified as transgender or gender nonconforming, lived in Massachusetts for at least 3 months in the last year, and had the ability to read/write in either English or Spanish. Participants completed a one-time survey assessing demographics, experiences of discrimination and victimization, and health. Participants provided informed consent before beginning the survey. Using community-based participatory research principles (Leung, Yen, & Minkler, 2004), between March–July 2013 a team of community-based advocates, transgender leaders, researchers, and LGBT policy experts, working with gender minority people in the Commonwealth, together created the survey instrument and data collection plan. Whenever possible, validated questions or survey items adapted from prior transgender health research were utilized to ensure comparability of findings, including those from such

sources as the U.S. National Transgender Discrimination Survey (Reisner, Conron, Scout, et al., 2014) and Behavioral Risk Factor Surveillance System (BRFSS) (CDC, 2012). The survey was designed for a 5th grade reading level. Participants could opt to be entered into a community raffle for two tablet computers. We followed best practices for Internet research with transgender people, including initial usability and pilot testing, quality management processes to ensure unduplicated responses and valid study respondents (Miner, Bockting, Romine, & Raman, 2011) to ensure the integrity and validity of online data collected (Reisner et al., 2015). Two versions of the Project VOICE survey were fielded. The short version did not ask participants about discrimination experiences; thus, only participants who completed the long survey were included in the analytic sample (n=412). The survey was translated and back translated into Spanish, with input from transgender community members to ensure cultural relevance and appropriate translation. Four respondents completed surveys in Spanish. All study activities were IRB-approved.

Measures

Posttraumatic Stress Disorder (PTSD) Symptoms—PTSD symptoms were assessed with a 4-item scale designed for primary care settings (Ouimette, Wade, Prins, & Schohn, 2008; Prins et al., 2003) recommended by the U.S. Department of Veteran's Affairs (U.S. Department of Veteran's Affairs, 2014). Participants were asked: "In your life, have you ever had any experience that was so frightening, horrible, or upsetting that, in the past month you: (1) Have had nightmares about it or thought about it when you did not want to? (2) Tried hard not to think about it or went out of your way to avoid situations that reminded you of it? (3) Were constantly on guard, watchful, or easily startled? (4) Felt numb or detached from others, activities, or your surroundings?" Participants responded to each item using binary (yes/no) responses. The PC-PTSD has a test-retest Pearson's correlation coefficient of 0.83 ($p<0.001$), correlates highly with the Clinician-Administered PTSD Scale (Blake et al., 1995) 0.83 ($p<0.001$), and has an overall diagnostic accuracy of 85% (Prins, et al., 2003; Prins et al., 2004). The scale has also demonstrated good internal consistency in non-transgender samples (Cronbach's alpha ranges from 0.79–0.93) (Maguen et al., 2010; Mason, Mennis, & Schmidt, 2011; Sayer et al., 2011). This study represent the first time this measure has been used in a sample of transgender individuals. A factor analysis supported a single factor solution in the current study data (Eigenvalue=2.9; proportion of variance explained (PVE)=71.9%). Items were summed and scores ranged from 0–4; higher scores reflected more traumatic stress symptoms (α=0.87 in the current study).

Discrimination Experiences—Participants completed the Everyday Discrimination Scale, which consists of 11 items assessing the frequency of participants' experiences of everyday discrimination in the past 12 months on a Likert scale ranging from 0="*never*" to 4="*very often*." Sample items: "You have been treated with less courtesy than other people;" "People have acted as if they think you are not smart" (Krieger, Smith, Naishadham, Hartman, & Barbeau, 2005; Williams, Yan, Jackson, & Anderson, 1997). The Everyday Discrimination Scale has demonstrated good reliability and validity (Taylor, Kamarck, & Shiffman, 2004; Williams et al., 2012; Williams, Neighbors, & Jackson, 2003). In sample of LGBT participants, Cronbach's alpha for the discrimination scale was 0.94, and discrimination scores were correlated positively with depressive symptoms, anxiety, and

substance use (Gamarel, Reisner, Laurenceau, Nemoto, & Operario, 2014; Gamarel, Reisner, Parsons, & Golub, 2012; Gordon & Meyer, 2008; S. L. Reisner, White, Bradford, & Mimiaga, 2014). A factor analysis confirmed a single factor solution in the current dataset (Eigenvalue=6.9; PVE=62.9%). Items were summed and scores ranged from 0–44, with higher scores indicating higher levels of everyday discrimination experiences (α=0.94 in current dataset).

Reasons Attributed to Discrimination—Fourteen items assessed participants' attributed reasons for everyday discrimination using binary (yes/no) responses. Domains included those from prior research (Gordon & Meyer, 2008; Williams, et al., 1997) and theoretically relevant to this study: age, sex, race, ethnicity, nationality, religion, sexual orientation, disability, education or income level, weight, gender expression, masculine/feminine appearance, other aspect of appearance, and other reason. The number of attributed domains was summed; scores ranged from 0–14 with higher scores indicating higher number of domains of discrimination endorsed.

Other forms of trauma—Participants completed brief measures of childhood abuse and intimate partner violence used in prior research (Reisner, Falb, Wagenen, Grasso, & Bradford, 2013). Childhood abuse was queried by asking: "Were you ever physically or sexually abused as a child under age 15 years-old?" Participants who indicated "yes" were compared to those who indicated "no." Similarly, intimate partner violence was assessed with the item: "Have you ever been slapped, punched, kicked, beaten up, or otherwise physically or sexually hurt by your spouse (or former spouse), a boyfriend/girlfriend, or some other intimate partner?" These items are similar to other screening instruments commonly used to assess childhood abuse and IPV in clinical settings (Basile, Hertz, & Back, 2007; Hulme, 2004; McFarlane, Parker, Soeken, & Bullock, 1992). Previous use of the scale with LGBT populations have found associations with adverse mental health outcomes (S.L. Reisner, et al., 2013).

Sociodemographics—Age in years was assessed continuously. Gender was assessed using a two-step method (S.L. Reisner, Conron, Tardiff, et al., 2014) asking: (1) assigned sex at birth (*female, male*) and (2) current gender identity (*man, woman, female-to-male (FTM)/trans man, male-to-female (MTF)/trans woman, genderqueer, gender variant, gender nonconforming, other*). The two items were cross-tabulated to categorize participants as being on the female-to-male (FTM) trans masculine or male-to-female (MTF) trans feminine spectrum according to their natal sex. Participants assigned female at birth with a current nonbinary gender identity were categorized as FTM trans masculine; those assigned male at birth with a current nonbinary gender identity were characterized as MTF trans feminine. An indicator of non-binary gender was created to compare respondents with non-binary gender identities (gender variant, genderqueer, androgynous, gender nonconforming) to those with binary gender identities (man, woman, FTM, MTF). We note that intersex is not an assigned sex at birth; all infants, including those who are intersex, are assigned either a male or female sex at birth on their birth certificate. Social gender transition was assessed by asking participants if they lived full-time in their felt gender identity (yes/no). Medical gender affirmation was operationalized as being on cross-sex hormone therapy and/or having had

gender-related reassignment surgery (yes/no). High visual gender nonconformity was coded as those who "most of the time" or "always" endorsed the statement: "People can tell I'm transgender even if I don't tell them" and were compared to those who endorsed "never," "occasionally," or "sometimes." Race/ethnicity captured whether participants were white (non-Hispanic), Black (non-Hispanic), Latino/Hispanic, Other race/ethnicity, and Multiracial. Participants were categorized as people of color (POC) or non-Hispanic white. Perceived income ranged from 0="*no income*" to 3="*high income/upper class.*" Educational attainment was queried and ranged from 1="high school or less" to 4="graduate school." Unstable housing was operationalized as "rarely," "sometimes," or "often" having trouble "finding a safe place to hang out or sleep (housing)" in the past 12 months and compared to stable housing (i.e., "never" having such trouble). Sexual orientation was assessed by asking respondents how they identify with response options as "heterosexual/straight," "lesbian/gay," "bisexual," "queer," or "another sexual orientation." Sexual minority (i.e., lesbian, gay, bisexual, queer, another sexual orientation) respondents were compared to non-sexual minority (i.e., heterosexual, straight) respondents. Survey mode (online or in-person) was included as a covariate.

Depressive symptoms—Participants completed the 10-item Center of Epidemiologic Studies Depression Scale (CES-D-10) (Radloff, 1977) to assess past-week depressive symptoms. In the current dataset, Cronbach's α=0.88; a two factor solution was supported (cumulative PVE=60.7%) for negative affect (factor 1, Eigenvalue=4.9) and positive affect (factor 2, Eigenvalue=1.1), consistent with previous validation studies (Bradley, Bagnell, & Brannen, 2010; Zhang et al., 2012). Scores were summed such that higher scores indicated higher depressive symptoms. A score of 10 or more was operationalized to indicate a positive screen for clinically significant depression as recommended in prior research (Andresen, Malmgren, Carter, & Patrick, 1994). The CES-D-10 has been shown to correlate highly with the 20-item CES-D (Carpenter et al., 1998), which is sensitive in detecting clinical diagnoses of major depressive disorder. Furthermore, Cronbach's alpha for the CES-D scale was 0.88 in a sample of transgender adults (Reisner, et al., 2014).

Substance use—Participants were asked if they had used marijuana, cocaine, crack, club drug, methamphetamine, heroin, poppers, hallucinogens, downers, painkillers, or any other drug in the past 12-months (Yes/No). Past-12 month polydrug drug use was assessed by summing the number of drugs participants reported in the last 12 months. Participants using two or more drugs were compared to those reporting none or one drug.

Data Analysis

Statistical analyses were performed in SAS v9.4.1. Distributions of individual items were assessed, including missingness. Because missingness violated the missing completely at random assumption required for valid statistical inferences using listwise deletion (Allison, 2003), data were multiply imputed. A fully conditional specification imputation method was used shown to perform well in many different scenarios of missingness (Lee & Carlin, 2010; van Buuren, 2007; van Buuren, Brand, Groothuis-Oudshoorn, & Rubin, 2006). All subsequent analyses were conducted using the imputed data.

Univariate statistics were used to summarize the distribution of variables (mean, standard deviation [SD], frequencies, proportion). Two-sided tests were conducted with statistical significance at alpha=0.05. Tests for normality were conducted to ensure statistical assumptions for linear regression models were tenable. Analyses then examined whether any sociodemographic, depressive symptoms or substance use factors were associated with everyday experiences of discrimination to identify those groups who reported higher discrimination experiences. A linear multivariable regression model was fit (Model 1), regressing everyday discrimination scores on: number of reasons attributed to discrimination experiences (continuous), other traumatic experiences (binary) [childhood abuse, intimate partner violence], and sociodemographics [age, income, education (each continuous); FTM spectrum, non-binary gender identity, live full-time, medical gender affirmation, high visual gender nonconformity, POC, unstably housed, sexual minority, online survey mode, past-week depression, polydrug use (each binary)]. Next, analyses examined whether everyday experiences of discrimination were statistically associated with PTSD symptom scores (Model 2), adjusting for all variables described in Model 1. Multicollinearity diagnostics were computed for all regression models using variance inflation factor (VIF) values. All VIF values were less than 10, indicating no detection of multicollinearity (Jou, Huang, & Cho, 2014).

Age, everyday discrimination experiences scale scores, number of reasons attributed to discrimination, and PTSD symptoms were transformed to z-scores (mean=0, SD=1) to facilitate interpretation. The regression of a standardized variable (e.g., PTSD symptoms) on a standardized predictor (e.g., everyday discrimination experiences) generates standardized slopes that range from −1.0 and 1.0 (beta weights). For a binary predictor (e.g., childhood abuse yes/no), the standardized slope represents the difference between the means of the two groups on the outcome. Because the outcome variable is standardized (z-scored), the mean differences are in SD. The slope (beta) or difference between the means equals Cohen's *d* (effect size estimates). A Cohen's *d* of 0.20 (i.e., a fifth of a standard deviation) is a small effect, 0.50 (i.e., half a SD) a medium effect, and 0.80 a large effect (Cohen, 1988). Beta coefficients can therefore be interpreted in terms of SD unit changes in the statistical predictor relative to the outcome.

Results

Sample Characteristics

Table 1 presents characteristics of study sample. Participants had a mean age of 32.7 (SD=12.8); 62.6% were FTM spectrum; 59.7% identified their gender as binary; 19.2% were POC (2.9% Black, 9.0% Latino/Hispanic, 2.9% Other race, 4.4% Multiracial). There was high prevalence of childhood abuse age <15 years (46.6%), intimate partner violence (33.3%), depression (26.5%), polydrug use (18.5%), and unstable housing (25.5%). PTSD symptom scores ranged from 0 to 4 (M=1.95, SD=1.71). Overall, 44.4% of the sample met criteria for probable PTSD (PTSD symptom score 3+) (Prins, et al., 2003). The mean everyday discrimination score was 19.9 (SD=9.6). The mean number of discrimination attributions was 4.8 (SD=2.4). The five most frequently reported reasons attributed to discrimination were: gender identity and/or expression (83.2%), how masculine/feminine

you appear (78.6%), sexual orientation (68.0%), sex (assigned sex at birth) (56.8%), and age (43.5%) (Table 2). Linear models adjusted for survey mode (online vs in-person) are presented in Table 3 showing the statistically significant associations of PTSD symptoms, everyday discrimination experiences, and number of attributed domains of discrimination.

Everyday Discrimination Experiences (Table 4)

As shown in Model 1, FTM spectrum, POC, high visual gender nonconformity, greater number of reasons attributed to discrimination, childhood abuse age <15 years, past-week depression, and unstable housing were each independently and significantly associated with increased everyday discrimination scores. In this same model, sexual minority status, higher income, non-binary gender, and online sampling were each protective and associated with lower everyday discrimination scores.

PTSD Symptoms (Table 4)

In Model 2, higher everyday discrimination scores, greater number of attributed reasons for discrimination, childhood abuse age <15 years, intimate partner violence, social gender transition (living full-time in one's identified gender–distinct from medical gender affirmation), high visual gender nonconformity, unstable housing, past-week depression, and past-12 month polydrug use were each independently and significantly associated with higher PTSD scores. On the contrary, younger age, FTM spectrum gender, medical gender affirmation, and online sampling were each independently and significantly associated with lower PTSD scores.

Discussion

In this community-based sample of transgender adults, associations were found between discrimination experiences and PTSD symptoms. The present findings are consistent with a burgeoning body of evidence documenting elevated risk for mental health problems among individuals who experience discrimination (Diaz, Ayala, Bein, Henne, & Marin, 2001; Landrine & Klonoff, 1996; Williams, et al., 2003), including transgender people (Shipherd, et al., 2011). Notably, the prevalence of PTSD symptoms reported here is much higher than national studies of the general population (Kessler, et al., 2005).

Many participants experienced known sources of trauma including childhood abuse and intimate partner violence, but the association between discrimination experiences and PTSD symptoms existed after statistically adjusting for these. Further, the magnitude of the association between discrimination and PTSD symptoms (β=0.25) was comparable to the magnitude of association between childhood abuse and PTSD symptoms (β=0.29), and exceeded the magnitude of association between intimate partner violence and PTSD symptoms (β=0.18). In other words, discrimination experiences were associated with PTSD symptoms regardless of reporting of other known traumatic experiences. These findings point to the importance of identifying mechanisms that explain associations between discrimination and PTSD symptoms, including both interpersonal and intrapersonal pathways (Hatzenbuehler, Nolen-Hoeksema, & Dovidio, 2009). For example, prior evidence suggests that emotion dysregulation (i.e., difficulty monitoring, evaluating, and modifying

emotional reactions) mediates associations between daily experiences of discrimination and subsequent daily depressive symptoms (Hatzenbuehler, et al., 2009) and explains evaluated PTSD symptoms in several samples (Bowleg et al., 2014).

In addition, a greater number of domains attributed to discrimination was independently associated with higher levels of PTSD symptoms in the present study, suggesting that co-occurrence of stigmatized minority statuses may be associated with greater exposure to discrimination, as well as more PTSD symptoms. Findings are consistent with the view that an individual's health cannot be fully understood by examining isolated systems of social oppression (Crenshaw, 1991). Individuals hold multiple co-existing identities, typically experienced as a unified self (Crenshaw, 1991; Hembree et al., 2009); however possessing multiple stigmatized identities might increase the chances of experiencing discrimination toward any one of those identities (Stuber et al., 2003). Thus, individuals who experience multiple forms of discrimination may be at high risk of poor mental health as a result of their disproportionate exposure to social oppressions, which can diminish coping resources and may exacerbate PTSD symptoms (Cole, 2009; Mizock & Mueser, 2014). These results are particularly important in light of research that suggests coping with cumulative stressors is associated with wear and tear on biological systems, termed "allostatic load" (Geronimus, 1992; McEwen & Stellar, 1993). These findings highlight the importance of examining multiple forms of discrimination, rather than a singular stressor, in the mental health of transgender people.

Gender affirmation—an interpersonal process through which a person's gender identity is socially recognized—has been theorized as a key determinant of health for transgender people of color (Sevelius, 2013). This study found that gender affirmation processes are important to consider in understanding PTSD symptoms in transgender people more broadly. Consistent with prior research (Bockting, et al., 2013; Grant, 2011), visibly gender nonconforming participants in the present study had significantly higher discrimination scores. No similar differences in discrimination were found for either social transition (i.e., living full-time) or medical gender affirmation (i.e., hormones and/or surgery). However, high visual gender nonconformity and social transition were each associated with increased PTSD symptoms. Medical gender affirmation was significantly protective and associated with significantly decreased PTSD symptoms, which is consistent with prior research showing that medical gender affirmation is associated with positive mental health outcomes in transgender people (Colizzi, Costa, & Todarello, 2014; Gómez-Gil et al., 2012; Keo-Meier et al., 2014; E. C. Wilson, Chen, Arayasirikul, Wenzel, & Raymond, 2015).

Of note, other known social determinants of health were also associated with PTSD symptoms in this sample, including younger age (Chiu, deRoon-Cassini, & Brasel, 2011). An interesting gender difference emerged: MTFs had significantly higher PTSD scores than FTMs. This difference is consistent with U.S. general population data showing approximately two-fold increased risk for PTSD in females than males (e.g., Tolin & Foa, 2006); however, conflation of sex and gender in much epidemiologic research (Krieger, 2003) makes the sex- and gender-linked pathways shaping differences in psychiatric conditions difficult to interpret (Tolin & Foa, 2006). Unstable housing was associated with elevated PTSD symptoms, supporting low socioeconomic status as a risk factor (Bender,

Ferguson, Thompson, Komlo, & Pollio, 2010). Additionally, childhood abuse, intimate partner violence, depression, and polydrug use statistically predicted PTSD symptoms in this sample, supporting known PTSD-specific psychosocial risk factors in the U.S. general population for transgender people (Balan et al., 2013; O'Donnell, Creamer, & Pattison, 2014; Ullman, Relyea, Peter-Hagene, & Vasquez, 2013).

Several limitations must be noted. As a cross-sectional study, findings demonstrate associations only; causality cannot be inferred. The presence of "Criterion A" or the "stressor criterion" (Breslau & Kessler, 2001) was not necessary for inclusion in this study, nor a prerequisite for assessment of PTSD symptoms. Given that 90% or more of the general population will experience a traumatic event in their lifetime (Breslau & Kessler, 2001; Breslau et al., 1998), assessment of traumatic exposure was excluded from the screening items (Prins, et al., 2003). The brief screening assessment for PTSD symptoms used in this study was designed for primary care settings, not for research purposes. Discrimination and PTSD symptoms were both self-reported subjective measures. Future research utilizing objective measures (e.g., clinician-assessed PTSD diagnosis) is needed to circumvent the possibility that self-reported discrimination experiences are confounded with mental health status (Meyer, 2003a). In addition, future mixed-methods research to explore the attributed reasons (e.g., sex, gender, race) for discrimination would make a valuable contribution. For example, the most frequent reason attributed to discrimination experiences was gender identity and/or expression; however, more than half of the sample reported experiencing discrimination due to sex. A more in-depth understanding of transgender experiences and perceptions regarding sex- and gender-based discrimination is warranted. There is substantial heterogeneity of trauma responses (Bonanno & Mancini, 2012), which the current study was not designed to assess. Future studies would benefit from considering transgender identity formation alongside gender affirmation (Devor, 2004). Children or adolescents may be abused because of discrimination related to their gender nonconforming presentation (Grossman & Howell, 2005); similarly, intimate partner violence may occur due to discrimination related to a partner's transgender status (Ard & Makadon, 2011; Brennan et al., 2012; Stotzer, 2009). Thus, childhood abuse and intimate partner violence can be driven by discrimination and may therefore not be necessarily distinct from it. Although the items for childhood abuse and intimate partner violence have been used in prior research (Reisner, et al., 2013), their brief single-item nature could be improved in future research by utilizing screeners with established psychometric properties.

Despite the limitations, our findings have implications for treatment interventions. (Maguen, Shipherd, & Harris, 2005). Considering everyday experiences of multiple forms of discrimination in PTSD treatment represents a critical aspect of clinical care for traumatized transgender people. Integrating evidenced-based treatments for PTSD, such as cognitive behavioral interventions (Forneris et al., 2013; Kar, 2011; Maguen, et al., 2005; Resick, Nishith, Weaver, Astin, & Feuer, 2002), with gender minority stress models (Hendricks & Testa, 2012) will ensure cultural responsiveness of interventions to meet the unique needs of transgender communities. Coping resources can act as a buffer against discrimination (Thoits, 1991); thus, skills-focused coping may represent an important component of clinical intervention. Given that only a minority of individuals who experience traumatic stressors develop PTSD symptomatology (Yehuda & McFarlane, 1995) and that the majority of

transgender individuals demonstrate resilience in a context of pervasive societal oppressions (Mizock & Lewis, 2008), uncovering the biopsychosocial mechanisms underlying vulnerability to and protection against PTSD represents a key future research direction with this population. Given that online respondents had statistically significantly lower discrimination and PTSD symptom scores relative to those completing the survey in-person, community efforts that engage transgender people "face-to-face" represent an important way of transgender people at-risk social stress and PTSD symptomatology.

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Table 1

Descriptive Statistics of Transgender Adults in Massachusetts (n=412)

	Mean (SD)	%	n
Outcome			
PTSD Symptom Scores (range 0–4)[+]			
Mean (SD)	1.95 (1.71)	--	412
Median (IQR)	2.00 (4.00)	--	412
Independent Variables			
Everyday Discrimination Scores (range 0–44)			
Mean (SD)	19.88 (9.58)	--	412
Median (IQR)	19.00 (13.00)	--	412
Number of Attributed Reasons for Discrimination Experiences			
Mean (SD) (range 0–14)	4.84 (2.39)	--	412
Median (IQR)	5.00 (3.00)	--	412
Covariates			
Childhood Abuse Age < 15 Years		46.6	192
Intimate Partner Violence		33.3	137
Depression (CESD Score 10+)		26.5	109
Substance Use, Past 12 Months (2 or More)		18.5	336
Age – Mean (SD) (range 18–72)	32.74 (12.79)	--	412
FTM Spectrum		62.6	258
Binary Gender Identity		59.7	246
Social Gender Transition (Live Full-Time)		76.9	317
Medical Gender Affirmation (Hormones and/or Surgery)		58.7	242
High Visual Nonconforming Gender Expression		21.6	89
People of Color (POC)		19.2	79
Socioeconomic Status			
Income (0–3)	1.39 (0.73)	--	412
Educational Attainment (1–4)	2.65 (0.97)	--	412
Unstably Housed		25.5	105
Sexual Minority (Lesbian/Gay/Bisexual/Queer/Other)		87.1	359
Online Survey Mode		87.9	362

[+]Note: 44.4% of the sample (n=183) met criteria for probable PTSD (score 3+)

Table 2

Reasons Attributed for Discrimination (14 Attributions) (n=412)

	%	n
Age	43.5	170
Sex	56.8	234
Race	11.9	49
Ethnicity	11.4	47
Nationality	5.8	24
Religion	13.4	55
Sexual Orientation	68.0	280
Disability	17.7	73
Education and/or Income	23.1	95
Weight	29.9	123
Gender Identity and/or Expression	83.2	343
How Masculine or Feminine You Appear	78.6	324
Other Appearance	30.1	124
Other Reason	10.6	44

Table 3

Linear Models Adjusted for Survey Mode Showing Associations Between PTSD Symptoms, Everyday Experiences of Discrimination, and Number of Reasons for Discrimination Among Transgender Adults in Massachusetts (n=412).

	PTSD Symptoms	Everyday Experiences of Discrimination	Number of Attributed Reasons for Discrimination
PTSD Symptoms	1.00		
Everyday Experiences of Discrimination	0.41 ***	1.00	
Number of Attributed Reasons for Discrimination	0.23 ***	0.38 ***	1.00

*** $p<0.0001$

Table 4

Multivariable Linear Models[+] Examining Everyday Experiences of Discrimination (Model 1) and PTSD Symptoms (Model 2) Among Transgender Adults in Massachusetts (n=412)

	Multivariable Model: Everyday Experiences of Discrimination		Multivariable Model: PTSD Symptoms	
	Beta (95% CL)	p-value	Beta (95% CL)	p-value
Independent Variables:				
Everyday Experiences of Discrimination	–	–	**0.25 (0.21, 0.30)**	**<0.0001**
Number of Attributed Reasons for Discrimination	**0.29 (0.25, 0.33)**	**<0.0001**	**0.05 (0.01, 0.10)**	**0.015**
Covariates:				
Physical and/or Sexual Abuse Age < 15 Years vs None	**0.31 (0.23, 0.39)**	**<0.0001**	**0.29 (0.21, 0.37)**	**<0.0001**
Intimate Partner Violence vs None	0.06 (−0.02, 0.14)	0.113	**0.18 (0.10, 0.26)**	**<0.0001**
Depression, Last 7 Days vs None	**0.44 (0.35, 0.53)**	**<0.0001**	**0.23 (0.14, 0.32)**	**<0.0001**
Polydrug Use, Last 12 Months (2+ Substances) vs 0/1 Substance	0.05 (−0.05, 0.15)	0.302	**0.13 (0.03, 0.23)**	**0.009**
Age (Continuous in Years)	0.01 (−0.03, 0.06)	0.521	**−0.17 (−0.21, −0.12)**	**<0.0001**
FTM Spectrum vs MTF Spectrum	**0.16 (0.06, 0.25)**	**0.001**	**−0.21 (−0.30, −0.11)**	**<0.0001**
Non-Binary Gender Identity vs Gender Binary Identity	**−0.14 (−0.23, −0.05)**	**0.003**	−0.03 (−0.13, 0.06)	0.493
Social Gender Transition (Live Full-Time) vs Not	0.07 (−0.03, 0.17)	0.167	**0.13 (0.03, 0.23)**	**0.014**
Medical Gender Affirmation (Hormones/Surgery) vs Not	0.03 (−0.06, 0.13)	0.459	**−0.10 (−0.19, −0.01)**	**0.043**
High Visual Gender Nonconformity vs Low/Moderate	**0.25 (0.16, 0.34)**	**<0.0001**	**0.17 (0.08, 0.27)**	**0.0003**
People of Color vs Non-White (Non-Hispanic)	**0.12 (0.02, 0.22)**	**0.016**	−0.05 (−0.15, 0.05)	0.312
Income (Continuous 0–3)	**−0.11 (−0.14, −0.07)**	**<0.0001**	−0.03 (−0.07, 0.01)	0.106
Educational Attainment (Continuous 1–4)	0.03 (−0.01, 0.07)	0.183	−0.02 (−0.07, 0.02)	0.262
Unstably Housed vs Stably Housed	**0.39 (0.30, 0.48)**	**<0.0001**	**0.24 (0.15, 0.33)**	**<0.0001**
Sexual Minority vs Heterosexual/Straight	**−0.12 (−0.23, −0.01)**	**0.034**	0.04 (−0.08, 0.15)	0.533
Online vs In-Person Survey Mode	**−0.30 (−0.43, −0.18)**	**<0.0001**	**−0.47 (−0.60, −0.34)**	**<0.0001**
R-Squared:	**0.323**		**0.296**	
F-Value:	**57.28**	**<0.0001**	**47.74**	**<0.0001**

[+]Z-scored variables: Everyday Discrimination Scale Scores, Number of Attributed Domains of Discrimination, PTSD Symptoms, Age.