Gonadal Suppressive and Cross-Sex Hormone Therapy for Gender Dysphoria in Adolescents and Adults

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Individuals with gender dysphoria experience distress associated with incongruence between their biologic sex and their identified gender. Gender dysphoric natal males receive treatment with antiandrogens and estrogens to become feminized (transsexual females), whereas natal females with gender dysphoria receive treatment with androgens to become masculinized (transsexual males). Because of the permanence associated with cross-sex hormone therapy (CSHT), adolescents diagnosed with gender dysphoria receive gonadotropin-releasing hormone analogs to suppress puberty. High rates of depression and suicide are linked to social marginalization and barriers to care. Behavior, emotional problems, depressive symptoms, and global functioning improve in adolescents receiving puberty suppression therapy. Gender dysphoria, psychological symptoms, quality of life, and sexual function improve in adults who receive CSHT. Within the first 6 months of CSHT, changes in transsexual females include breast growth, decreased testicular volume, and decreased spontaneous erections, and changes in transsexual males include cessation of menses, breast atrophy, clitoral enlargement, and voice deepening. Both transsexual females and males experience changes in body fat redistribution, muscle mass, and hair growth. Desired effects from CSHT can take between 3 and 5 years; however, effects that occur during puberty, such as voice deepening and skeletal structure changes, cannot be reversed with CSHT. Decreased sexual desire is a greater concern in transsexual females than in transsexual males, with testosterone concentrations linked to sexual desire in both. Regarding CSHT safety, bone mineral density is preserved with adequate hormone supplementation, but long-term fracture risk has not been studied. The transition away from high-dose traditional regimens is tied to a lower risk of venous thromboembolism and cardiovascular disease, but data quality is poor. Breast cancer has been reported in both transsexual males and females, but preliminary data suggest that CSHT does not increase the risk. Cancer screenings for individuals of both natal and transitioned sexes should occur as recommended. More long-term studies are needed to ensure that CSHT regimens with the best outcomes can continue to be prescribed for the transsexual population.

KEY WORDS gender dysphoria, cross-sex hormone therapy, transsexualism, puberty suppression, transsexual male, transsexual female, women's health.

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Hormone therapy has helped individuals alter their physical appearance toward a desired gender since the first half of the 20th century. The first professional organization devoted to the topic—the Harry Benjamin International Gender

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Dysphoria Association—was established in 1979 but is now known as the World Professional Association of Transgender Health (WPATH).[1, 2] The most recent WPATH standards of care were updated in 2011, and practice guidelines were developed by the Endocrine Society in 2009.[1, 2]

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V), individuals whose assigned gender at the time of birth is not the gender with which they identify or experience are considered to have gender dysphoria.[3] This designation was traditionally referred to as transgender or gender identity disorder. This updated term was intended to better characterize the experience of affected children, adolescents, and adults and to remove the pathology attached to gender nonconformity, a common expression of gender dysphoria that has been linked to social stigma. By using the term *gender dysphoria,* the focus is placed on the psychological distress caused by the discrepancy between natal sex and gender identity.[4] Available published research may use these terms interchangeably. For the purpose of this review and in accordance with currently accepted terminology, a transsexual male is an individual with the primary and/or secondary sex characteristics of a natal female who desires to take on male characteristics.[1] Alternatively, a transsexual female is an individual with the primary and/or secondary sex characteristics of a natal male who desires to take on female characteristics. Table 1 lists definitions of these and additional terms related to gender dysphoria and transsexualism.

The incidence and prevalence of gender dysphoria is currently unknown due to underreporting and variations in cultural expression of gender. The available data therefore come from studies of transsexual individuals who have received treatment for gender dysphoria in the form of cross-sex hormone therapy (CSHT) and/or sex reassignment surgery (SRS). From research conducted in 10 studies from eight predominantly European countries, the prevalence of transsexualism is estimated to be between 1 in 11,900 and 1 in 45,000 individuals for transsexual females and between 1 in 30,400 and 1 in 200,000 individuals for transsexual males.[1]

The diagnosis of gender dysphoria should be made by a mental health professional before medical interventions are considered.[2] Those seeking sex reassignment are advised to live as the desired sex for a minimum of 1 year before CSHT or surgical intervention is used. For those who are ready and eligible to initiate a gender transition, CSHT is the cornerstone of management. It involves the administration of androgen therapy for transsexual males and a combination of estrogens and antiandrogen therapy for transsexual females.[2] In adolescents, CSHT and SRS are commonly delayed until later in adolescence when informed decisions regarding the use of CSHT, which can cause irreversible physical changes, can be made.[5] Gonadotropin-releasing hormone (GnRH) analogs are used to block the release of sex hormones, thereby halting further pubertal development. It is important to note that the decision to withhold therapy is not a neutral option because of the potential psychological consequences associated with progressing puberty.[1] A review of the CSHT and puberty suppression therapies included in the transsexualism literature and recommended in guidelines are included in Table 2.

From a recent cohort study of individuals who sought sex reassignment between 1973 and 2003, after adjustment for psychiatric morbidity, the all-cause mortality rate in transsexual individuals was found to be significantly increased compared with age-matched controls (adjusted hazard ratio [HR] 2.8, 95% confidence interval [CI] 1.8–4.3).[8] Adjusted HRs for mortality were no longer significant when only the years 1989–2003 were evaluated (adjusted HR 1.9, 95% CI 0.7–5.0). Another recent study of 1331 transsexual individuals receiving care from a gender clinic between 1975 and 2009 reported significantly increased mortality in transsexual females (standardized mortality ratio 1.51, 95% CI 1.47–1.55) but not in transsexual males (standardized mortality ratio 1.12, 95% CI 0.87–1.42).[7] Increased mortality has been linked to suicide, acquired immunodeficiency syndrome (AIDS), cardiovascular disease, and substance abuse.[7, 8] Improved care is believed to be the factor responsible for the nonsignificant adjusted HR for mortality after the 1990s; however, both studies were conducted in countries where medical care for gender dysphoria is more widely available (Sweden and the Netherlands).[8]

Transsexual individuals experience frequent discrimination and social marginalization that puts them at risk for mental health problems, abuse or neglect, and economic hardship.[1] Major barriers to care include lack of access to health care providers knowledgeable about the needs of transsexual individuals, lack of available transgender medicine specialists to receive referrals

Table 1. Gender Dysphoria and Sex Reassignment Terminology

Terminology	Definition
Gender identity	A person's intrinsic sense of being male (a boy or a man), female (a girl or a woman), or an alternative gender (e.g., boygirl, girlboy, transgender, genderqueer, eunuch)[1]
Gender nonconformity	The extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex[1]
Gender dysphoria (formerly known as gender identity disorder)	Discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics)[1]
Sex	Attributes that characterize biologic maleness or femaleness; the best known attributes include the sex-determining genes, the sex chromosomes, internal and external genitalia, and secondary sex characteristics[2]
Natal male or natal female	The sex associated with the individual at birth based on genes, sex chromosomes, genitalia, and/or secondary sex characteristics[1]
Transgender	A diverse group of individuals who cross or transcend culturally defined categories of gender. The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth[1]
Transsexual male or transsexual female (formerly known as female-to-male individuals and male-to-female individuals, respectively)	Individuals who seek to change or who have changed their primary and/or secondary sex characteristics through feminizing or masculinizing medical interventions (hormones and/or surgery), typically accompanied by a permanent change in gender role[1]
Sex reassignment	The complete treatment procedure for those who want to adapt their bodies to the desired sex[2]
Cross-sex hormone therapy	Pharmacologic compounds or regimens designed to induce secondary sex characteristic development associated with the desired sex and to diminish characteristics associated with the natal sex[5]
Sex reassignment surgery	Surgery to change primary and/or secondary sex characteristics to affirm a person's gender identity[1]

from other health care providers, and lack of health insurance coverage for therapies and/or procedures.[1, 9] Barriers to care may also be as subtle as having a health care setting ill adapted to the needs of transsexual individuals. Examples can include assigning nonprivate hospital rooms by natal gender; providing limited options for selecting gender on intake forms (male/female); denying insurance reimbursement for disease screenings based on gender (e.g., no breast cancer screening for natal males); and failing to develop, disseminate, and enforce policies against gender discrimination.[9] Psychological distress is a product of the environment and not inherent to being transsexual or gender nonconforming, so it is important to be sensitive to the impact associated with the quality of care being provided.[1] The use of self-acquired hormone therapy and genital surgery performed outside of a health care setting are also widely reported, adding to the risk associated with barriers to care.[10]

The initial assessment process should be conducted by a mental health practitioner with knowledge of gender-nonconforming identities and the expression of those identities. Although this would seem to create a sizable barrier to care, any health care professional culturally competent in gender identity issues can assist a patient with accessing care and support. The ability to identify someone with gender dysphoria who is in crisis can have a significant impact on morbidity and mortality in these individuals. Pharmacotherapy should ideally be initiated in a comprehensive and coordinated primary care setting specializing in gender dysphoria (i.e., a transgender health clinic), but long-term monitoring for adverse effects related to CSHT can be facilitated by a variety of health care providers in a variety of primary care settings with access to expertise in transgender health for more complex issues.[1]

Expressions of gender nonconformity in response to gender dysphoria exist on a spectrum.[4] Some individuals opt for early initiation of CSHT followed by SRS involving augmentation mammoplasty, penectomy, orchiectomy, vaginoplasty, clitoroplasty, or vulvoplasty in transsexual females or subcutaneous mastectomy, hysterectomy, salpingo-oophorectomy, metoidioplasty, phalloplasty, penile/scrotal prosthesis implantation, vaginectomy, or scrotoplasty in transsexual males.[4] Others prefer to manage their gender dysphoria with drug therapy alone

Table 2. Hormone-Suppressive and Cross-Sex Hormone Therapy Regimens[2, 4, 6, 7]

Hormone-suppressive therapy	Mechanism of action	Practical experience
Leuprolide 3.75–7 mg i.m. every month Histrelin implant 50 μg/day released over a period of 12 mo Triptorelin 3.75 mg i.m. every month Goserelin acetate 3.8 mg s.c. every 4 wks	GnRH agonists initially increase FSH and LH release followed by a cessation of release of these pituitary hormones through a negative feedback mechanism that desensitizes the gonadotropic cells of the pituitary to endogenous GnRH stimulation; the result is a cessation of FSH and LH release from the pituitary, a cessation of testosterone and dihydrotestosterone release from the testes in males and a cessation of estradiol and estrone release from the ovaries in females	Primary indications include prostate cancer, endometriosis, and precocious puberty. Reproductive studies in animals involving GnRH agonist exposure have identified adverse events, and it is recommended that pregnancy be excluded before therapy initiation in reproductive-age females. Hot flashes or flushes occur in up to 40–77% of patients who receive GnRH agonists, but they are not often associated with discontinuation of therapy. Decreased bone density is associated with long-term GnRH agonist therapy in men, but most of this research involves women receiving this therapy for endometriosis. Loss in bone mineral density is minor but may not be completely irreversible on discontinuation. In women with endometriosis, norethindrone is used as "add-back" therapy to reduce the loss of bone mineral density. It is used in early adolescence to inhibit physical changes associated with puberty in males and females with gender dysphoria. It is also used in combination with estrogen therapy in transsexual females to block the effects of endogenous testosterone on physical appearance.
Spironolactone 100–200 mg/day p.o.	Weak inhibitor of testosterone synthesis and testosterone receptor binding; the inhibition of 17-α hydroxylase inhibits testosterone synthesis but can also result in an increase of progesterone through inhibition of the same enzyme; inhibits aldosterone in the distal renal tubules	It has been used for many cardiovascular and endocrine indications including hirsutism in women and precocious puberty in children. Dehydration is a concern in patients taking diuretics; hyperkalemia is a concern when combined with potassium supplements and other potassium-sparing medications. It is used in combination with estrogen therapy in transsexual women for the primary purpose of blocking effects of endogenous androgens on physical appearance.
Cyproterone acetate 50–100 mg/day p.o.	Cyproterone acetate is also an antiandrogen that works through competitive dihydrotestosterone antagonism at the level of target tissues; it also has progestational activity that results in an inhibition of LH and FSH release from the pituitary, thereby causing a decrease in testosterone concentrations	Primary indications include hirsutism and prostate cancer. It is not available in the United States but it has been used for decades in other countries for its androgen-blocking properties in transsexual women. It has also been used in combination with spironolactone.
Finasteride 5 mg/day p.o.	Inhibits 5α-reductase, which metabolizes testosterone to DHT in the prostate and other tissues; this inhibition leads to significant reductions in serum and tissue DHT	Indications for finasteride are benign prostatic hyperplasia and male pattern baldness. Use in transsexual females blocks the effects of endogenous testosterone, providing favorable effects on scalp hair loss, body hair growth, and skin consistency. Safety concerns include teratogenicity in pregnant women. Increased risk of high-grade prostate cancer has been reported due to its ability to lower PSA.

(continued)

Table 2. (continued)

Hormone-suppressive therapy	Mechanism of action	Practical experience
Cross-sex hormone therapy for transsexual females		
Estradiol valerate 2–6 mg/day p.o. 17β-estradiol 2–6 mg/day p.o.	Estrogen preparations are synthetic derivatives of estrogen hormones that are principally secreted by the ovarian follicles, adrenals, corpus luteum, placenta, and testes; estrogens play an important role in the reproductive, skeletal, and cardiovascular systems, as well as the central nervous system of natal women; estradiol is the most active endogenous estrogen, and ethinyl estradiol is the most potent of the synthetic estrogens, with 15–20 times more activity than estradiol; estradiol valerate has a duration of action of 14–21 days, and estradiol cypionate has a duration of action of 14–28 days; exogenous estrogens can elicit a variety of effects that are all the pharmacologic responses typically produced by endogenous estrogens; endogenous estrogens are essential for normal growth and development of the female sex organs and maintenance of secondary sex characteristics; the exact mechanism has not been established, but estrogen is known to contribute to the shaping of body contours and the skeleton	Indications for oral, transdermal, or topical preparations of estradiol are management of moderate to severe vasomotor symptoms associated with menopause and management of vulvar and vaginal atrophy. Transdermal and oral estradiol can be used in the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. Use in transsexual females achieves two goals of CSHT: reduction of endogenous hormone levels and secondary sex characteristics of the natal sex, and the replacement of the endogenous sex hormones levels with the reassigned or desired sex by using hormone replacement using principles from the treatment of hypogonadal patients. Safety concerns include thromboembolism and cardiovascular complications; thus transsexual females are highly encouraged to undergo tobacco cessation to decrease overall risk. Metabolic screening should be conducted to determine risk of adverse effects associated with CSHT including hypertension, dyslipidemia, diabetes mellitus, osteoporosis, hepatic function, and prolactin levels to assess for prolactinoma.
Estradiol valerate 5–20 mg i.m. every 2 wks		Estradiol valerate is indicated for management of moderate to severe vasomotor symptoms associated with menopause as well as management of vulvar and vaginal atrophy, female hypogonadism and castration, and primary ovarian failure. Safety concerns include risk of adverse cardiovascular effects.
Estradiol cypionate 2–10 mg i.m. every week		Estradiol cypionate is indicated for management of moderate to severe vasomotor symptoms associated with menopause and female hypogonadism.

(continued)

Table 2. (continued)

Hormone-suppressive therapy	Mechanism of action	Practical experience
Cross-sex hormone therapy for transsexual males		
Testosterone undecanoate 160–240 mg/day p.o. Testosterone enanthate or cypionate 100–250 mg i.m. every 2–3 wks (or one-half the dose every week) Testosterone undecanoate 1000 mg i.m. every 12 wks Testosterone gel 1% 2.5–10 g/day Testosterone patch 2.5–7.5 mg/day	Testosterone is an androgen sex hormone responsible for the development of male growth and masculine characteristics; testosterone is primarily secreted by the testicles in natal males and is considered to be the principal endogenous androgen and naturally occurring androgenic anabolic steroid; through feedback inhibition of LH, exogenous administration of testosterone inhibits the release of endogenous testosterone; used for replacement or substitution purposes due to the absence of testicular hormone	Indications for testosterone preparations currently include treatment of men who lack or have low testosterone levels associated with a medical condition; these conditions include hypogonadism, male climacteric or andropause, delayed puberty, corticosteroid-induced hypogonadism and osteoporosis, and erectile dysfunction. Indications in females include inoperable carcinoma of the breast, postpartum breast pain and engorgement, and menopause. Testosterone is also used in male transsexuals, similar to its use in hypogonadal males. Safety concerns include increased red blood cell mass that can increase the risk for thromboembolic events; changes in serum lipid levels; hypercalcemia; cardiac dysfunction including edema with or without congestive heart failure; and renal and hepatic dysfunction. Testosterone is contraindicated in hormone-dependent tumors including known or suspected carcinoma of the prostate or breast. Increases in PSA levels have been seen in older males ($\geq$ 50 yrs of age) that could also increase the risk of prostate cancer. Reports of hepatocellular carcinoma have occurred in patients receiving long-term therapy with high doses of testosterone.

CSHT = cross-sex hormone therapy; DHT = dihydrotestosterone; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; i.m. = intramuscular; LH = luteinizing hormone; p.o. = orally; PSA = prostate-specific antigen; s.c. = subcutaneous.

or drug therapy plus a major or minor surgery. Goals of treatment should be highly individualized without presumptions about future needs or concerns.

This review summarizes the efficacy and safety surrounding the CSHT used to manage gender dysphoria in adolescents and adults. In addition, the safety and efficacy surrounding the medications used to inhibit endogenous hormone release in this population are discussed.

Pediatric Considerations

In children and adolescents with gender dysphoria, the process of identifying and managing the condition is markedly different. Cases of gender dysphoria that present during childhood persist into adulthood 6–27% of the time.[1] Presentation is heterogeneous in childhood, with some children exhibiting extreme gender-nonconforming behaviors accompanied by severe discomfort and other children showing less intense characteristics. However, adolescents with gender dysphoria have considerably higher rates of persistence, with the physical changes of puberty intensifying body aversion. Not all adolescents with gender dysphoria experience symptoms in early childhood, but those who do often present with more extreme gender nonconformity. The prevalence of gender dysphoria in adolescence is not currently known due to sampling difficulty associated with this population. Externalizing comorbidities such as anxiety and depression are common as is autism spectrum disorder in children and adolescents with gender dysphoria. For this reason, the diagnosis should be made by a mental health professional with child and adolescent developmental psychopathology training.[2] After children or adolescents have met the DSM-V criteria for gender dysphoria, according to practice guidelines, they must have experienced at least Tanner stage 2 puberty with an associated worsening of gender dysphoria.[2] In girls, Tanner stage 2 is characterized by the development of breast buds, areola enlargement, and sparse pubic hair.[11] In boys, Tanner stage 2 is associated with initial enlargement of the scrotum and testes and the appearance of sparse pubic hair at the base of the penis.[12] At this point, practice guidelines describe eligibility for puberty suppression therapy, assuming the child or adolescent will receive adequate social and psychological support during treatment.[2]

An approach used since at least the late 1990s in the Netherlands involves the administration of GnRH analogs to adolescents as a means to delay the onset of puberty. The primary purpose of this approach has been to alleviate the negative psychological effects associated with the onset of puberty in gender dysphoric adolescents. Current clinical practice guidelines advocate for the use of long-acting GnRH analogs for adolescents fulfilling readiness criteria for sex reassignment.[2] In addition to the psychological benefits, delaying puberty until CSHT can be started will likely result in more satisfactory physical outcomes.[13] Delaying pubertal development in males prevents the accentuation of brow, zygoma, and mandible bones; Adam's apple development and unwanted phallic growth are also prevented. Progression of the permanent changes in voice and hair growth patterns will also cease. When cross-gender hormone therapy is begun in the early stages of puberty, increases in breast tissue and testicular volume can regress.[14] When started later in adolescence, late stages of breast development, voice changes, and facial hair development will not regress completely. A premature fusion of the growth plates in response to estrogen administration to transsexual females results in a lower final adult height more consistent with the height of natal females. A delay in the fusion of the growth plate in transsexual males can conversely allow for an increased final adult height. Treatment with a GnRH analog is thought to be a diagnostic aid as well as a therapeutic intervention for this age group because stopping the progression of the physical changes of puberty would be expected to partially alleviate gender dysphoria symptoms in true gender dysphoria.[2] If the patient has a clear understanding of the expected outcomes from GnRH analog therapy, compliance is enhanced and adverse mental health effects can be prevented.

The puberty suppression approach, also called the Dutch protocol, is the most well studied approach in this population, especially with respect to psychological outcomes. The regimen used is triptorelin 3.75 mg subcutaneously or intramuscularly every 2 weeks for 4 weeks, then every 4 weeks thereafter.[14] Children present at a mean age of 10–12 years and receive GnRH analog therapy until age 16 years, which is the age at which Dutch children can consent to their own medical treatments and begin CSHT. However, a more recent retrospective study from British Columbia describes beginning CSHT at a mean age of 14.7 years (SD 2.2 yrs, range 13.3–22.3 yrs) in 37 transsexual females and a mean

age of 17.0 years (SD 1.6 yrs, range 13.7–19.8 yrs) in 45 transsexual males.[15] Adverse effects reported in association with GnRH agonist therapy included sterile abscess, leg pains, headaches, and weight gain.

The first prospective study of psychological outcomes in adolescents with a mean ± SD age at time zero of 13.65 ± 1.85 years, which was followed by a mean ± SD of 1.88 ± 1.05 years of puberty suppression therapy, showed a statistically significant improvement in behavior, emotional problems, and general functioning after puberty suppression.[16] Depression measured by using the Beck Depression Inventory was also significantly improved compared with baseline; however, mean scores at baseline were below clinical thresholds for depression (p=0.004). Gender dysphoria and body image scores did not improve after puberty suppression therapy compared with baseline. The clinical significance of these results is not clear, but previous research supports the finding that gender dysphoria does not improve significantly before CSHT and/or SRS. Because all children in this study received puberty suppression therapy, the benefits of drug therapy cannot be separated from the benefits of study participation. Treatment of gender dysphoria is multifaceted and includes psychotherapy, puberty suppression when appropriate, CSHT, and SRS, which have varying levels of benefit.

A single case report described the long-term outcomes associated with puberty delay in a transsexual adolescent.[17] A 13-year-old natal girl received 4.9 years of triptorelin followed by intramuscular testosterone every 2–3 weeks and surgery 7 and 9 years later. By the age of 35 years, height and bone mineral density (BMD) were found to be higher than natal females and lower than natal males. The effects of pubertal suppression on future BMD and cognitive development in this population have not been studied systematically. To date, long-term outcome data are limited to psychological effects and a single study center. Psychological outcomes associated with an eventual gender transition following puberty suppression have also not yet been thoroughly explored.

Discussions surrounding the effects of cross-gender hormone therapy on future fertility should also occur with adolescents contemplating cross-gender hormone therapy. Ideally, education and consent should involve the parents, members of the adolescent's support group, and the referring mental health professional. No formally evaluated decision practice guidelines are currently available for this purpose. Cryopreservation of sperm or oocytes could be facilitated, but this would require spontaneous or induced gonadotropin release, which could also be associated with physical manifestations of puberty. Multiyear treatment with GnRH analog therapy should not compromise fertility; however, the effects of multiyear CSHT do not favor future reproductive function. Longitudinal reproductive clinical outcome data for this population are not currently available.[2]

Efficacy and Quality of Life of Cross-Sex Hormone Therapy

Psychological Functioning

A recent systematic review and meta-analysis of almost 30 trials of CSHT for gender dysphoria found significant improvement in psychological and physiologic symptoms as well as overall quality of life after starting therapy.[18] Of those evaluated, 80% (95% CI 68–89; 8 studies; $I^2 = 82\%$) reported significant improvement in gender dysphoria, 78% (95% CI 56–94; 7 studies; $I^2 = 86\%$) reported significant improvement in psychological symptoms, 80% (95% CI 72–88; 16 studies; $I^2 = 78\%$) reported improvement in quality of life, and 72% (95% CI 60–81%; 15 studies; $I^2 = 78\%$) reported significant improvement in sexual function.

Physical Appearance

Transsexual Females

The desired physical effects in transsexual females can include decreased spontaneous erections, reduced testicular size, increased ratio of body fat to muscle mass, and increased breast size, with adequate secondary sexual characteristics directly correlating to the individual's psychological wellness.[1, 19] Once CSHT is initiated, body fat redistribution, initial breast growth, decreased muscle mass, decreased testicular volume, and decreased spontaneous erections can occur within the first 6 months.[1] Full effects can take as little as 1 year for muscle mass changes or as long as 5 years for body fat redistribution.[1] Body and facial hair changes take the longest, with the onset occurring after 6–12 months of hormone therapy and the full effect taking more than 3 years.[1] Desired skeletal structure (e.g., chest, hips, face) and some aspects of voice can-

not be modified with CSHT when the transition occurs later in life.[5] Erections associated with sexual excitement will continue to occur, but spontaneous erections will fully or partially diminish.[20]

The development of breast tissue in transsexual females receiving estrogen therapy follows the same stages as those seen during natal female puberty; however, due to anatomic differences in the thorax of natal males, the appearance of the breast is often found to be unsatisfactory, thus precipitating the need for breast augmentation.[19] In a small retrospective case-control study of transsexual females receiving CSHT from a gender identity clinic or through self-acquisition (Internet or other health care providers), the need for augmentation surgery was not significantly associated with any particular type of estrogen therapy; nor was there an association with serum concentrations of estradiol, testosterone, dihydrotestosterone, sex hormone-binding globulin, luteinizing hormone (LH), or follicle-stimulating hormone.[19] Among antiandrogen therapies consisting of cyproterone, finasteride, dutasteride, GnRH analogs, or spironolactone, only spironolactone was associated with increased requests for breast augmentation (16% augmentation vs 6% no augmentation, $p=0.025$). The study reported an association between self-medication and requests for breast augmentation; however, the lack of randomization makes interpretation of this difference problematic. Two years after CSHT, another study reported that 70% of subjects were not satisfied with the extent of their breast development despite 40% achieving the size of a B cup bra.[21]

An older study that studied estrogen preparations, which are no longer recommended for gender dysphoria (conjugated estrogens and ethinyl estradiol), found no significant differences in penis length in transsexual females not yet undergoing SRS but found a significant difference in testicular size (25% decrease, $p<0.05$) after a mean of 15.6 months of follow-up (SD 12.9 months).[22] Patients in this study did not uniformly receive antiandrogen therapy, but those who did received an agent that is no longer recommended (medroxyprogesterone).

With respect to hair growth, after 1 year of combination estrogen and antiandrogen therapy, Ferriman and Gallwey scores, a validated scoring tool often used for hirsutism, significantly decreased from a median (interquartile range) of 21 (19–25) at baseline to 10 (8–13.8) ($p<0.001$).[23] Clinically, suppression of beard hair appearance lagged behind abdominal hair appearance, which can best be explained by the high hair density and diameter on the face.

Transsexual Males

In transsexual males, desirable characteristics can include deepening of the voice, growth of facial and body hair, cessation of menses, atrophy of breast tissue, decreased ratio of body fat to muscle mass, and clitoral enlargement. Within 6 months of CSHT, transsexual males will see increases in face and body hair, redistribution of body fat, cessation of menses, voice deepening, clitoral enlargement, and vaginal atrophy.[1, 24] Increases in muscle mass can take as long as 12 months to change.[1] Maximal effects on clitoral size and voice can take as long as 2 years, and maximal effects on hair growth, muscle mass, and body fat redistribution can take as long as 5 years.[1] Positive changes can be accompanied by negative effects associated with testosterone administration including acne and scalp alopecia.[1]

From limited data, maximal clitoral size was approximately 6 cm, and breast size did not significantly change after testosterone therapy.[22] Higher testosterone doses (250 mg every 2 wks) are associated with earlier physical changes compared with lower doses (125 mg every 2 wks or 250 mg every 3 wks), but outcomes are no longer significantly different after 6 months of CSHT. Higher and lower doses in these ranges result in concentrations similar to those of natal males.[24] Progestational agents can be added to testosterone therapy in transsexual males with continued uterine bleeding; however, specific agents and doses have not been adequately studied.[2]

Summary

Once CSHT is initiated, the desired effects of feminization and masculinization are both time and dose dependent.[1, 2, 24] Genital appearance is not changed greatly by estrogen therapy, but some transsexual females will be encouraged by small changes in testicular size.[22] CSHT is effective in promoting breast development in transsexual females but less effective in reducing male patterns of hair growth, especially with respect to facial hair. Transsexual males experience a relatively more rapid onset of changes in skin, hair growth, and menstrual patterns, but

they experience limited or no physical changes with respect to genital appearance from CSHT alone. Physical appearance is not well correlated with target hormone concentrations, but practice guidelines recommend target CSHT doses that are associated with serum hormone concentrations in the adult ranges for the desired sex.[2]

Sexual Function

Transsexual Females

In a small observational study of transsexual females who underwent SRS a minimum of 6 months before the study, general functioning scores were similar to a control group of Dutch and American women.[25] When compared with historical data from nontranssexual Dutch women, Female Sexual Function Index (FSFI) scores were significantly lower for arousal, lubrication, and pain ($p<0.05$). Neither testosterone concentrations nor estradiol concentrations correlated with FSFI scores.

In an observational study conducted in Belgium and the Netherlands, compared with natal females, transsexual females who had received SRS had similar rates of hypoactive sexual desire disorder diagnosis (33.9%) compared with premenopausal natal females (23.3%).[26] Sexual satisfaction, however, was significantly decreased compared with natal females ($p=0.002$) with no significant difference in general life and relationship satisfaction. Contrary to previous research in premenopausal natal females, sexual desire in transsexual females did not correlate with free or total testosterone concentrations ($r = -0.06$ to 0.1, $p>0.05$). A small pilot study of seven transsexual females reported improved sexual desire associated with administration of a 300 μg/day testosterone patch, with no reported adverse effects.[27]

Transsexual Males

Compared with the prehormone state, testosterone administration in transsexual males resulted in a statistically significant increase in desire ($p=0.0014$) and arousal ($p<0.0005$) after 12 months of CSHT in one study.[28] Relationship satisfaction and orgasm were unchanged in this evaluation, but frequency of sexual intercourse was correlated with testosterone concentrations ($p=0.039$, $\eta^2 = 0.054$). In a similar study, sexual desire was reported to be higher or much higher in 72.7% of transsexual males, with 25% reporting similar sexual desire and 1% reporting worse sexual desire.[29] Suppressed LH concentrations in transsexual males indicate that testosterone therapy is excessive, and low LH concentration was found to be associated with excessive sexual desire ($p=0.007$). Free and total testosterone concentrations were not found to be associated with measures of sexual desire in this study.

Summary

Transsexual females experience hypoactive sexual desire disorder at a rate similar to natal females but report increased concerns regarding desire, pain, and lubrication despite achieving goal estrogen concentrations. Further research is needed regarding the safety and efficacy of low-dose add-back testosterone administration for decreased sexual desire. Transsexual males experience improved sexual desire in response to testosterone therapy; however, similar to transsexual females, problems with sexual functioning do not always correlate with testosterone concentrations. Effects of sexual functioning on overall satisfaction with relationships and quality of life deserve further study.

Safety of Cross-Sex Hormone Therapy

Similar risk profiles are believed to be associated with CSHT when compared with hormone replacement therapy associated with the natal sex.[2] Unfortunately, long-term disease risk in untreated individuals or those receiving placebo is difficult to assess for ethical reasons.

Bone Health

Transsexual Females

Androgens play a key role in maintaining bone mass in aging males. Androgen deprivation for treatment of prostate cancer using GnRH analogs is associated with a loss of BMD.[2] However, estrogen in aging natal males correlates more with improved BMD and peak bone mass than testosterone.[2]

Transsexual females who have not undergone SRS and were treated with an antiandrogen and estrogens for 3 years or more showed an increase in BMD (difference in *T*-score lumbar spine = 0.7, $p=0.04$; difference in *T*-score femoral neck = 0.8, $p=0.01$) when adjusted for height and weight, with no significant change in markers of bone turnover.[30] This suggests that estrogen

activity is sufficient to maintain normal bone mass in transsexual females. Treatment with estrogens plus goserelin, a GnRH analog, for 24 months resulted in a significant increase in BMD at the lumbar spine and at the femoral neck.[31]

In transsexual females who have undergone SRS and are receiving CSHT with estrogen alone, BMD remains the same or is similar to untreated males.[32, 33] In a study of transsexual females who underwent SRS and were treated with cyproterone plus estrogens, BMD was significantly decreased (difference in *Z* score −1.1, $p<0.001$, at both the lumbar spine and femoral neck).[34] In this study, transsexual females had significantly lower testosterone levels but similar estrogen levels compared with the untreated male controls, leading to low levels of C-terminal telopeptides and procollagen 1 aminoterminal propeptide, markers of bone resorption and formation, respectively, which may have contributed to the lower measured BMD.

Transsexual Males

Multiple studies have found androgen therapy to be effective in preventing bone loss after oophorectomy in transsexual males by increasing cortical BMD compared with baseline in untreated age-matched females.[33, 35–37] This may be due to cortical bone having more androgen receptors than trabecular bone.[33]

Forty-five transsexual males who had not undergone SRS and had been treated with testosterone undecanoate 1000 mg intramuscularly every 12 weeks for 24 months had no change in BMD compared with baseline.[36]

Transsexual males who had undergone SRS and who received CSHT with testosterone had similar lumbar and femoral neck BMD results compared with untreated females.[33, 35, 37] Cortical thickness and tibial BMD were significantly increased compared to untreated females.[33, 37] A group of 19 transsexual males who had undergone SRS and were being treated with testosterone for 3.5 years had a significant decrease in BMD ($p=0.003$).[32] However, serum testosterone levels were below the normal range for males, suggesting that the patients may have had insufficient testosterone supplementation. Transsexual males who had undergone SRS and were treated with testosterone and letrozole, an aromatase inhibitor, showed significantly decreased BMD at the lumbar spine (difference in *T* score −0.9, $p=0.008$) compared with transsexual males treated with testosterone monotherapy, suggesting that the conversion of testosterone to estradiol is sufficient to maintain BMD.[38]

Summary

To our knowledge, no fracture data are available for transsexual males or females who are using CSHT; thus fracture risk in these individuals is unknown. The Endocrine Society guidelines recommend measuring BMD if the patient has risk factors for osteoporosis, especially if they have undergone SRS and stop hormone therapy.[2] Expert opinion recommends checking BMD at baseline and every 1–2 years if the patient has risk factors for fracture or stops taking hormone treatment.[5] Therefore, it is important to maintain normal hormone levels for their current gender to help prevent the loss of BMD.

Thromboembolic Disease

Transsexual Females

In epidemiological research, venous thromboembolism (VTE) rates have varied from 0–143 cases/10,000 patient-years in transsexual females.[7, 19, 39–43] Although the data are retrospective and subject to recall and reporting bias, the high rate in these studies can be at least somewhat explained by pre-1990 frequent use of oral ethinyl estradiol (50–100 μg/day), oral conjugated equine estrogens (5–10 mg/day), and self-procured estradiol (200–800 mg/mo) administered intramuscularly.[41, 42] In contemporary practice, estradiol is used more frequently in accordance with current guidelines.[2] In two of these studies of the same population of transsexual females receiving comprehensive care from a Dutch clinic, the rate of VTE decreased from 143 cases/10,000 treatment-years between 1972 and 1986[42] to 58 cases/10,000 treatment-years between 1975 and 1994,[41] which can potentially be explained by different estrogen formulations in later years. A more recent study on thrombophilia and venous thrombosis in transsexual females involving 866 treatment-years both before and after SRS found no cases of VTE with the use of transdermal estradiol combined with presurgery antiandrogen therapy despite discovering activated protein C resistance in 10% of the transsexual females.[40] One would expect to see 5 cases or more in this study if the rate of VTE were comparable to the previous rate of 58

cases/10,000 treatment-years, but more long-term data on the rate of VTE in patients receiving estradiol are needed.

Transsexual Males

A recently published retrospective observational study of transsexual males receiving testosterone esters described no cases of VTE associated with 496 treatment-years.[39] Another study found a 5.6% incidence of activated protein C resistance but no cases of VTE in 349 treatment-years of testosterone therapy.[40] The largest study of morbidity in transsexual males receiving testosterone therapy included 2418 treatment-years and identified one case of VTE for an incidence rate of 4 cases/10,000 treatment-years.[41]

Summary

A history of thromboembolism is a contraindication to combination hormonal contraception or hormone replacement therapy in natal females. Because gender dysphoria is associated with high morbidity and mortality if untreated, likely surpassing the mortality rate associated with VTE, it would make sense that the safety threshold would also be higher. A few cases of the use of estrogen therapy in transsexual females with a history of VTE were reported.[7] Oral anticoagulant therapy and hormone therapy have also been coadministered, including in a transsexual female patient homozygous for the factor V Leiden mutation.[40] The risk of thromboembolism does not seem to be increased in transsexual males receiving testosterone compared with natal females.

Cardiovascular Disease and Stroke

Transsexual Females

Continuous use of ethinyl estradiol in transsexual females is associated with an increased risk for cardiovascular disease mortality (4.1% vs 1.3% for continuous use of ethinyl estradiol vs former use of or never used ethinyl estradiol) even after adjustment for age and smoking history (HR 3.64, 95% CI 1.52–8.73, p=0.004).[7] One proposed mechanism for this increased thrombotic risk is through an inhibitory effect on tissue-type plasminogen activator (tPA) and plasminogen activator inhibitor (PAI)-1. This has been documented in a small subset of transsexual females after 4 months of cross-gender hormone administration.[23] Inhibition of tPA and PAI-1 is less pronounced with transdermal estradiol. Oral ethinyl estradiol is believed to increase the hepatic clearance of tPA.

For the same population of transsexual females receiving care in the Netherlands, the rate of stroke was 7.5/10,000 treatment-years from 1975–1994 for a follow-up period of 7734 treatment-years.[41] This rate was similar to the rate that was identified from 1972–1986, which represented 1333 treatment-years.[42] More recent data show a stroke mortality rate of 2.7 cases/10,000 treatment-years during a follow-up period between 1975 and 2007 representing 18,678 treatment-years.[7] The standardized mortality ratio for stroke was 1.26 (95% CI 0.93–1.64) when compared with the general population of Dutch natal males of similar age.

Hypertension, an important risk factor for stroke, which was defined as a systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 95 mm Hg, did not occur at a rate greater than that associated with the age-matched general Dutch population in a large study of 7734 patient-years in transsexual females (incidence rate ratio 0.98, 95% CI 0.75–1.26).[41] In a Belgian study representing 473 hormone treatment years in transsexual females and 496 hormone treatment years in transsexual males, the transsexual females had a lower diastolic blood pressure (mean ± SD 77.1 ± 10.1 vs 81.3 ± 10.7 mm Hg) and mean arterial blood pressure (mean ± SD 93.0 ± 11.2 vs 95.8 ± 10.1 mm Hg) compared with transsexual males (p=0.002 and p=0.008, respectively).[39] In the same study group, a comparable number of transsexual males and females had self-reported elevated blood pressure and/or were being treated with antihypertensive medications during the study period. In a smaller Dutch study representing the observation period between 1972 and 1986 and 1333 treatment-years, 14 cases of hypertension (105/10,000 treatment-years) were identified in transsexual females.[42] In the observation period between 1975 and 1994, representing 7734 treatment-years for the same population, hypertension rates decreased in transsexual females (79/10,000 treatment-years) compared with earlier study periods.[41] The decrease in hypertension rates could have been related to a switch from conjugated estrogen–based and ethinyl estradiol–based regimens to transdermal estradiol–based and oral estradiol valerate–based regimens. A change in hyperten-

sion rates due to lifestyle changes secondary to awareness of risk factors and complications of hypertension cannot be ruled out.

Transsexual Males

For the same population of transsexual males receiving care in the Netherlands, in the longest follow-up period, no cases of stroke were reported between 1975 and 2007, representing 6866 treatment-years.[7] Conclusions regarding stroke risk cannot be made at this time because of the lack of available comparison data between transsexual males and the natal female general Dutch population. In the same study, the rate of ischemic heart disease was 1.45 cases/10,000 treatment-years, with a standardized mortality ratio of 1.19 (95% CI 0.39–2.74), indicating a rate similar to the age-matched general Dutch population.

Hypertension, again defined as a systolic blood pressure higher than 160 mm Hg or diastolic blood pressure higher than 95 mm Hg, did not occur at a rate greater than in the general Dutch population in a study of 2418 treatment-years in transsexual males (incidence rate ratio 0.84, 95% CI 0.43–1.47).[41] In the Belgian study described previously, the diastolic blood pressure and mean arterial blood pressure were significantly higher in transsexual males versus transsexual females.[39] In a smaller Dutch study representing the observation period between 1972 and 1986, three cases of hypertension were identified in transsexual males (68/10,000 treatment-years).[42] In the observation period between 1975 and 1994 in the same population, hypertension rates decreased slightly in transsexual males (50/10,000 treatment-years).[41]

Summary

Clinical practice guidelines recommend the monitoring of blood pressure, lipid levels, and serum glucose levels regularly with the management of cardiovascular risk factors as they emerge in transsexual males and females according to guidelines established for nontranssexual individuals.[2] The rate of cardiovascular disease mortality in transsexual females taking ethinyl estradiol was recently found to be higher compared with nontranssexual individuals.[7] Because ethinyl estradiol is no longer recommended, studies will need to be repeated with an adequate sample of patients who are taking the currently recommended estrogen regimens. Although testosterone therapy in transsexual males is associated with a less favorable lipid profile, from the limited data and low-quality research available, cardiovascular disease risk is not increased in transsexual males compared with natal females.[2]

Cancer

Transsexual Females

Epidemiological data suggest that the rate of cancer-related death is similar between transsexual females and natal males. A study of 966 transsexual females over 18,678 patient-years of follow-up identified 28 cases of malignant neoplasms for a standardized mortality ratio of 0.98 (95% CI 0.88–1.08). Most of the cancers identified involved lung or blood cancers that were believed to be linked to smoking and AIDS cases (16 deaths), respectively.[7]

Breast cancer in natal males accounts for less than 1% of all cancers in men.[44] Guidelines recommend the same breast cancer screening used for natal females due to the handful of reported cases in the literature of breast cancer in transsexual females.[2] Five cases of breast cancer in transsexual females receiving CSHT were reported in the literature.[45–48] Two cases of estrogen receptor–negative ductal carcinoma of the breast reported in the late 1980s and early 1990s were associated with 10 or more years of conjugated estrogen therapy (0.625 mg/day and 1.25 mg/day, respectively) in patients in their mid-30s who had undergone orchiectomy.[46, 47] One additional case from the Amsterdam gender clinic was also reported.[48]

A family history of breast or ovarian cancer is reported in 15–20% of natal males with breast cancer with the *BRCA2* gene identified as the most strongly associated mutation.[44] This mutation confers a lifetime risk of breast cancer of 5–10% in natal males compared with the general male population.[44] Although thousands of transsexual females have received estrogen therapy, the variability in the drug and dosage prescribed and the duration of therapy make risk estimations difficult.[48] In addition, cancer risk is correlated with age, making the limited duration of experience (30 yrs with the longest running programs) with these individuals a barrier to assessing risk.

Androgen deprivation results in a decrease in prostate volume, and estrogen exposure has not been linked to prostate hyperplasia or malignancy. Removal of the prostate is not considered

part of SRS. From epidemiologic research, orchiectomy before the age of 40 years results in a decreased risk of prostate hypertrophy or cancer.[48] The three cases of prostate cancer reported in the literature described transsexual females who began CSHT later in life (after age 50 yrs)[48] compared with the age when most individuals with gender dysphoria begin CSHT. Prostate cancer monitoring should be performed in accordance with screening recommendations for nontranssexual individuals.[2]

Transsexual Males

Although cancers of reproductive organs and breasts are common in natal females, and risk might be expected to increase or decrease in response to a cessation of gonadal function or the administration of CSHT, limited data suggest that cancer rates are similar between transsexual and nontranssexual individuals. One study evaluating 6866 treatment-years for 365 transsexual males found no cancer-related deaths for a calculated standardized mortality ratio of 0.99 (95% CI 0.65–1.44) for any type of cancer compared with individuals of similar age, natal sex, and country of residence (the Netherlands).[7] In another retrospective study of transsexual males that included 50 patients and 473 treatment-years, no cancer cases or cancer-related deaths were reported.[39]

Epidemiological evidence suggests an association between circulating androgen concentrations and pre- and postmenopausal breast cancer in natal females.[49] Other types of research, including in vivo, in vitro, and clinical evidence, suggest that androgens may confer a protective effect against breast cancer. Conclusions regarding long-term risk cannot be drawn at this point due to a lack of data on transsexual males who have been receiving CSHT for multiple decades or for the years of life that are associated with the highest risk for breast and gynecologic cancers.[48] Case reports suggest that the risk of breast cancer still exists, even after SRS.[50, 51] There are currently four case reports of breast cancer in transsexual males in the literature.[50–52] Ages at diagnosis were 33, 53, 27, and 42 years; before diagnosis, the duration of hormone therapy was 13, 5, 6, and 2.5 years, respectively. All but one of the four patients described in the literature continued androgen therapy concurrently or after cancer therapy. The mastectomy procedure performed in transsexual males can be nipple-sparing or involve a nipple reimplantation. One of the four cases described in the literature occurred in a transsexual male who had previously received nipple-sparing bilateral mastectomy.[50]

Total hysterectomy and bilateral salpingo-oophorectomy may be performed on some but not all transsexual males. Although the procedure is recommended to be laparoscopic, scarring and other surgery-related risks exist.[1] Currently, it is debated as to whether ovariectomy or hysterectomy are medically necessary to reduce the risk of ovarian and endometrial cancers, respectively. Ovarian cancer was reported in three transsexual males in the literature.[48] It was initially thought that transsexual males were at a higher risk for the development of polycystic ovarian syndrome. More recent research suggests that polycystic ovaries identified on ultrasound in transsexual males do not resemble polycystic ovaries seen in natal females with polycystic ovarian syndrome due to a higher number of atretic follicles present in transsexual males.[53] This was a small study, and confirmatory research is needed. Women with polycystic ovaries are not thought to be at a significantly greater risk for ovarian cancer compared with women without polycystic ovaries. Oophorectomy for the purpose of preventing ovarian cancer would not seem to be necessary at this point based on the currently available literature. The risk of endometrial cancer has been tied to endometrial hyperplasia seen when estrogen concentrations are high and progesterone concentrations are low (i.e., unopposed estrogen). In transsexual males receiving CSHT, estrogen concentrations remain in the physiologic range.[48] Progestin administration and/or yearly ultrasound examination of the uterus has been suggested in transsexual males as a means of preventing and mitigating the risk of endometrial cancer.

Summary

Based on the available research, cancer is not more prevalent in transsexual females or males compared with the general population. A more thorough understanding of the risks versus benefits of SRS on the incidence of cancer is sorely needed, but it does not seem at this time that SRS is required to mitigate the risk of cancer. The consequences of discontinuing hormone therapy in transsexual females and males diagnosed with an estrogen- or testosterone-responsive cancer are not clear from the perspective of

recurrence prevention but could present a significant problem in terms of mental well-being, which is likely why the limited case reports of cancer in transsexual individuals describe continuing hormone therapy after diagnosis.[51, 52, 54]

Conclusion

Gender dysphoria is well described in the literature, but comparative research on drug regimens with respect to efficacy and long-term safety is sorely needed. The most well-documented work in this population comes from established clinics in the Netherlands, but little data exist in other populations. For those individuals seeking sex reassignment, the range of care sought is highly variable, making outcomes research difficult and providing individualized care very important. Physical effects of CSHT can vary depending on the age at which treatment is initiated, making early diagnosis of gender dysphoria in adolescents and adults an important goal. Preliminary efficacy data on puberty suppression in adolescents prior to CSHT are promising, but long-term safety data are severely lacking.

The safety of CSHT depends on hormone type, route of administration, and dosage. Coincidental to a cessation of the use of higher doses and certain estrogen preparations, morbidity and mortality rates due to VTE and cardiovascular disease improved after the 1980s. In limited European populations, overall mortality has improved in recent decades as well. Adverse effects that remain of the highest concern in this population due to a lack of high-quality research include VTE, fractures, cardiovascular disease, stroke, and hormone-dependent cancers. Health care professionals who are aware of the risks associated with gender dysphoria undertreatment, the risks associated with self-acquisition of CSHT, and the potential adverse effects associated with CSHT for the purpose of monitoring can contribute to improved care in this population.

References

1. **Coleman E, Bockting W, Botzer M, et al.** Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. Int J Transgend 2011;13:165–232.
2. **Hembree WC, Cohen-Kettenis PT, Delemarre-van de Waal HA, et al.** Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2009;94:3132–54.
3. **American Psychiatric Association.** Gender Dysphoria, 2013. Available from www.psychiatry.org. Accessed March 23, 2014.
4. **Unger CA.** Care of the transgender patient: the role of the gynecologist. Am J Obstet Gynecol 2014;210:16–26.
5. **Gooren LJ.** Care of transsexual persons. N Engl J Med 2011;364:1251–7.
6. **American Society of Health-System Pharmacists.** AHFS Drug Information, c. 1959–2014. Available from: www.ahfsdruginformation.com. Accessed March 31, 2014.
7. **Asscheman H, Giltay EJ, Megens JAJ, de Ronde W, van Trostenburg MAA, Gooren LJG.** A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 2011;164:635–42.
8. **Dhejne C, Lichtenstein P, Boman M, Johansson ALV, Langstrom N, Landen M.** Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS ONE 2011;6:16885.
9. **Snelgrove JW, Jasudavisius AM, Rowe BW, Head EM, Bauer GR.** "Completely out-at-sea" with "two-gender medicine": a qualitative analysis of physician-side barriers to providing healthcare for transgender patients. BMC Health Serv Res 2012;12:110.
10. **Rotondi NK, Bauer GR, Scanlon K, Kaay M, Travers R, Travers A.** Nonprescribed hormone use and self-performed surgeries: "do-it-yourself" transitions in transgender communities in Ontario, Canada. Am J Public Health 2013;103:1830–6.
11. **Marshall WA, Tanner JM.** Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44:291–303.
12. **Marshall WA, Tanner JM.** Variations in the pattern of pubertal changes in boys. Arch Dis Child 1970;45:13–23.
13. **Edwards-Leeper L, Spack NP.** Psychological evaluation and medical treatment of transgender youth in an interdisciplinary "gender management" (GeMS) in a major pediatric center. J Homosex 2012;59:321–36.
14. **Delemarre-van de Waal HA, Cohen-Kettenis PT.** Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. Eur J Endocrinol 2006;155:S131–7.
15. **Khatchadourian K, Amed S, Metzger DL.** Clinical management of youth with gender dysphoria in Vancouver. J Pediatr 2014;164:906–11.
16. **de Vries ALC, Steensma TD, Doreleijeres TAH, Cohen-Kettenis PT.** Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. J Sex Med 2011;8:2276–83.
17. **Cohen-Kettenis PT, Schagen SEE, Steensma TD, de Vries ALC, Delemarre-van de Waal HA.** Puberty suppression in a gender dysphoric adolescent: a 22-year follow-up. Arch Sex Behav 2011;40:843–7.
18. **Murad MH, Elamin MB, Garcia MZ, et al.** Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol 2010;72:214–31.
19. **Seal LJ, Franklin S, Richards C, Shishkareva A, Sinclaire C, Barrett J.** Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens. J Clin Endocrinol Metab 2012;97:4422–8.
20. **Bettocchi C, Palumbo F, Cormio L, Ditonno P, Battaglia M, Selvaggi FP.** The effects of androgen depletion on human erectile function: a prospective study in male-to-female transsexuals. Int J Impot Res 2004;16:544–6.
21. **Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann MW, Mueller A.** Endocrine treatment of male-to-female transsexuals using gonadotropin-releasing hormone agonists. Exp Clin Endocrinol Diabetes 2005;113:586–92.
22. **Meyer WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA.** Physical and hormonal evaluation of transsexual patients: a longitudinal study. Arch Sex Behav 1986;15:121–38.
23. **Giltay EJ, Gooren LJG.** Effects of sex steroid deprivation/administration on hair growth and skin sebum production in transsexual males and females. J Clin Endocrinol Metab 2000;85:2913–21.
24. **Nakamura A, Watanabe M, Sugimoto M, et al.** Dose-response analysis of testosterone replacement therapy in patients with

female to male gender identity disorder. Endocr J 2013;60:275–81.
25. **Weyers S, Elaut E, Sutter PD, et al.** Long-term assessment of the physical, mental, and sexual health among transsexual women. J Sex Med 2009;6:752–60.
26. **Elaut E, Cuypere GD, Sutter PD, et al.** Hypoactive sexual desire in transsexual women: prevalence and association with testosterone levels. Eur J Endocrinol 2008;158:393–9.
27. **Kronawitter D, Gooren LJ, Zollver H, et al.** Effects of transdermal testosterone or oral dydrogesterone on hypoactive sexual desire disorder in transsexual women: results of a pilot study. Eur J Endocrinol 2009;161:363–8.
28. **Constantino A, Cerpolini S, Alvisi S, Morselli PG, Venturoli S, Meriggiola MC.** A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. J Sex Marital Ther 2013;39:321–35.
29. **Wierckx K, Elaut E, Van Caenegem E, et al.** Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. Eur J Endocrinol 2011;165: 331–7.
30. **Sosa M, Jodar E, Arbelo E, et al.** Bone mass, turnover, vitamin D, and estrogen receptor gene polymorphisms in male to female transsexuals: the effects of estrogenic treatment on bone metabolism of the male. J Clin Densitom 2003;6:297–304.
31. **Mueller A, Dittrich R, Binder H, et al.** High dose estrogen treatment increases bone mineral density in male-to-female transsexuals receiving gonadotropin-releasing hormone agonist in the absence of testosterone. Eur J Endocrinol 2005;153:107–13.
32. **van Kesteren P, Lips P, Gooren LJG, Asscheman H, Megens J.** Long-term follow-up of bone mineral density and bone metabolism in transsexuals treated with cross-sex hormones. Clin Endocrinol 1998;48:347–54.
33. **Ruetsche AG, Kneubuehl R, Birkhaeuser MH, Lippuner K.** Cortical and trabecular bone mineral density in transsexuals after long-term cross-sex hormonal treatment: a cross-sectional study. Osteoporos Int 2005;16:791–8.
34. **Lapauw B, Taes Y, Simoens S, et al.** Body composition, volumetric and areal bone parameters in male-to-female transsexual persons. Bone 2008;43:1016–21.
35. **Van Caenegem EV, Wierckx K, Taes Y, et al.** Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. J Clin Endocrinol Metab 2012;97:2503–11.
36. **Mueller A, Haeberle L, Zollver H, et al.** Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. J Sex Med 2010;7:3190–8.
37. **Lips P, van Kesteren JM, Asscheman H, Gooren LJG.** The effect of androgen treatment on bone metabolism in female to male transsexuals. J Bone Miner Res 1996;11:1769–73.
38. **Meriggiola MC, Armillotta F, Constantino A, et al.** Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. J Sex Med 2008;5:2442–53.
39. **Wierckx K, Mueller S, Weyers S, et al.** Long-term evaluation of cross-sex hormone treatment in transsexual persons. J Sex Med 2012;9:2641–51.
40. **Ott J, Kaufmann U, Bentz EK, Huber J, Tempfer CB.** Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. Fertil Steril 2010;93:1267–72.
41. **van Kesteren PJM, Asscheman H, Megens JAJ, Gooren LJG.** Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol 1997;47:337–42.
42. **Asscheman H, Gooren LJG, Eklund PLE.** Mortality and morbidity in transsexual patients with cross-gender hormone treatment. Metabolism 1989;38:869–73.
43. **Leinung MC, Urizar MF, Patel N, Sood SC.** Endocrine treatment of transsexual persons: extensive personal experience. Endocr Pract 2013;19:644–50.
44. **Korde LA, Zujewski A, Kamin L, et al.** Multidisciplinary meeting on male breast cancer: summary and research recommendations. J Clin Oncol 2010;28:2114–22.
45. **Symmers WS.** Carcinoma of the breast in trans-sexual individuals after surgical and hormonal interference with the primary and secondary sex characteristics. Br Med J 1968;2:83–5.
46. **Ganly I, Taylor W.** Breast cancer in a trans-sexual man receiving hormone replacement therapy. Br J Surg 1995;82:341.
47. **Pritchard TJ, Pankowsky DA, Crowe JP, Abdul-Karim FW.** Breast cancer in a male to female transsexual: a case report. JAMA 1988;259:2278–80.
48. **Mueller A, Gooren L.** Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 2008;159:197–202.
49. **Kotsopoulos J, Narod SA.** Androgens and breast cancer. Steroids 2012;77:1–9.
50. **Nikolic DV, Djordjevic ML, Granic M, et al.** Importance of revealing a rare case of breast cancer in a male to female transsexual after bilateral mastectomy. World J Surg Oncol 2012;10:280.
51. **Shao T, Grossbard ML, Klein P.** Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. Clin Breast Cancer 2011;11:417–9.
52. **Burcombe RJ, Makris A, Pittam M, Finer N.** Breast cancer after bilateral mastectomy in female-to-male trans-sexual. Breast 2003;12:290–3.
53. **Ikeda K, Baba T, Noguchi H, et al.** Excessive androgen exposure in female-to-male transsexual persons of reproductive age induces hyperplasia of the ovarian cortex and stroma but not polycystic ovary morphology. Hum Reprod 2013;28:453–61.
54. **Dorff TB, Shazer RL, Nepomuceno EM, Tucker SJ.** Successful treatment of metastatic androgen-independent prostate carcinoma in a transsexual patient. Clin Genitourin Cancer 2007;5:344–6.