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MEDICAL INTERVENTIONS FOR TRANSGENDER YOUTH

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ABSTRACT

Up to 1.8% of youth and 0.6% of adults in the United States identify as transgender, meaning their gender identity differs from or is opposite their sex at birth. This chapter reviews epidemiology, gender development, and medical interventions for transgender youth as outlined in the Endocrine Society Clinical Practice Guidelines and World Professional Association for Transgender Health Standards of Care. The chapter concludes with research on mental health in this population and future directions in research.

INTRODUCTION

Throughout history, and across cultures there have been people who live with, what we would now term, gender incongruence (definitions in Table 1). Prior to identification of sex steroids in the 1930s (1-5),and the development of exogenous sex steroids and surgical techniques, there were no options to change one's secondary sex characteristics. The first modern orchiectomy for gender reassignment was performed in 1930 (6), and the first feminizing genital surgeries in the 1940s and 50s in Germany and Denmark, respectively (7,8). Harry Benjamin, known for his 1966 book, The Transsexual Phenomenon (9), treated Christine Jorgensen, the first widely published case of a transgender female in the United States (U.S.), treated with feminizing hormones and surgery. In 1979, the Harry Benjamin International Gender Dysphoria Association was formed, now known as the World Professional Association for Transgender Health (WPATH). The first standards of care were published in 1979, with the 8th edition released in 2022 (10). The Endocrine Society first published a clinical practice guideline regarding the care of transgender persons, including support for pubertal suppression and gender affirming hormone therapy (GAHT) in 2009, with an updated guideline released in 2017 (11,12). In the over 40 years since the first edition of the WPATH Standards of Care, transgender rights, access to care, bathroom use, and sports participation, among other topics, are often featured and steadily more debated in mainstream media, politics, and healthcare (13). Furthermore, as care becomes increasingly politicized, numerous bills to both expand or limit the rights of transgender people and their access to medical care are being introduced in the U.S. (14). Medical care that respects the gender identity of the patient is recommended by numerous medical organizations, including the American Academy of Pediatrics (15,16), Endocrine Society (12), and the American Psychological Association (17,18).

Table 1. Definitions	
Agender	A person with very little or no connection to the traditional systems of gender; existing without gender
Cisgender	Gender identity aligns with biologic sex
Gender affirming hormone therapy	Hormones, including testosterone and /or estradiol, that are prescribed to eligible individuals to induce development of secondary sex characteristics that align with gender identity
Gender affirming surgery (sometimes referred to as gender-confirming or gender-reassignment surgery)	Surgery or surgeries to align one's body with one's gender identity
Gender diverse	Individuals with a variety of gender identities across the gender spectrum, including those who identify as transgender
Gender dysphoria	Distress experienced when gender identity and body are not congruent. Defined in the DSM-5, which replaced "gender identity disorder" in the DSM-IV
Gender expression	External manifestations of gender, expressed through name, pronouns, clothing, haircut, behavior, voice or other characteristics
Gender identity/experienced gender	One's internal, deeply held sense of gender; not visible to others
Gender incongruence	Umbrella term used when gender identity and/or expression differ from what is typically/societally associated with their sex at birth
Gender role	Behaviors, attitudes and personality trait that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with the typical social role of men or women
Non-binary	A person whose gender identity is neither male nor female, both male and female or some combination of genders
Sex	Attributes that characterize biologic maleness or femaleness; factors that influence sex include sex chromosomes, gonads, sex steroids, internal reproductive structures, external genitalia, secondary sex characteristics
Sexual orientation	Physical and emotional attraction to others. Gender identity and sexual orientation are not the same

Transgender	Gender identity differs from sex at birth
Transgender male (also transgender man, female-to-male)	Individuals with a female sex who identify and live as men
Transgender female (also transgender woman, male-to-female)	Individuals with a male sex who identify and live as women
Transition	Process during which persons change their physical, social and/or legal characteristics consistent with their affirmed gender identity
Adapted from Table 1 in the 2017 Endocrine Society Guidelines (12)	

Centers around the world are seeing a rise in the number of transgender and gender diverse (TGD, Table 1) people seeking care to align their bodies with their identities (19). Despite the rise in the number of TGD people seeking care, there remains a lack of education and knowledge among providers as to how best serve this group (20). In this article, we define terminology, briefly review gender development, review current guidelines regarding medical treatment of pediatric TGD individuals and mental health considerations.

EPIDEMIOLOGY

Population-based studies in the U.S. report that 1.8% of youth and 0.6% of adults identify as transgender (21,22). Gender diverse describes individuals with a variety of gender identities across the gender spectrum, including those who identify as transgender (Table 1). Gender dysphoria, which describes the distress associated with a conflict between gender identity and anatomy or sex, is a listed diagnosis in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5, Table 2) (23).

Table 2. Diagnostic Criteria
DSM-5 Criteria for Gender Dysphoria (23)
A marked A marked incongruence between one's experienced/expressed gender and natal gender of at least 6mo in duration, as manifested by at least two of the following: 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) 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) A strong desire for the primary and/or secondary sex characteristics of the other gender A strong desire to be of the other gender (or some alternative gender different from one's designated gender) A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender) 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)
The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning. Specify if:

The condition exists with a disorder of sex development. The condition is post-transitional, 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).
ICD-10 Criteria for Gender Incongruence (24)
A disorder characterized by a strong and persistent cross-gender identification (such as stating a desire to be the other sex or frequently passing as the other sex) coupled with persistent discomfort with his or her sex (manifested in adults, for example, as a preoccupation with altering primary and secondary sex characteristics through hormonal manipulation or surgery). *Note proposed changes in the ICD-11 (25)*

One's sex refers to the physical attributes that characterize biologic maleness or femaleness and is typically assigned or designated at birth based on the appearance of the external genitalia (or prior to birth based on sex chromosome complement and/or the appearance of the genitalia on the prenatal anatomy ultrasound).

Note that terminology in this field is constantly evolving, and for clinicians, it is important to ask individuals what terms they use to describe their gender identity, and what that term means to them. Table 3 includes suggestions on how to ask these questions.

Table 3. Suggested Ways of Asking About Name and Gender Identity	
Name	"Is there a name you go by other than your legal name?" "What name do you go by?" "What would you like me to call you?"
Pronouns	"What pronouns do you use?" "I'd like to use the pronouns that feel best to you. What pronouns would you like me to use?" "Hello, my name is Dr. ____ I use ___ pronouns. What do you go by and what pronouns do you use?"
Gender identity	"How do you identify your gender?" "What does [gender identity term] mean to you?" Suggestion for children: "Some kids tell me think of themselves as girls, some as boys, some as part girl and boy, or something entirely different. How do you think about yourself?" Suggestion for adolescents: "There are lots of ways people think about their gender identity, how do you think of yours?"

GENDER IDENTITY DEVELOPMENT AND NATURAL HISTORY OF GENDER INCONGRUENCE

Gender identity is multidimensional with biological, cultural, and environmental contributions (26,27). Studies of gender identity among individuals with differences/disorders of sex development underscore the influence of the hormonal milieu, and prenatal androgen exposure in particular, for gender development (28-31). There are also genetic influences, as some studies report concordance rates of gender dysphoria up to 39% among identical twins (32). Although studies have sought to identify genes associated with transgender identity, results have largely been inconsistent or inconclusive, with a possible role for genes related to sex steroids and their receptors (33-37).

In childhood, learning about gender starts early, and progress through many stages.(38) In their review of gender development in childhood, Perry, Pauletti and Cooper describe eight dimensions of gender identity: (1) gender self-categorization, (2) felt same-gender typicality, (3) felt other-gender typicality, (4) gender contentedness, (5) felt pressure for gender differentiation, (6) intergroup bias, (7) gender centrality, and (8) gender frustration. By age 18-24 months most children can categorize their own and others' gender (39), and by age 6, have a developed gender identity (40). More individuals with a female sex at birth express dissatisfaction with their gender (41,42). This reflects the current sex ratio of individuals being referred to gender clinics, with more individuals with a female sex at birth currently referred, but the opposite being true prior to the 2000s (43-45).

Despite adolescence being a period of identity formation (46,47), there is a surprising lack of research on adolescent gender identity development. Development of identity is an individual and social process and shaped by external surroundings (47). Numerous psychological and biological factors influence gender identity, as outlined in a review by Steensma and colleagues (48).

Overall, there is still much to learn about gender development among gender variant or nonconforming individuals. Prospective studies of children referred to gender clinics, primarily in Europe, show that less than a quarter of children will meet criteria for gender identity disorder (the DSM-IV diagnosis prior to the DSM-5 gender dysphoria) after adolescence (49-52). In follow-up studies, the period of early adolescence/puberty, age 10-13 is critically important. One population-based study (ages 11-26) demonstrated that gender non-contentedness peaked in early adolescence at 11% and decreased with age, with 4% of participants reporting gender non-contentedness by their early-to-mid 20s (53). Furthermore, it is important to recognize and support early exploration as persistent non-contentedness was associated with lower self-esteem and decreased mental health (53). There are three possible factors that contribute to an increase or decrease in gender discomfort and cross-gender identification: (1) physical puberty, (2) changing environment and being treated as their sex at birth, and (3) the discovery of sexuality (52). Ongoing studies are needed to better understand the persistence or evolution of gender identity over time.

MEDICAL MANAGEMENT

The WPATH Standards of Care (10,54), outline three categories of physical interventions for adolescents: (1) fully reversible interventions, such as the use of gonadotropin releasing hormone (GnRH) agonists, medications to suppress menses (such as progestins), and medications to decrease the effects of androgens (such as spironolactone); (2) partially reversible interventions, including testosterone or estradiol; and (3) irreversible interventions, such as surgical procedures. Many individuals also seek care, including behavioral health consultation, for reversible interventions such as name, pronoun, and gender marker change, discussing gender identity with

friends, family and school, voice therapy, or wearables (including binders and packers to flatten the chest or give the appearance of male genitalia, respectively).

Pubertal Blockade

The onset of puberty (gonadarche) is characterized by breast budding in people with a female sex at birth and by testicular enlargement to 4mL or greater in people with a male sex at birth, characterized as Tanner or Sexual Maturity Rating stage 2 (55,56). The average age of pubertal onset is age 10-11 years in someone with a female sex at birth (range 8-13 years, can be younger in African Americans), and 11-12 years in individuals with a male sex birth (range 9-14 years). For individuals with a male sex at birth, external virilization typically starts around a testicular volume of 10 mL (12), voice drop at ≥8-10mL (57), and spermarche at 10-12 mL (58). In individuals with a female sex at birth, breast developmental progresses from stage 2 to 5 (fully developed) within 4-5 years and menarche typically occurs about 2-2.5 years after breast budding (59). Pubic hair and/or axillary hair and/or body odor reflect the onset of adrenarche or adrenal androgen production, which, by themselves are not indicative of central puberty (55,56). Height velocity increases during puberty and peaks about 2.5 years after the start of pubertal growth acceleration (60). An understanding of typical pubertal development and timing of external secondary sex characteristics is useful in counseling families about the timeliness and risk/benefit of GnRH agonist therapy to halt further pubertal progression. For example, towards the end of puberty or in post-pubertal individuals, GnRH agonist therapy may be used in certain circumstances for sex steroid suppression but would not block any outward pubertal changes, as these are, by then, complete.

GnRH agonists were first used in youth for the treatment of central precocious puberty in the 1980s (61). In 1998, physicians in the Netherlands published the first report of a transgender patient treated with triptorelin, a GnRH agonist (62). The “Dutch model” of using pubertal suppression followed by gender affirming hormones (testosterone or estradiol) subsequently became incorporated into the WPATH and Endocrine Society standards of care (10,12). Their use became more widespread in the U.S. after publication of the 2009 Endocrine Society guidelines (11). The 2017 Endocrine Society guidelines suggest that “adolescents who meet diagnostic criteria for gender dysphoria/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development”(12). The guidelines suggest beginning pubertal hormone suppression after the onset of the physical changes of puberty (Tanner Stage or Sexual Maturity Rating 2) for individuals who meet criteria, including being diagnosed with gender dysphoria/gender incongruence, experienced worsening dysphoria or ongoing incongruence with the onset of puberty, existing psychological, medical and/or social problems are addressed and the adolescent has sufficient mental capacity to consent to treatment (12). Treatment with a GnRH agonist suppresses gonadotropins (after an initial increase of gonadotropins) (63). There are also gonadotropin releasing hormone antagonists that immediately suppress gonadotropins, but are not available in children. GnRH agonists are typically administered as either an injection (IM or SQ) or as an implant (preparations listed in Table 4). Insurance coverage for this off-label, and costly therapy, varies (64). GnRH agonist treatment will pause or halt pubertal changes and may cause slight regression of breast tissue or testicular volume (12). On their own, these are reversible interventions, and if the individual decided that they wanted to progress through their endogenous puberty, these medications can be discontinued. During GnRH agonist treatment, the Endocrine Society recommends measurement of height, weight, sitting height, blood pressure and Tanner stages every 3-6 months, measurement of LH, FSH, estradiol or testosterone and 25OH vitamin D every 6-12 months and bone density using dual-energy X-ray absorptiometry (DXA) and bone age x-ray of the left hand every 1-2 years (Table 5) (12).

Table 4. Hormonal Interventions for Transgender Adolescents	
Pubertal blockade/inhibition of sex steroid secretion	
GnRH agonist: inhibition of the hypothalamic-pituitary-gonadal access	Leuprolide acetate IM (1-, 3-, 4- or 6-mo preparations) or SQ (1-, 3-, 4- or 6-mo preparation) Triptorelin IM (4-, 12- or 24-week preparation) Histrelin acetate SQ implant (one-yearly dosing, although reports of longer effectiveness)
Medroxyprogesterone acetate: inhibition of the hypothalamic-pituitary-gonadal access and direct inhibition of gonadal steroidogenesis	Orally (up to 40 mg/day) or IM (150 mg every 3 mo, may be given more frequently for suppression of sex steroids)
Inhibition of testosterone secretion or action	
Spironolactone: inhibition of testosterone synthesis and action	Titrate up to 10-300 mg/day orally (typically in divided doses)
Cyproterone acetate: inhibition of testosterone synthesis and action (not available in US)	25-50 mg/day orally
Finasteride: inhibition of type II 5 α-reductase, blocks conversion of testosterone to 5 α-dihydrotestosterone	2.5-5 mg/day orally
Bicalutamide: androgen receptor blockade	25-50 mg daily or every other day orally
Sex steroids	
Estrogen/17β-estradiol	Oral/sublingual: start with lower doses for pubertal induction, titrate up to adult doses 2-6 mg/day Transdermal: start with lower doses for pubertal induction, titrate up to adult doses 0.025-0.2 mg/day (patches are typically once or twice weekly) Parenteral: estradiol valerate (5-30 mg every 2 weeks) or cypionate (2-10 mg IM every week)
Testosterone	Parenteral IM or SQ testosterone cypionate or enanthate (start at 12.5 mg/week or 25 mg q2 week with gradual increases to 50-100 mg/week or 100-200 mg every 2 weeks) Transdermal (typically after full adult dose has been achieved parenterally): patch (2.5-7.5 mg/day or 1% or 1.6% gel
Note that all medications are currently off-label for gender non-conforming/transgender youth. Note that certain GnRH preparations are approved in children for central precocious puberty	

and other formulations are approved for adults only, with off-label use in children. Different formulations are available in different countries. This table was adapted from the following references (12,65). Note that some centers/providers also use GnRH agonists for testosterone blockade in older adolescents and/or adults. GnRH: gonadotropin releasing hormone, IM: intramuscular, SQ: subcutaneous

Table 5. Recommended Monitoring Hormonal Interventions for Transgender Adolescents	
Pubertal suppression	
Gonadotropin releasing hormone agonist monotherapy	Measure height, weight, sitting height, blood pressure and Tanner stages every 3-6 months Measure LH, FSH, estradiol or testosterone and 25OH vitamin D every 6-12 months DXA and bone age x-ray of the left hand every 1-2 years
Pubertal induction for adolescents	
Testosterone	Measure height, weight, sitting height, blood pressure and Tanner stages every 3-6 months Measure hemoglobin/hematocrit, lipids, testosterone and 25OH vitamin D every 6-12 months DXA and bone age (if clinically indicated or the patient is still growing) every 1-2 years
Estradiol	Measure height, weight, sitting height, blood pressure and Tanner stages every 3-6 months Measure prolactin, estradiol and 25OH vitamin D every 6-12 months DXA and bone age (if clinically indicated or the patient is still growing) every 1-2 years
Adapted from Table 9 in the 2017 Endocrine Society Guidelines (12). DXA: dual-energy X-ray absorptiometry, FSH: follicle stimulating hormone, LH: luteinizing hormone	

Reviews of puberty blockade have been published (66-68). Small studies have demonstrated effectiveness of GnRH agonist treatment for suppression of the hypothalamic-pituitary-gonadal axis in transgender youth (69). Studies, primarily in Europe, have demonstrated improvements in psychological functioning, behavioral/emotional problems, and depressive symptoms during GnRH agonist treatment in transgender youth (70,71). A systematic review found that GnRH agonist therapy is associated with decreased suicidality in adulthood, improved affect and psychological functioning, and improved social life (67). A 2025 review of 51 studies found mental health improved significantly, including reduced depression, anxiety, and suicidality, especially when GnRH agonist treatment was followed by gender-affirming hormone therapy (72). Quality of life improved over time, while body dissatisfaction often persisted during suppression and improved after hormone therapy or surgery (72). However, a meta-analysis of 10 studies concluded that the overall quality of evidence for outcomes related to gender dysphoria, global function, and depression was low (73).

Potential risks of GnRH agonist therapy include impacts on growth, bone health, body composition, fertility, and neurodevelopment, as well as difficulties

accessing treatment due to cost and/or insurance coverage (67,68,74). GnRH agonist use in TGD youth is associated with increased body fat and decrease in lean mass after initiation (75,76), compared to age- and BMI-matched control youth (77), and may also have an adverse effect on insulin sensitivity (77).

If GnRH agonists are started prior to skeletal maturity, they will decrease skeletal advancement during monotherapy due to suppression of sex steroids, which are necessary for growth plate closure (78,79). Adult height arises from a multifactorial interplay of genetic determinants (including the contribution of sex chromosomes), together with prenatal and postnatal (including environmental and nutritional) influences, with sex steroids constituting only one of several regulatory factors. Transgender youth treated with GnRH agonist and subsequent testosterone or estradiol achieve an adult height similar to their predicted genetic target, with slight variability depending on timing, dose and escalation regimen (80,81). One multicenter study in the U.S. showed that transgender youth treated with GnRH therapy have growth velocity similar to prepubertal children, but those who start GnRH agonist treatment later in puberty have growth velocity below the prepubertal range (82). The growth spurt and skeletal advancement will progress either when exogenous testosterone or estradiol are started, or if the GnRH agonists are discontinued and the individual progresses through their endogenous puberty.

There is a growing body of research of bone health in transgender individuals, as well as the impact of GnRH agonists and later gender affirming hormones on bone health. Studies in the Netherlands have demonstrated decreased bone turnover, and a decrease in bone mineral apparent density Z-scores of the lumbar spine in transwomen after initiation of GnRH agonist therapy (83). However, studies in the U.S. (84), United Kingdom (85), and Netherlands (83,86) have also shown decreased bone mineral density Z-scores determined by DXA are low prior to treatment with GnRH agonist, and some studies showing Z-scores did not completely normalize with sex hormone treatment (83,86). More recently, studies have shown pubertal suppression causes transient declines in bone mineral density Z-scores, particularly in those with a male sex at birth, and subsequent estradiol/testosterone treatment helps to restore bone mass (87). In the U.S., the individuals with lower baseline bone mineral density Z-scores also reported less physical activity, an area warrants further research (84).

Overall, there is a paucity of research on neurodevelopment (88) and a consensus parameter was published with recommended research methodologies to evaluate the neurodevelopmental effects of puberty suppression in this population (89). There is also very little research on sexual function and future surgical options among individuals who received early puberty blockade aside from one qualitative study (90). More information is needed on the impact of GnRH agonist treatment on future sexual function (91,92) (particularly for individuals with a male sex as GnRH agonists limit penile and testicular growth/size (93)) and on implications for future surgical intervention for those individuals pursuing vaginoplasty (as the penile tissue is used to construct the vagina) (93). One study found that sexual function and dysfunction was similar among adolescents who had received GnRH agonist treatment for puberty suppression compared to those who started hormone treatment in adulthood (94). Finally, treatment with GnRH agonists will impair spermatogenesis and oocyte maturation temporarily, and the Endocrine Society recommends fertility counseling (12). Treatment may be delayed to preserve fertility, but many individuals do not chose this, as delay will also cause further progression of unwanted secondary sex characteristics (12). Sperm retrieval via testicular biopsy has been successful with a testicular volume of at least 10 mL or greater (95).

If GnRH analogues are not available or are cost prohibitive, medroxyprogesterone may be used as an alternative agent for pubertal suppression (Table 4) (12). At high doses, medroxyprogesterone inhibits the pituitary-gonadal axis and suppresses testosterone

(96-98). Medroxyprogesterone was used for treatment of precocious puberty in the 1960s and 70s (99-101). It is typically safe, although may have some side effects, including due to the estrogenic effects (bloating, nausea/vomiting, breast fullness, breakthrough bleeding for those menstruating, irritability, headache, hypertension), pro-gestational effects (headache, breast pain/tenderness, hypertension) and androgenic effects (acne, oily skin, weight gain, hirsutism, fatigue, depression) (102). At extremely high doses (100 mg four times a day, not recommended doses for transgender individuals), Cushing's syndrome, adrenal insufficiency, and diabetes have been reported (103). There is one small study of medroxyprogesterone in transgender youth demonstrating effective sex steroid suppression with doses of oral medroxyprogesterone 10-30 mg BID or 150 mg IM every 2-3 months (104).

Gender Affirming Hormone Therapy

Gender affirming hormone therapy or GAHT refers to hormones that induce secondary sex characteristics to align the body with one's gender identity. The Endocrine Society recommends treatment with sex steroids (testosterone or estradiol) "using a gradually increasing dose schedule after a multidisciplinary team of medical and mental health professionals has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years" (full criteria in guidelines) (12). However, they also state that "there may be compelling reasons to initiate sex hormone treatment prior to age 16 years in some adolescents" (12). The WPATH Standards of Care 8 criteria for hormone therapy are: "(a) gender diversity/incongruence is marked and sustained over time; (b) meets the diagnostic criteria of gender incongruence in situations where a diagnosis is necessary to access health care; (c) demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment; (d) mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed; sufficiently so that gender-affirming medical treatment can be provided optimally; (e) informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility; (f) reached Tanner stage 2"(10). It is recommended, that for adolescents who have not reached the age of majority in their country, that consent from all parents or medical decision-makers is obtained prior to starting this partially irreversible therapy.

FEMINIZING HORMONE THERAPY

Estradiol Therapy

For eligible adolescents, the Endocrine Society recommends a gradually increasing dose schedule of oral or transdermal 17β-estradiol (12). This will cause feminization of the body, with expected effects including body fat redistribution, decreased muscle mass/strength, softening of the skin/decreased oiliness, decreased libido/erections, breast growth, decreased testicular volume, decreased sperm production, and thinning and slowed growth of body and facial hair occurring one to several months after treatment with maximum effects generally about 2-3 years or more into treatment (12,54). For younger individuals, the Endocrine Society recommends starting oral estradiol at a dose of 5 μg/kg/day and increasing doses every 6 months up to a dose of 2-6 mg/day for an adult (12). In post-pubertal individuals, the starting dose may be higher and titrated more quickly (start at 1 mg/day for 6 months and increase to 2 mg/day orally) (12). For transdermal estradiol, it is recommended to start at a dose of 6.25-12.5 μg/24 hours and increase the dose every 6 months to an adult dose of 50-200 μg/24 hours. During induction of puberty, it is recommended to measure height, weight, sitting height, blood pressure and Tanner stages every 3-6 months, and measure prolactin, estradiol and 25OH vitamin D every 6-12 months (Table 5) (12). Additionally, DXA and bone age (if clinically indicated or a growing patient) is recommended every 1-2 years (12).

Potential adverse effects of estradiol therapy as outlined in the Endocrine Society guidelines include thromboembolic disease, macroprolactinoma, breast cancer, coronary artery disease, cerebrovascular disease, cholelithiasis, and hypertriglyceridemia (12).

In adults, studies using three large cohorts have shown an increased risk of myocardial infarction and venous thromboembolism. In Europe, transgender women on estradiol therapy have a higher risk of stroke and venous thromboembolism than both cisgender reference women and men, and a higher risk of myocardial infarction than cisgender women (but not men) (105). In the U.S., two large cohorts have been used to examine outcomes, the Kaiser STRONG cohort and self-report data from the Behavioral Risk Factor Surveillance System (BRFSS). Data on hormone treatment is not collected in BRFSS. Transgender women in BRFSS were more likely (>2-fold increase risk) to have a history of myocardial infarction than cisgender women (but not men) (106,107). In the Kaiser STRONG cohort (108), both prevalent and incident type 2 diabetes was more common in the transfeminine cohort compared to cisgender females (109). In a meta-analysis commissioned by the Endocrine Society to accompany the 2017 updated guidelines, transgender women on estradiol therapy had increased triglycerides, but no changes in other lipid parameters (110). There have been several reviews and meta-analyses on the risk of cardiovascular disease and hormone therapy. Several studies show transgender women on hormone therapy have a higher risk of venous thromboembolism compared to cisgender men (111). Compared to cisgender women, transgender women on hormone therapy have an increased risk of myocardial infarction, ischemic stroke and venous thromboembolism (105,112,113), with one study also showing an increased risk of type 2 diabetes (but this was unrelated to hormone therapy) (109). One study after three months of feminizing hormone therapy showed improvements in measured glomerular filtration rate and kidney perfusion (114). It is well-established that transgender women on estradiol therapy have increases in body weight and fat and decreases in lean body mass (115).

Estradiol therapy is associated with increases in lumbar spine bone mineral density compared to baseline (116). Among individuals followed from initiation of GnRH agonist therapy into young adulthood, Z-scores returned to pretreatment values after hormone therapy except for lumbar spine Z-scores in individuals with a male sex at birth treated with estradiol (117). There are numerous contributors to bone mineral density including body mass index, physical activity, vitamin D and calcium, as well as age and pubertal stage at which GnRH agonists and subsequent hormone therapy are initiated (87).

In youth, there is a growing body of literature on the effects of GAHT, particularly on cardiometabolic health. TGD youth on estradiol have changes in HDL, aspartate aminotransferase, potassium, prolactin and hemoglobin after about two years (118). One study found that transgender females on estradiol therapy were more insulin resistant than matched cisgender males (119). The presence of obesity attenuates the beneficial effect of estradiol on HDL (120). There are also studies investigating baseline differences between TGD youth and cisgender controls prior to hormone therapy, with recent studies showing TGD youth have lower HDL and low bone mineral density (82,121).

Testosterone Blockade/Suppression

There are many options for blockade and/or suppression of testosterone (all off-label use, Table 4). When available and affordable, some centers utilize GnRH agonists for suppression of testosterone. For example, in the United Kingdom, GnRH analogues are heavily subsidized (122). There are also many antiandrogens available, and a systemic review of options has recently been published (123). Spironolactone is widely available, inexpensive and commonly used in the U.S. and Australia. Spironolactone is a weak androgen receptor antagonist (124,125), weak progesterone receptor

agonist and weak estrogen receptor agonist (123). Spironolactone also partially inhibits 17α-hydroxylase/17,20 lyase, which are involved in testosterone synthesis (126). Even at high doses, spironolactone does not cause a significant reduction in serum total testosterone concentration (127). Although the combination of spironolactone with estradiol does appear to suppress testosterone in transgender women (128). Side effects include irregular menses (only for people who are menstruating, not a consideration for transgender women), hypotension, polyuria, and hyperkalemia (129,130).

Cyproterone acetate is available in Europe and Australia, but not in the U.S. and is a moderate androgen receptor antagonist, strong progesterone receptor agonist and does not have any estrogen receptor activity but does suppress the hypothalamic pituitary gonadal axis (123). Cyproterone acetate use has been associated with increased risk of meningiomas (131) and prolactinomas (132). Other side effects include weight gain, headache, gastrointestinal disorders, mood effects, and edema (133).

Nonsteroidal anti-androgens, such as bicalutamide have also been used at some centers. Bicalutamide has strong androgen receptor antagonist activity and does not have any estrogen or progesterone agonist activity (123); it does not cause a reduction in testosterone concentrations. There is some feminization, thought to be due to increased aromatization of testosterone to estradiol (134). There are a few studies evaluating use of bicalutamide in transgender adolescents as an alternative to GnRH agonists (134-136). In these studies, there was effective androgen suppression with a favorable short-term safety profile (134-136), though there is a need for longer-term data in larger cohorts. Although concerns have been raised, including a case report of hepatotoxicity in an adolescent (137), an editorial emphasized that such rare outcomes should be considered in light of broader clinical experience and benefit-risk analysis (138).

Finally, 5-alpha reductase inhibitors, such as finasteride, block conversion of testosterone to dihydrotestosterone. These are not recommended by the Endocrine Society due to adverse effects (12), but the WPATH guidelines state, “these medications have beneficial effects on scalp hair loss, body hair growth, sebaceous glands, and skin consistency” (54). Side effects include sexual dysfunction and decreased muscle mass (which may be perceived as a risk of benefit in this population), anhedonia, and trouble concentrating (139).

Overall, the selection of which agent alone or in combination with estradiol depends on many factors including patient age, country, insurance coverage, cost, availability, goals of care, and tolerability of side effects (e.g. severe and fatal hepatotoxicity has been reported with cyproterone acetate and bicalutamide (140)). Further studies are needed to determine superiority for relevant patient outcomes including body composition, breast development, facial and body hair (123).

MASCULINIZING HORMONE THERAPY

Testosterone Therapy

For eligible adolescents, the Endocrine Society recommends a gradually increasing dose schedule of testosterone (typically injectable IM or SQ) (12). This will cause masculinization of the body, with expected effects including skin oiliness/acne, facial/body hair growth, scalp hair loss, increased muscle mass/strength, body fat redistribution, cessation of menses, clitoral enlargement, vaginal atrophy, and deepened voice with onset occurring one to several months after treatment with maximum effects generally about 2-5 years or more into treatment (12,54). For younger individuals, the Endocrine Society recommends starting injectable testosterone esters at a dose of 25 mg/m2 IM or SQ every 2 weeks and increasing every 6 months up to an adult dose of 100-200 mg every 2 weeks (12). In post-pubertal individuals, the starting dose may be higher and

titrated more quickly (start at 75 mg every 2 weeks for 6 months and increase to 125 mg every 2 weeks) (12). Subcutaneous testosterone is gaining in popularity and has shown to be effective and preferred by patients (141-143). Pharmacokinetic studies of weekly subcutaneous testosterone injections show that steady state is approached after the third dose, and that serum concentrations stay relatively constant throughout the week between doses (144). Finally, SQ testosterone doses may be lower than those delivered IM, with two studies reporting doses of 50-80 mg/week to achieve target testosterone concentrations in adults or older adolescents (141,142). During induction of puberty, it is recommended to measure height, weight, sitting height, blood pressure, and Tanner stages every 3-6 months, and measure hemoglobin/hematocrit, lipids, testosterone, and 25OH vitamin D every 6-12 months (Table 5) (12). Additionally, DXA and bone age (if clinically indicated or a growing patient) is recommended every 1-2 years (12).

The most common adverse effect of testosterone is erythrocytosis/polycythemia (hematocrit >50%) (12). A 2023 cohort study of 511 transgender individuals on testosterone individuals reported a 22% incidence of polycythemia, particularly in those with BMI >30 kg/m^2, obstructive sleep apnea, or higher testosterone dosing (145). Other risks as outlined in the Endocrine Society guidelines include liver dysfunction, coronary artery disease, cerebrovascular disease, hypertension, and breast or uterine cancer (12).

In a meta-analysis, testosterone therapy in transgender men was associated with increases in serum triglycerides and low-density lipoprotein cholesterol (LDL-C) concentrations and decreases in high-density lipoprotein cholesterol (HDL) (110). In adults, studies using three large cohorts have shown conflicting results regarding cardiovascular events. In Europe, transgender men on testosterone therapy have a higher risk of myocardial infarction than cisgender women (but not men) and no increased risk of stroke or venous thromboembolism compared to reference populations (105). Transgender men in the U.S. BRFSS survey (years 2014-2017, hormone treatment was not collected in the survey) had a >2-fold increase risk of myocardial infarction compared to cisgender men and an almost 5-fold increase compared to cisgender women (107). In the Kaiser STRONG cohort, there was no increased risk of type 2 diabetes among transgender men compared to cisgender men (109). A meta-analysis showed that transgender men on testosterone showed no difference in risk of myocardial infarction compared to cisgender women (111). Testosterone therapy in transgender men is known to result in increased body weight and lean mass and decreased body fat.(115) In meta-analyses, testosterone therapy is not associated with significant changes in bone mineral density (116,146). Among individuals followed from initiation of GnRH agonist therapy into young adulthood, Z-scores were similar or slightly improved from pretreatment values after testosterone therapy (117).

Among TGD youth starting testosterone therapy, there is an increase in BMI and decrease in HDL (147). The decrease in HDL is exacerbated by obesity (120). Other studies have found that testosterone treatment in TGD youth is associated with statistical, but not clinically significant increases in triglycerides, alanine aminotransferase, potassium, and hemoglobin (118). There are very limited data regarding differences in cardiometabolic health among youth who did or did not receive GnRH agonist therapy. In one small longitudinal study, youth who had been on a GnRH agonist (and continued on it for the first year of testosterone therapy) had lower brachial artery flow mediated dilation than those not on a GnRH agonist, with convergence of results after 12 months of testosterone therapy (148).

Non-Binary Care

Non-binary and gender non-conforming individuals comprise an increasing proportion of patients presenting to gender clinics, and Chapter 8 of the WPATH Standards of Care outlines recommendations for their care (10). Nonbinary people may have additional challenges accessing healthcare (149).

Limited studies have reported worse mental and physical health among individuals who identify as gender non-conforming compared to matched controls (106). An individualized approach to understand the individual's gender identity, sources of dysphoria (if any), and gender goals are important. Some individuals may desire reversible interventions such as menstrual suppression, others may request certain hormones and/or surgical interventions as a part of their gender goals.

MENSTRUAL MANAGEMENT

Many transmasculine and non-binary individuals who have a female sex at birth seek medical attention or desire interventions for menstrual management (150). Some also utilize these methods for contraception. It is important to ask individuals about their individual goals, as well as their sexual orientation, partners (including sex at birth and what body parts they currently have), and types of sex they are engaging in. These factors can guide choice of intervention for menstrual management and/or contraception. An overview of options is in Table 6. Progestin-only methods, including norethindrone or depo medroxyprogesterone are particularly popular choices among this population (150). Review of options for menstrual management and contraceptive options for transgender individuals exist (151). For those patients wishing to and eligible for testosterone therapy, menses suppression typically is achieved within 6-12 months of the start of testosterone therapy (152).

Table 6. Options for Menstrual Suppression/Management
Combined hormonal contraceptives (pills, patch, ring)
Progestins
Norethindrone acetate (5-15 mg/day orally)
Medroxyprogesterone acetate (150 mg IM every 3 months)
Etonogestrel implant
Levonorgestrel intrauterine device

SURGICAL MANAGEMENT

Surgeries that impact fertility are generally not available until the individual has reached the age of majority in their country. There are a wide variety of surgical options for transgender adults (and some options, primarily chest surgery, for adolescents) (153). Physicians (including surgeons and non-surgeons) and behavioral health providers should be aware of the criteria needed for each surgical procedure, including whether social transition is recommended, whether hormonal therapy is needed (and length), and how many referral letters are needed and by whom (10). Recommendations for surgeons and criteria for surgeries are outlined in the WPATH Standards of Care (10). Table 7 summarizes the various gender affirming surgical options.

Table 7. Gender Affirming Surgical Options	
Feminizing Surgeries	
Breast augmentation	Increasing the size of the breasts
Facial feminization surgery	May include: forehead feminization, rhinoplasty, periorbital rejuvenation, rhytidectomy (face lift), cheek augmentation, rhinoplasty, lip feminization, gonial angle shave, genioplasty
Genital surgery/vaginoplasty	May include penectomy, orchiectomy, surgical creation of a vagina (penile inversion, intestinal conduit), clitoroplasty, labiaplasty
Orchiectomy	Removal of testes
Tracheal shave	Thyroid cartilage shave
Masculinizing Surgeries	
Chest masculinizing surgery (mastectomy)	Removal of breast tissue
Facial masculinization surgery	Rhinoplasty, gonial implants, genioplasty
Hysterectomy, salpingectomy, oophorectomy	Removal of uterus and/or fallopian tubes, and/or ovaries
Metoidioplasty	Creation of a phallus using existing genital tissue
Phalloplasty	Construction of phallus, glansplasty, urethroplasty, erectile prosthesis, scrotoplasty, testicular implants

BEHAVIORAL HEALTH AND CO-OCCURING CONDITIONS

Recent studies have demonstrated a high prevalence of behavioral health disorders among youth diagnosed with gender dysphoria (up to 60%) (154,155). Research on behavioral health among TGD youth consistently demonstrates disproportionately high prevalence of anxiety (155-157), depression (156-159), suicidality (22,155-157,160), self-harm (155-158), and substance use problems (22). Large surveys of TGD individuals in the U.S. have shown that 40% of adults (161) and 35% of youth (22) have attempted suicide. Poor behavioral health outcomes may be conceptualized as the result of complex and layered socio-cultural and political factors that impact TGD youth (17,162). Risk factors that are likely to impact overall mental health for TGD individuals include minority stress (e.g., victimization, discrimination) (22,163), gender dysphoria and appearance congruence (164), feelings of isolation, inadequate family support (165), emotional/social isolation (166), lack of autonomy over decision making (166), barriers to accessing gender affirming care (166-168), employment discrimination (166), and limited financial resources (166). In the Youth Risk Behavior Survey, TGD youth were two to six times more likely to be victimized, including experiencing sexual dating violence, experiencing physical dating violence, being bullied at school, being electronically bullied, feeling unsafe during travel to or from school, and being forced to have sexual intercourse (22).

Protective factors including social support (169,170), parental support/affirmation of gender identity (171,172), higher self-esteem (169), resiliency

(169,173), and access to affirming care (167,174,175) have resulted in improved wellbeing and less mental health distress. Access to gender-affirming interventions, including hormone therapy and surgery, has been shown to improve gender dysphoria, psychological symptoms and quality of life in small samples and meta-analyses (28. Recent studies have shown that those who were older at presentation have worse mental health than those who presented to care at a younger age (176) and those who had access to GnRH agonists had lower lifetime odds of suicidal ideation than those who did not have access (167). The Trans Youth Care - United States study found that after 24 months of hormone therapy, there were significant improvements in appearance congruence, psychological well-being, social and life satisfaction, self-efficacy, positive affect, and significant reductions in depression and anxiety symptoms, negative affect, and negative social perception (177,178). A study utilizing electronic health records of six hospitals found that TGD youth prescribed hormone therapy had a 43.6% lower risk of suicidality compared with those never prescribed hormone therapy (or prior to hormone therapy initiation) (179).

The co-occurrence of autism spectrum disorder (ASD) and gender dysphoria is a growing area of interest, with a scoping review recently published (180). A meta-analysis found that the prevalence of ASD diagnoses among people with gender dysphoria/incongruence was 11% (181). In a large 2020 study, TGD individuals were 3.0 to 6.4 times more likely to be diagnosed with ASD than their cisgender counterparts (159). Other samples have shown that youth with gender dysphoria are about 2 to 3 times as likely to have a diagnosis of ASD than their matched cisgender counterparts (154,155). The exact link between GD and ASD is not known, but factors contributing may include: symptom overlap between the two diagnoses, misclassification due to symptom overlap, children with ASD may be more likely to express their gender identity and dysphoria, or they may be more likely to be referred to care to be diagnosed with either GD or ASD (182).

Finally, there are many other important topics that impact the care of transgender individuals that are beyond the scope of this chapter including dermatologic considerations and hair loss (183-185), chest binding (186), sexual health (92), HIV prevention and treatment (187-189), fertility (190), sleep (191), athletic performance and sports participation (192,193), eating disorders (194,195), homelessness, the impact of family support, and the underpinnings of links between gender diversity and neurodiversity.

CONCLUSION

An improved understanding of the variety of individual gender trajectories is needed, as well as how best to individualize care, how to improve mental health and minimize risks of medical interventions. Large, multi-center, prospective cohorts established in the U.S. (108,196) and Europe (197), should help answer some of these important questions. There is also much to be learned about the impact of early GnRH agonist therapy on growth, bone health, physical development, long-term health, mental health, cognitive development, and overall wellbeing. The American Heart Association published a scientific statement with recommendations to assess and address cardiovascular health among TGD people (198). Finally, an improved understanding on the impact of other stressors including minority stress and depression on overall health (199,200) for TGD persons is needed.

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