

# Gender Variance and Dysphoria in Children and Adolescents



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## KEYWORDS

- Gender dysphoria • Gender identity • Gender variance • Cross-sex hormones
- Pubertal blockers • Transgender youth

## KEY POINTS

- Gender nonconforming and transgender youth are seeking medical care at younger ages.
- Youth with gender variance are often marginalized and misunderstood by their health care providers.
- Mental health comorbidities in youth with gender dysphoria significantly diminish when receiving gender-affirming care.
- Providers should understand the use of hormone blockers and cross-sex hormones as a strategy in addressing gender dysphoria.
- Prompt referrals by medical professionals should be made to an interdisciplinary team experienced in addressing the unique challenges faced by transgender youth and their families.

Over the past decade, there has been an increase in the number of gender variant children and adolescents seeking care at gender clinics and centers around the world.<sup>1</sup> Many of these gender variant youth are seeking care at younger ages for many reasons, including greater access to information about transgender or gender variant youth via the Internet, more exposure to gender variant or transgender characters in the media, and greater openness toward dialogue concerning one's gender with his or her peers and family members.

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*Gender variance* is an umbrella term used to describe the behaviors, interests, appearance, expression, or an identity of persons who do not conform to culturally defined norms expected of their natal gender.<sup>2</sup> Related terms include *gender nonconforming*, *gender creative*, *transgender*, and, in Aboriginal culture, *two-spirited*. To meet the needs of such youth, there has been an increase in the number of pediatric clinics in Canada, the United States, and Europe that specialize in the care of gender variant children and adolescents.<sup>3</sup>

For most youth, the natal gender (ie, the gender assumed based on the physical sex characteristics present at birth) is consistent with their gender identity (a person's intrinsic sense of self as male, female, or an alternative gender). In a small minority, however, there is a discrepancy between assigned (or natal) gender and gender identity. The distress that is caused by this discrepancy is called *gender dysphoria* (GD).<sup>4</sup> This article reviews the epidemiology of youth with gender variance and GD and the models of care used to manage youth with GD.

## TERMINOLOGY

When working with youth and their families, medical professionals should be inclusive, sensitive, and respectful regarding the use of preferred names and gender pronouns. There is an abundance of gender-related terms that may be used by youth, their families, and health care professionals.

### ***Biological/Anatomic Sex***

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*Biological/anatomic sex* are the physical attributes that characterize maleness or femaleness (eg, the genitalia).

### ***Cisgender***

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*Cisgender* refers to individuals whose affirmed gender matches their physical sex characteristics.

### ***Gender Dysphoria***

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*GD* is distress that is caused by a discrepancy between a person's gender identity and that person's natal gender (ie, the gender that is assumed based on the physical sex characteristics present at birth). Not all gender-variant individuals experience GD.<sup>2</sup>

### ***Gender Identity (or Affirmed Gender)***

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*Gender identity* is a person's intrinsic sense of self as male, female, or an alternate gender. Gender identity likely reflects a complex interplay of biological, environmental, and cultural factors.<sup>2,5,6</sup>

### ***Gender Nonconforming***

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*Gender nonconforming* is an adjective used to describe individuals whose gender identity, role, or expression differs from what is normative for their assigned sex in a given culture and historical period.

### ***Gender Role or Expression***

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*Gender role or expression* refers to characteristics in personality, appearance, and behavior that, in a given culture and historical period, are designated as masculine or feminine (that is, more typical of the male or female social role).<sup>7</sup> Although most individuals present socially in clearly masculine or feminine gender roles, some people

present in an alternative gender role. Gender expression does not always correlate with gender identity or physical sex characteristics.

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### **Gender Variance**

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The term *gender variance* refers to the behaviors, appearance, or identity of people who do not conform to culturally defined norms for their assigned gender.<sup>2</sup>

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### **Female-to-Male**

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*Female-to-male* (FTM) refers to assigned female persons who identify as male.

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### **Male-to-Female**

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*Male-to-female* (MTF) refers to assigned male persons who identify as female.

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### **Transgender**

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*Transgender* is an adjective to describe individuals with an affirmed gender identity different than their physical sex characteristics. *Transgender* can also be used to describe people whose gender identity, expression, or behaviors cross or transcend culturally defined categories of gender.<sup>2</sup>

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### **Transitioning**

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*Transitioning* is a process whereby individuals change their social and/or physical characteristics for the purpose of living in their desired gender role. Transitioning may or may not include hormonal and/or surgical procedures.<sup>2</sup>

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### **Sexual Orientation**

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*Sexual orientation* is the personal quality inclining persons to be romantically or physically attracted to persons of the same sex, opposite sex, both sexes, or neither sex. Sexual orientation is distinct from gender identity and gender expression.<sup>2</sup>

## **EPIDEMIOLOGY**

The prevalence of gender variant behavior and GD in childhood and adolescence are largely unknown. One study investigating gender variant behavior found that 2% to 4% of boys and 5% to 10% of girls behaved as the opposite sex from time to time.<sup>8,9</sup> Another study found that 22.8% of boys and 38.6% of girls exhibited 10 or more different “gender atypical behaviors.”<sup>9</sup>

As opposed to studies of gender variant behavior, other studies have attempted to investigate the prevalence of GD, a psychiatric diagnosis present in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*). Using such criteria in adults, the prevalence of GD ranges from 0.005% to 0.014% for assigned men and 0.002% to 0.003% for assigned women.<sup>4</sup> Such numbers are based on referrals to medical and surgical reassignment clinics and are likely modest underestimates. Sex differences are also noted in referrals to pediatric specialty clinics focused on gender variant youth. In children, sex ratios from natal boys to girls range from 2:1 to 4.5:1, whereas in adolescents the sex ratio is close to parity.<sup>4</sup>

In May 2013, the *DSM-5* replaced the term *gender identity disorder* (GID) previously found in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*) with the term *GD* after much complex debate. Many view the replacement as a paradigmatic shift toward depathologizing gender variant identity and behavior. The criteria for GD (with or without a disorder of sex development) are detailed in

the DSM-5. No studies have thus far used these newer criteria to determine the prevalence of GD in children and adolescents.

## GENDER IDENTITY DEVELOPMENT

Gender identity development begins around 2 to 3 years of age. At this age, children have a general sense of what is male or female and identify their own gender soon after. At 6 to 7 years of age, a child realizes that one's gender is likely to remain constant.<sup>10,11</sup>

The findings from studies investigating the trajectory of gender variant children who meet the criteria for GID or GD as an adult are inconsistent. The percentage of children initially diagnosed with GID who display persistence of GID range from 12% to 27%.<sup>12,13</sup> Such studies suggest most children who meet the criteria for GD do not have persistence of GD by the time they have initiated puberty. There is research to suggest, however, that this may be caused, in part, by an internalizing pressure to conform rather than a natural progression to non-gender variance.<sup>14,15</sup> Studies have also indicated that a significant percent of prepubertal gender-nonconforming youth eventually identify as gay at puberty and may not have been on a transgender trajectory in the first place, as discussed later. Studies have been carried out to identify predictors of persistence of GD. Factors that increase the likelihood of persistence of GD in adulthood include more gender-variant behavior in childhood, greater intensity of GD in childhood, and persistence of GD during adolescence. Qualitative research also found that cognitive statements were predictive of gender identity outcome (eg, *I am of the other gender.*) versus affective statements (eg, *I wish to be of the other gender.*).<sup>12,16–18</sup> There are also many individuals whose GD emerged in adolescence and adulthood.

Sexual orientation is often confused with gender identity. Just as cisgender individuals can have any sexual orientation, the same holds true for transgender individuals.

## ISSUES FACED BY GENDER VARIANT AND TRANSGENDER YOUTH AND THEIR FAMILIES

Although gender variance is not a disorder, many gender variant youth face a variety of issues that affect emotional and psychological wellbeing. Very often, gender variant youth experience levels of stigma, social ostracizing, and verbal and physical violence so great that their psychological well-being is compromised, potentially leading to depression and/or anxiety.<sup>19</sup> A recent study found that gender variance during childhood was a risk factor for experiencing childhood physical, psychological, and sexual abuse.<sup>20</sup> Moreover, gender nonconformity predicted an increased risk of lifetime post-traumatic stress disorder. A recent study investigating transgender-identified youth and younger adults found very high rates of suicidal ideation and suicide attempts.<sup>21,22</sup> These studies suggest that such rates increase as youth reach adulthood.

Gender variant children experience a higher level of social rejection from their peers, and this may increase through their years in school. A study examining transphobia in the education system found that 56% of gender variant students were called names, made fun of, or bullied compared with only 33% of their cisgender peers.<sup>23</sup> A Canadian survey found that 90% of trans youth heard transphobic comments daily or weekly from other students. Moreover, the rates of verbal and physical harassment of transgender students because of their gender expression were 74% and 37%, respectively.<sup>24</sup> More than three-quarters (78%) of transgender students indicated feeling unsafe in some way at school. For such reasons, the truancy rates were also much higher in lesbian, gay, bisexual, transgender, and questioning (LGBTQ) teens than non-LGTBQ teens.

Some parents continue to have intolerant views toward their child's gender expression. Studies have found that gender variant children have poorer relationships with their parents. Another study found that gender variant youth were more likely than nongender variant children to experience abuse and violence from their own family members.<sup>20</sup> A recent report from Ontario, Canada found greater satisfaction with life and self-esteem in transgender youth whose parents were "very supportive" versus those whose parents were "somewhat to not at all supportive."<sup>25</sup> At the same time, depression and suicide attempts were significantly decreased in transgender youth whose parents were supportive in comparison with those whose parents were not supportive.<sup>25</sup> Unfortunately, many youth feel unsafe at home and leave their homes, being rejected or forced out by their families because of their sexual orientation or gender identity.<sup>26</sup> LGBTQ youth are also overrepresented in youth accessing housing programs, such as shelters.

Just as gender variant youth may face rejection from their peers, some families may face rejection from friends and family members who do not accept their child's gender expression and behavior or the parent's decision to affirm their child's gender expression and behavior.<sup>14,27</sup> Although many are well intentioned, some parents may also have conflict with each other in deciding how to support their child. Lastly, various professionals and child welfare authorities may incorrectly seek reparative approaches and apprehend gender variant children from their parents out of concern that support of gender variant expression and behavior constitutes child abuse.

## EVOLVING APPROACH TO PREPUBERTAL GENDER VARIANT CHILDREN

In the 1960s, children with gender variance began to be viewed through a disease medical model whereby such behaviors, expression, and identity were pathologic and needed correction.<sup>28,29</sup> Such children and adolescents were subjected to psychological interventions to attempt to redirect behaviors, expression, and identity so they were consistent with social norms. The main goal of this reparative approach was to prevent children and adolescents from identifying as transgender. The inclusion of GID in children in the *DSM-IV* in 1980 was seen by many to further pathologize nonconforming gender identity and expression and reinforce gender stereotypes.

There has been a steady shift from the reparative approach in gender variance in childhood and adolescence toward an affirmative model that validates and encourages parents supporting their gender variant children and adolescents.<sup>5</sup> The major premises of the gender affirmative model are as follows: (1) Gender variations are not disorders. (2) Gender presentations are diverse and varied across cultures and, therefore, require our cultural sensitivity. (3) To the best of the authors' knowledge at present, gender involves an interweaving of biology, development and socialization, and culture and context, with all of these factors influencing an individual's gender self. (4) Gender may be fluid and is often not binary, both at a particular time and, if and when it changes within an individual, across time. (5) If there are mental health or behavioral concerns, it more often stems from negative cultural reactions (eg, transphobia) rather than from within the child. In this approach, the goals are not to pathologize the child or adolescent's behavior or identity but to destigmatize gender variance, promote the child's self-worth, allow for opportunities to access peer support, and enable parents and other community members to create safer spaces for such children in day care, schools, and other social environments. Although a gender-affirmative model encourages parents of gender variant children to follow their child's lead, parents should be careful to avoid imposing their own preferences on their children.

Many parents who favor the gender affirmative approach will support their child's social transition. A social transition consists of a change in social role to their affirmed gender and may include a change of name, clothing, appearance, and gender pronoun.<sup>30</sup> Parent and clinician reports suggest that children's happiness may vastly improve after socially transitioning.<sup>19,31</sup> Because the approach is completely reversible, proponents of social transition argue that children can be reminded that they may return to their natal gender at any time and another transition is possible.<sup>32</sup> Those who oppose social transitioning in prepubertal children argue that it may contribute to GD persistence and increase one's likelihood of identifying as transgender in adolescence.<sup>16,33</sup> The decision for a child to socially transition is not a simple one and should be made jointly among the child, the parents, and supportive professionals if available.

Many prepubertal gender variant children do not seek help from medical centers. In these cases, parents and the adults surrounding such gender variant children are able to create safe environments where these youth are able to explore their gender and are supported in living in a gender role that corresponds to their internal gender identity. Other prepubertal gender variant children and their parents may present to medical centers seeking guidance and resources. These parents may be either supportive or not supportive of their child's gender expression and/or identity. These children and their families may benefit from validation of their gender concerns and learning about puberty and the physical changes that may occur in the upcoming years. Meetings at earlier ages may also facilitate greater comfort with medical professionals, as many youth may not want their parents to address or monitor pubertal development. Lastly, medical clinics may coordinate or facilitate access to individual or group therapy to provide greater insight and understanding of their gender identity, screen and monitor for mental health concerns, and improve resiliency through peer support. Recent evidence indicates that youth in gender clinics incorporating an affirmative model have experienced significantly fewer behavioral problems.<sup>32</sup>

### APPROACH TO PUBERTAL YOUTH

Many gender variant youth may experience discomfort during puberty. For assigned females, the first sign of puberty is usually breast budding, whereas, for assigned males, the first sign is an increase in testicular volume. Gender variant youth who may identify as male may experience significant distress as breast development occurs. For many gender variant youth, such changes may cause much discomfort and, for some, even represent a traumatic experience. Increasing GD during puberty may also result in many negative psychosocial outcomes, such as depression, anxiety, social withdrawal, cutting and other self-harming behavior, suicidal ideation, suicide attempts, sexual behavioral risks, and substance use.

Youth with GD may not directly present with gender concerns. Instead, such youth may present with declining academic performance, behavioral problems at home and/or school, or drug use.<sup>34,35</sup> Other gender dysphoric youth may present with disordered eating, for example, male-affirmed natal females may restrict food intake to avoid a more feminine body type. Many youth may have been diagnosed and may be currently treated for depression, anxiety, and/or other mood disorders.

Even if a provider asks, many youth may deny gender concerns. Clinicians should, therefore, incorporate gender inclusive questions as part of their adolescent screen to facilitate future disclosure of such gender issues and concerns. A more gender-inclusive environment can also be created with the presence of LGBTQ posters, brochures, and/or other media and a visible nondiscrimination statement stating that

equal care will be provided to all patients, regardless of age, race, ethnicity, physical ability or attributes, religion, sexual identity, and gender identity.

If available, referrals should be made to a qualified mental health professional who specializes in gender concerns and who is also able to assess for the presence of other concurrent mental health issues. The following section addresses the use of puberty suppression and cross-sex hormones in pubertal youth with GD.

## PUBERTY SUPPRESSION

There are many reasons to suppress puberty in youth with GD. First and foremost, pubertal suppression allows youth to explore their gender identity and expression without having to worry about impending pubertal changes and undesired secondary sexual characteristics. Youth have more time to access appropriate resources and support, such as individual or group therapy. Depending on when youth share their gender concerns with their families, some parents may need more time to process and incorporate such information, find community support and resources for their child and themselves, and provides more time to make future decisions. Lastly, puberty suppression likely prevents surgical procedures that might otherwise be sought in adulthood in an attempt to undue physical characteristics of the undesired puberty.<sup>36</sup> Puberty suppression entails the use of medications for the purpose of suppressing endogenous hormones that lead to the development of secondary sexual characteristics during puberty, such as laryngeal prominence, increased muscle development, deepening voice in natal boys, and breast development and menstruation in natal girls.

## PUBERTY-SUPPRESSING MEDICATIONS

The initiation of puberty begins when gonadotropin-releasing hormone (GnRH) is secreted in a pulsatile manner from the hypothalamus and triggers the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These pituitary hormones act on the gonads to release sex steroids that either feminize or masculinize the body. GnRH agonists put puberty on hold by providing a nonpulsatile, continuous release of a GnRH analogue that desensitizes the GnRH receptors on the pituitary gland and inhibits the secretion of LH and FSH.<sup>37</sup> With markedly reduced LH and FSH, the ovaries and testes, in turn, reduce secretion of gonadal sex steroids leading, in a short period of time, to a prepubertal physiologic state. Pubertal suppression with GnRH agonists is completely reversible, as pubertal development will resume if and when the GnRH agonist is discontinued. **Table 1** lists different medical options for pubertal suppression. Some clinics will start with a monthly GnRH analogue formulation (such as leuprolide acetate depot) for several months before switching to a longer-acting formulation.

## TIMING OF PUBERTY SUPPRESSION

Pioneering studies from the Netherlands among adolescents with GD endorsed the use of GnRH agonists to induce pubertal suppression at Tanner stage II to III if those youth were at least 12 years of age.<sup>36</sup> The US Endocrine Society released their clinical practice guidelines in 2009.<sup>38</sup> These guidelines recommend that adolescents who maintain a strong and consistent cross-gender identification should be considered for GnRH agonists at Tanner stage II to III, independent of chronologic age. The World Professional Association for Transgender Health (WPATH) Standards of Care Version 7, released in 2011, also endorsed this approach.<sup>2</sup>

Type	Dose	Frequency
GnRH analogues: inhibition of the HPG axis (FTM and MTF)		
Leuprolide acetate	7.5 mg SC	Monthly
	22.5 mg SC	Every 3 mo
	40 mg SC	Every 4 mo
	45 mg SC	Every 6 mo
Leuprolide acetate	7.5 mg IM	Monthly
	11.25 mg IM	Every 3 mo
Histrelin SC implant (50 mg)	65 mcg/d	Every 12 mo (may have longer duration of action)
Alternative approaches		
Medroxyprogesterone acetate (FTM and MTF)	150 mg IM	Every 3 mo
Spirolactone (MTF)	100–300 mg/d oral	Twice daily
Finasteride (FTM)	2.5–5.0 mg/d oral	Once daily

*Abbreviations:* HPG, hypothalamic-pituitary-gonadal; IM, intramuscular; SC, subcutaneous.

There are several reasons why older transgender adolescents who have already developed undesirable secondary sexual characteristics may still benefit from GnRH agonists. First, the administration of puberty blockers is useful in preventing further progression of puberty and giving time to youth to consolidate their gender identity. Second, some parents may disagree with their child's desire for cross-sex hormones. The use of puberty blockers may allow for more time to reach consensus among youth, families, and their medical team. Third, the administration of GnRH agonists for both transgender male and female youth effectively ceases the production of gonadal sex steroids, thereby potentially lowering the doses of cross-sex hormones needed for future feminization or masculinization.

## MONITORING AND SIDE EFFECTS

Puberty suppression should be assessed both clinically and biochemically through measurements of LH, FSH, estradiol, and/or testosterone 1 to 3 months following administration of the puberty blocker. Recommendations for surveillance (as per the current Endocrine Society's clinical practice guidelines) during pubertal suppression are summarized in [Table 2](#). Utility, need, and the cost-effectiveness of several of these measures need to be studied and established.

Because of their agonist effects, GnRH analogues may temporarily increase pubertal signs in the first few weeks after initiation of GnRH agonist (eg, increased moodiness, increased breast development, hot flashes, and vaginal bleeding in natal females; increased aggressiveness in natal males). Such effects will reverse once secretion of LH, FSH, and the gonadal sex steroids are reduced. Other side effects may depend on the type of administration. If given intramuscularly, youth may experience pain and swelling at the injection site and a small chance of developing a sterile abscess. GnRH agonists are also commonly given by subcutaneous implants that can be effective for 1 to 2 years.

Many youth who are administered puberty blockers for GD may go on to use cross-sex hormones for phenotypic transition (see later discussion). Under such circumstances, fertility will likely be compromised, particularly if pubertal blockers are



	Every 3 mo	Yearly
Anthropometry	Height Weight Sitting height Tanner stages	—
Laboratory	LH FSH Estradiol Testosterone	Renal function Liver function Lipids Glucose Insulin HbA <sub>1c</sub>
Imaging	—	Bone density Bone age

*Abbreviation:* HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>.

*Data from* Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2009;94(9):3142.

initiated at the earliest stages of puberty. For such reasons, issues regarding future fertility should be addressed before consent and the commencement of pubertal blockers and potential subsequent use of cross-sex hormones. Gender dysphoric youth who have gone through significant pubertal maturation may choose to cryopreserve gametes through sperm banking or egg preservation before any hormonal treatments are initiated. Once testosterone is administered in transgender men, the ovaries will release fewer eggs. There are cases, however, in which transgender men (who have not had sex reassignment surgery) have interrupted their testosterone therapy to allow their ovarian function to recover and some have even chosen to carry pregnancy. Estrogen administration decreases sperm count, although it may increase if estrogen therapy is interrupted.

## PHYSIOLOGIC AND MEDICAL OUTCOMES

A principal concern of GnRH agonist treatment is decreased bone mineral density. The lack of endogenous sex steroid hormones in youth administered GnRH agonists results in slower accrual of bone mineral density compared with those whose puberty is not blocked. The bone density of youth on puberty blockers remained unchanged during GnRH agonist administration.<sup>36</sup> When cross-sex hormones were administered, however, bone density significantly increased and reached age-appropriate levels in both affirmed males and females.<sup>36</sup> The same study also found that the percentage of fat mass increased and stabilized and lean body mass decreased and stabilized over the 2-year follow-up. There were also no changes in lipid or carbohydrate metabolism.<sup>36</sup>

## PSYCHOLOGICAL AND MENTAL HEALTH OUTCOMES

There have been few studies investigating the mental health effects of puberty blockers. One Dutch study measured psychological outcomes before and during puberty suppression in 70 youth diagnosed with GID according to *DSM-IV* criteria.<sup>39</sup> After pubertal suppression, most behavioral and emotional problems and depressive

symptoms decreased and general functioning improved significantly; however, feelings of anxiety and anger persisted, and GD did not change. Of note, no adolescent discontinued puberty suppression, and all eventually started cross-sex hormone treatment.<sup>39</sup>

### CROSS-SEX HORMONES

Many youth who identify as transgender in adolescence will continue to identify as transgender into adulthood and would benefit from cross-sex hormones during adolescence. Cross-sex hormones allow the youth to either physically masculinize or feminize their body in alignment with their affirmed gender. Ideally a multidisciplinary team composed of both mental and medical professionals will help youth and their families.<sup>2</sup>

The cornerstone of hormonal treatment of FTM transgender adolescents who wish to undergo physical transition is testosterone. As per the Endocrine Society's clinical practice guidelines, puberty would have been previously suppressed at Tanner stage II (or later depending on when the youth sought medical care) with GnRH agonists, with testosterone subsequently administered to induce masculinization.<sup>38</sup> Desired effects of testosterone therapy include deepened voice, facial hair, cessation of regular menses, increased muscle mass, and fat distribution leading to a more masculine body habitus. Although breast tissue may lose glandularity, the amount of breast tissue will not decrease. Voice changes, clitoral growth, and fat redistribution are irreversible changes. Coarsening of body and facial hair begins soon after initiation of testosterone but will take several years to reach full growth. Clitoral growth usually begins in the first few months of therapy.

Testosterone is administered by either injectable or transdermal preparations (Table 3). Injectable intramuscular formulations of testosterone cypionate or enanthate are most commonly used, although subcutaneous routes may also be used. The advantage of transdermal preparations is the relatively steady state of

Medication	Full Adult Dosage
<b>MTF Persons</b>	
Estrogens 17-β estradiol	
17-β estradiol (oral)	2–6 mg daily
17-β estradiol (transdermal)	0.1–0.4 mg twice weekly
Estradiol cypionate (parenteral)	5–20 mg IM every 2 wk
Estradiol valerate	2–10 mg IM every wk
<b>FTM Persons</b>	
Testosterone	
Testosterone cypionate or enanthate (parenteral: IM or SC)	100–200 mg every 2 wk, 50–100 mg every wk
1% Gel (transdermal)	2.5–10.0 mg daily
Patch (transdermal)	2.5–7.5 mg daily

Note that induction of puberty with cross-sex hormones will start at one-quarter of adult dose and increased every 6 months until adult dose is reached. Induction of puberty may be administered over a shorter or longer period of time depending on the clinical situation.

*Abbreviations:* IM, intramuscular; SC, subcutaneous.

testosterone, as opposed to the fluctuations with injectables, although it may take longer for clinical changes to take place in transdermal preparations. Oral versions of testosterone are available but not in North America.

The cornerstone of cross-sex hormonal treatment for MTF transgender adolescents is estrogen with an antiandrogen. If used as a monotherapy, high doses of estrogen would be needed to adequately suppress androgens. Thus, estrogen is usually administered concurrently with another medication that lowers the levels of androgens or blocks their activity. The reduction of androgen action results in decreasing facial and body hair, whereas estrogen increases female secondary sex characteristics, such as breast and hip development. GnRH agonists or other puberty blockers decrease androgen levels or action and allow for lower doses of estrogen to be used. For youth who do not have access to GnRH agonists, antiandrogens, such as spironolactone or finasteride, are commonly prescribed.

The most common regimens for estrogen include oral estradiol, transdermal estrogens, and injectable estrogens (see [Table 3](#)). No studies have confirmed that one form of estrogen results in more desired physical effects. 17- $\beta$  Estradiol is the preferred form of estrogen used for hormonal transition; it can be administered in oral or transdermal formulations, and serum levels can be monitored. Because transdermal formulations avoid first pass through the liver, they are thought to have fewer hepatic side effects. Injectable estrogens (in the form of estradiol valerate or cypionate) are also not subject to hepatic first pass metabolism and have the benefit of weekly or biweekly administration. Oral 17- $\beta$  estradiol can also be given sublingually.

## EVALUATING READINESS

Before the administration of cross-sex hormones, mental health professionals may reevaluate GD, screen for concurrent mental health disorders, provide individual psychotherapy for youth and counseling for families, and connect the youth and families with community resources to improve resiliency. Both mental and medical health professionals can also give information to adolescents about gender transition and cross-sex hormone therapy.

Both WPATH and the Endocrine Society advocate for a real-life experience or test (RLE or RLT, respectively) before cross-sex hormones. RLE is a period of time in which transgender individuals live full-time in their affirmed gender. The purpose of RLE is to help youth confirm their affirmed gender and evaluate their ability to function as a member of that gender before initiating cross-sex hormones. Some providers do not require RLE and may follow an individualized plan for transitioning as many youth may feel more comfortable in socially transitioning when cross-sex hormones have been started.

Fertility counseling, as noted earlier, should be rediscussed with the adolescent and family before cross-sex hormone therapy.<sup>2</sup>

## MEDICAL EVALUATION

Before cross-sex hormone administration, the medical professional will screen for contraindications and other medical conditions that could be exacerbated by cross-sex hormones.<sup>38</sup> Contraindications to cross-sex hormone therapy may include ischemic cardiovascular disease, cerebrovascular disease, history of deep vein thrombosis or pulmonary embolus, marked hypertriglyceridemia, hyperprolactinemia, estrogen-dependent cancer, uncontrolled high blood pressure, pregnancy, or psychiatric conditions that limit the ability to provide informed consent. Such conditions will require referral to subspecialists for further evaluation and medical clearance. Other

precautions include other cardiac disease, family history of abnormal clotting, smoking status, history of benign intracranial hypertension, metabolic syndrome, refractory migraine or focal migraine, seizure disorder, strong family of breast cancer, and/or family history of porphyria.

A physical examination should be performed including height, weight, and blood pressure. Genital and breast examinations for Tanner staging should be performed before the administration of cross-sex hormones but only after rapport has been developed between youth and the professional. Recommendations for laboratory surveillance based on the Endocrine Society's current clinical practice guidelines are summarized in **Boxes 1** and **2**.

Routine medical care and screening should continue to take place at follow-up visits and annual physical examinations if youth do not have a primary care provider. Even then, some transgender youth may feel more comfortable with the medical professional providing transgender care. For such reasons, medical care professionals should provide holistic comprehensive care that also includes sexual and reproductive care. Regardless of their affirmed gender, persons with a cervix and uterus should be provided gynecologic care. Screening for sexual and blood-borne infections, such as human immunodeficiency virus, gonorrhea, chlamydia, syphilis, and laboratory work for hepatitis A, B, and C, should be performed depending on risk factors. The use of tobacco and other substances should be addressed. Medical professionals should be able to use the HEADSS assessment (home, education, activities, drugs, sex, and suicide) to screen for other risk factors and tailor their care accordingly.

### TIMING OF CROSS-SEX HORMONES

According to the Endocrine Society's clinical practice guidelines, transgender adolescents should have their endogenous puberty suppressed until 16 years of age, after which cross-sex hormones may be given. Delay of cross-sex hormone therapy may unnecessarily lead to negative mental health outcomes.<sup>3</sup> In some cases, a thoughtful decision among the youth, families, and care providers may suggest earlier administration of cross-sex hormones. With the use of puberty blockers, more youth without

#### Box 1

##### Monitoring of MTF persons on cross-sex hormone therapy

1. Evaluate patients every 2 to 3 months to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Monitor complete blood count, liver function, renal function, lipids, glucose, insulin, and hemoglobin A<sub>1c</sub> at the initial and annual visit.
3. Measure serum LH, FSH, testosterone, and estradiol every 3 months.
  - a. Serum testosterone levels should not exceed the peak physiologic range for young healthy females.
  - b. Serum estradiol should not exceed the peak physiologic range for young healthy females.
  - c. Doses of estrogen should be adjusted according to the serum levels of estradiol.
4. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 2 to 3 months initially in the first year.
5. Monitor bone density and bone age annually.

**Box 2****Monitoring of FTM persons on cross-sex hormone therapy**

1. Evaluate patients every 2 to 3 months to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Monitor complete blood count, liver function, renal function, lipids, glucose, insulin, and hemoglobin A<sub>1c</sub> at the initial and annual visit.
3. Measure serum testosterone every 2 to 3 months until levels are in the normal physiologic male range:
  - a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. If the level is greater than 700 ng/dL or less than 350 ng/dL, adjust the dose accordingly.
  - b. For transdermal testosterone, the testosterone level can be measured at any time after 1 week.
4. Monitor bone density and bone age annually.

exposure to cross-sex hormones may be at risk for bone mineral density loss; earlier administration of cross-sex hormones may decrease this risk.

Induction of puberty with cross-sex hormones (ie, testosterone or estradiol) may start with quarter doses of the adult dose and increased every 6 months until the adult dose is reached after 2 years. If phenotypic transition is started after endogenous puberty has been completed, sex steroids are typically increased to full adult doses more rapidly.

### **SIDE EFFECTS OF CROSS-SEX HORMONES**

Unwanted side effects of testosterone include increased weight, acne, body odor, mood changes, and male-pattern balding as well as more serious side effects, such as increased risk for coronary artery disease and altered hematologic and lipid profiles that match genetic males. For such reasons, medical professionals should suggest affirmed males maintain an exercise program to avoid excess weight gain. Moreover, attempts to increase muscle mass through weightlifting should be done slowly as there has been evidence of tendon rupture with testosterone administration. Mood changes may occur with testosterone, with many affirmed males being aware of when testosterone levels have decreased between doses.

The negative side effects of estrogen therapy have been illustrated in both postmenopausal females and MTF individuals. The Women's Health Initiative, a study investigating the effect of estrogen in combination with a progestin on a large cohort of menopausal women, showed increased incidence of breast cancer, heart disease, and stroke.<sup>40</sup> Synthetic estrogen (eg, ethinyl estradiol), as compared with 17- $\beta$  estradiol, is associated with higher rates of deep vein thrombosis and death from cardiovascular causes and should not be used.<sup>41,42</sup>

### **PROGESTERONE**

Anecdotally, some individuals and clinicians think the administration of progesterone leads to better areolar growth, more natural appearance, and/or more breastlike tissue. The negative findings from the Women's Health Initiative have resulted in many protocols preferring estrogen-only therapy. Common side effects associated with progesterone are depression, weight gain, and edema.

## CROSS-SEX HORMONES AND GENDER-AFFIRMING SURGERY

A recent study following 55 transgender youth found the use of puberty suppression, cross-sex hormones, and gender reassignment surgery alleviated GD and steadily improved psychological functioning.<sup>43</sup> Improvements in psychological functioning were positively correlated with postsurgical subjective well-being. Moreover, the well-being of these young adults was similar to or better than same-age young adults from the general population.<sup>43</sup>

Surgical options for FTM young adults may include mastectomy and male chest contouring, whereas MTF young adults may elect for breast augmentation; such surgeries are also known as *top surgeries*. FTM young adults may choose to have a hysterectomy and/or oophorectomy, and FTM or MTF adults may also consider genital reconstruction; such surgeries are also known as *bottom surgeries*. Current guidelines endorse the potential for sex-reassignment surgery at 18 years of age.

## SUMMARY

Gender nonconforming and transgender youth are seeking medical care at younger ages, some even before the onset of puberty. Pediatricians and other primary care physicians are often the first professionals who encounter such youth and, therefore, have a responsibility to create inclusive spaces to raise potential issues concerning gender and educate these youth and their families that a gender variant identity is not considered pathologic but, rather, may be viewed as a normal variant of human development. Medical professionals should understand the rationale for both social and medical transitioning and the use of puberty suppression and cross-sex hormones to address GD. The best current evidence suggests that mental health comorbidities in youth with GD significantly diminish or resolve when such youth are subject to a gender-affirming model of care. Prompt referrals by medical professionals should be made to an interdisciplinary team that understands the unique challenges faced by transgender youth and their families. If such a clinic is not available, there are also many medical professionals who are able to provide care by comanaging with a specialized clinic. In doing so, medical professionals are able to advocate for the mental and physical health of this marginalized population and facilitate this much-needed access to care.

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