19 Care of Transgender/Gender Nonconforming Youth

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CHAPTER OUTLINE

INTRODUCTION

Concurrent with increasing public awareness of individuals whose gender identity is not aligned with their physical sex characteristics, there has been an increasing number of gender nonconforming/transgender youth seeking medical services to enable the development of physical characteristics consistent with their experienced gender. In eligible individuals, current clinical practice guidelines endorse use of agents to block endogenous puberty at Tanner stage 2 development with subsequent use of gender-affirming sex hormones, and are based on longitudinal studies demonstrating that youth first identified as gender dysphoric in childhood and who continue to meet mental health criteria for gender dysphoria (GD)/gender incongruence (GI) at early puberty are likely to be transgender as adults. Limited outcomes data support current practice and long-term studies are necessary to optimize care. This chapter reviews definitions relevant to gender nonconforming/transgender youth, epidemiology, developmental trajectories of gender, evidence supporting a role for biology in gender identity development, mental health comorbidities associated with GD, current treatment models, barriers to care, and priorities for research.

DEFINITIONS AND EPIDEMIOLOGY

According to the *Merriam-Webster's Medical Dictionary*, sex and gender have distinct meanings. Sex refers to "either of two major forms of individuals that occur in many species and that are distinguished respectively as female or male, especially on the basis of their reproductive organs and structures." In contrast, gender refers to the "behavioral, cultural, or psychological traits typically associated with one sex." Gender itself is then subdivided into gender identity and gender role/behavior. Gender identity is a person's internal sense of being male or female, whereas gender role is the expression of masculinity or femininity.[1] There has been increasing recognition that gender identity exists on a spectrum and that some individuals identify as nonbinary.[2,3] Sexual orientation is one's sexual attraction toward partners of the opposite sex/gender (heterosexual), same sex/gender (homosexual), or both (bisexual). Gender identity does not predict sexual orientation. A person of any gender may have any sexual orientation.

"Gender Dysphoria," listed in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) *V* refers to clinically significant distress of at least 6 months, duration, related to the incongruence between one's affirmed or experienced gender and one's "assigned (or natal) gender" (gender incongruence).[4] This term replaces *gender identity disorder* (GID), which was included in the earlier DSM IV. Replacing the term "disorder" with "dysphoria" underscores the concept that a transgender identity, in and of itself, is no longer considered pathological, and focuses clinical concern on the distress that an individual with GI may experience. A summary of terms used in this chapter is detailed in Box 19.1.

A 2017 report from the Williams Institute of the University of California Los Angeles School of Law, informed by state level population-based surveys, indicated that 0.6% of US adults (25–64 years) and 0.7% of adolescents and young adults (13–24 years) identify as transgender.[5] A population-based study of self-reported gender identity in 80,929 Minnesota high school students reported a prevalence of 2.7% gender nonconforming or transgender.[6] Transgender prevalence estimates ranging from 0.5% to 1.3% of birth-assigned males and 0.4% to 1.2% of birth-assigned females have been reported in a recent international review, representing an estimate of 25 million transgender people worldwide.[7] In recent years, there has been a striking inversion in the sex ratio of adolescents seeking services for GD, with a predominance of birth-assigned females.[8]

BIOLOGICAL DETERMINANTS OF GENDER IDENTITY

Studies from several biomedical disciplines—genetics, endocrinology, and neurology—support the concept that there are biological underpinnings to gender identity development. Results of these studies support the concept that gender identity is not simply a psychosocial construct but likely reflects a complex interplay of biological, environmental, and cultural factors.[9]

With respect to genetics and gender identity, a recent study reports heritability estimates for gender identity in the range of 30% to 60%.[10] A study supporting a role for genetic factors in gender identity outcome in transgender individuals

BOX 19.1 Definitions of Terms Used in This Chapter

Biological sex, biological male or female: These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (e.g., a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided.

Cisgender: This means not transgender. An alternative way to describe individuals who are not transgender is "nontransgender people."

Gender-affirming (hormone) treatment: See "gender reassignment"

Gender dysphoria: This is the distress and unease experienced if gender identity and designated gender are not completely congruent. In 2013 the American Psychiatric Association released the fifth edition of the DSM-5, which replaced "gender identity disorder" with "gender dysphoria" and changed the criteria for diagnosis.

Gender expression: This refers to external manifestations of gender, expressed through one's name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender.

Gender identity/experienced gender: This refers to one's internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see later), gender identity is not visible to others.

Gender identity disorder: This is the term used for GD/gender incongruence in previous versions of DSM (see "gender dysphoria"). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using "gender incongruence of childhood."

Gender incongruence: This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity–related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment.

Gender variance: See "gender incongruence"

Gender reassignment: This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called *gender-confirming* or *gender-affirming treatment*.

Gender-reassignment surgery (gender-confirming/gender-affirming surgery): These terms refer only to the surgical part of gender confirming/gender-affirming treatment.

Gender role: This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women.

Sex designated at birth: This refers to sex assigned at birth, usually based on genital anatomy.

Sex: This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.

Sexual orientation: This term describes an individual's enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer.

Transgender: This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment.

Transgender male (also: trans man, female-to-male, transgender male): This refers to individuals assigned female at birth but who identify and live as men.

Transgender woman (also: trans woman, male-to female, transgender female): This refers to individuals assigned male at birth but who identify and live as women.

Transition: This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.

Transsexual: This is an older term that originated in the medical and psychologic communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.

(From Hembree, W.C. et al. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrine Metab, 102 (11), 1–35; by permission of the Endocrine Society.)

demonstrated a 39.1% concordance for GID (based on DSM-IV criteria) in 23 pairs of monozygotic twins, with no concordance for GID in 21 same-sex dizygotic female and male twin pairs or in seven opposite sex twin pairs.[11] Although a number of investigators have sought to identify polymorphisms in specific candidate genes that may be more prevalent in transgender versus nontransgender controls, such studies have been inconsistent and lacking strong statistical significance.[12–15]

With respect to hormonal influences on gender identity, it should be noted that most transgender individuals do not have a disorder/difference of sex development (DSD) or any obvious abnormality in sex steroid production or response. However, studies in individuals with a variety of DSDs have informed our understanding of the role that hormones (prenatal and early postnatal androgens, in particular) may play in gender identity development. For example, in studies of 46 XX individuals reared female, with virilizing congenital adrenal hyperplasia (CAH) caused by mutations in the *CYP21A2* gene, there is a greater degree of a transgender identity outcome (female-to-male) than what would be expected in the general population.[16–18] In a meta-analysis of 250 adults with this condition, raised female, although nearly 95% accepted a female gender identity, 5.2% reported either a male gender identity or GD.[16] By comparison, the prevalence of a transgender identity in adults in recent population estimates in the United States is 0.5% to 0.7%.[5] A separate study of adult 46 XX individuals with classical 21-hydroxylase deficiency demonstrated a relationship between severity of disease and gender identity outcome. Of 42 patients with the salt-wasting form, three (7.1%) either had GD or a male gender identity; no GD was seen in less severely affected individuals.[17] A study in 46 XX youth with 21-hydroxylase deficiency (salt-wasting or simple virilizing) found that 12.8% demonstrated cross-gender identification.[18] In a recent cross-sectional study from Europe, of 221 individuals with 46 XX CAH, 28 were noted to have experienced a "gender change"; in 25, this was reported to have occurred prepubertally; in one postpubertally; and in two the timing of "gender change" was unknown.[19] The 25 individuals in this study described as having a prepubertal "gender change," were, in fact, individuals who underwent feminizing genital surgery in the newborn period (before one's gender identity is known); furthermore, the one individual reported in this study to have a gender change postpubertally was, in fact, a 46 XX individual with a male gender identity who had undergone masculinizing genital surgery (personal communication with Dr. Baudewijntje P.C. Kreukels, VU University Medical Center, Amsterdam). The

report of this cross-sectional European study did not indicate the number of 46 XX CAH individuals reared female that actually developed either gender dysphonia or a male gender identity (personal communication with B.P.C. Kreukels). It is noteworthy that in 46 XX individuals with virilizing CAH from 21-hydroxylase deficiency, prenatal androgens are more likely to affect gender expression/behavior and sexual orientation than gender identity.[20,21] A role for prenatal/early postnatal androgens in gender identity development is also supported by studies in a variety of other hormonal and nonhormonal DSDs.[22]

With respect to brain and gender identity, numerous studies in transgender adults, carried out before treatment with gender-affirming sex hormones, indicate that some sexually dimorphic brain structures are more closely aligned with gender identity than with physical sex characteristics.[23,24] A gray matter study in gender dysphoric youth has shown a similar trend.[25] In addition, functional studies (e.g., analysis of hypothalamic blood flow in response to smelling odorous compounds and brain-imaging studies carried out during mental rotation tasks) demonstrate that patterns typically observed to be sexually dimorphic were more closely aligned with gender identity than with physical sex characteristics, even before treatment with gender-affirming sex hormones, in both transgender adolescents and adults.[26–28]

EMERGENCE AND DEVELOPMENTAL TRAJECTORIES OF GENDER

To identify when a child is exhibiting gender nonconforming behavior, it is necessary to understand what gender behaviors are typical at various developmental stages and how these behaviors may change over time.[29] It is also important to appreciate how some expressions of gender vary in different environments.[30,31] Recent reports of higher estimated prevalence rates of GD among youth in Australasia, Western Europe, and North America[32–36] may reflect a greater willingness of people to seek treatment, as a result increased access to multidisciplinary gender clinics, as well as societal changes in attitudes about gender diversity.

Infancy

Although sex differentiation begins during early fetal development, gender differences from birth throughout infancy are limited to gross movement and emotional expressivity. For example, boys produce fewer tongue movements and weaker suckling than girls during early life;[37,38] however, infant boys spend more time awake and produce greater movement of their trunk and limbs.[39] Finally, infant girls smile more than boys and are less likely to exhibit angry facial expressions.[39,40] Additional differences in behavior between boys and girls either do not yet exist, or are unable to be detected with current technology at this very young time.

Early Childhood

An important milestone that starts to occur between 18 months and the second year of life is the emergence of gender identity.[29,41] This occurs around the time language skills develop so that young children increasingly use gender labels (e.g., girl, boy, woman, man) as their speech evolves.[42] Boys begin to exhibit preferences for gender-typed toys, such as trucks by 2 years of age,[43,44] and by the third year of life children prefer same-sex peers and this preference intensifies over time.[45,46] Interestingly, young children who understand and use gender labels are more likely to prefer gender-typed toys,[47] in support of the self-socialization theory of gender development that posits children socialize themselves into gender categories.[29]

Children referred for treatment of GD prefer cross-sex toys, activities,[48] and playmates[49] more than their gender conforming peers and siblings. These differences in early childhood are not surprising, as the majority of transgender teens and adults recall that the onset of their GD occurred before puberty.[50,51] Unknown at this time, is whether children with GD use gender labels differently during early childhood or experience the emergence of gender identity differently from gender conforming peers, during the first 2 years of life. Also unknown at this time is whether or not preferences for same- or cross-sex toys, activities, and playmates are stable throughout childhood for either gender conforming or nonconforming children.

Adolescence

Fewer studies of gender development have been conducted in adolescents compared with younger children. The theory of gender intensification suggests that adolescents experience increased pressure to conform to societal expectations of masculinity and femininity, and this pressure acts to further strengthen their gender identity.[52] Although some studies support this theory, others do not.[53] Some adolescents who experienced GD as younger children no longer do so as adolescents (desisters), whereas others continue to experience GD, as they mature (persisters).[54] Thus for some people, gender identity evolves during adolescence in ways not predicted from earlier childhood. As noted earlier, the stability of gender from early childhood through later life has not been well studied. However, some investigators have attempted to identify factors that predict GD "persisters" versus "desisters," as detailed in the section on "Natural History of Gender Dysphoria," later. One of the recommended areas of future research in youth with GD is to identify additional predictors of GD persistence.[55,56]

MENTAL HEALTH COMORBIDITIES ASSOCIATED WITH GENDER DYSPHORIA

Gender nonconforming people have historically presented with psychological symptoms, such as anxiety, depression, and suicidality and self-harm at rates much higher than the general population.[34,57] Until recently, most studies of psychiatric comorbidities associated with GD were conducted in transgender adults who had limited family and peer support, as well as poor access to gender-affirming treatment and counseling.[58] As research on mental health of gender nonconforming youth broadens to include those who are both supported during their social transition and who receive multidisciplinary care,[3] comorbidities are fewer. Nonetheless, behavioral and emotional problems for gender nonconforming youth in the community who are, and are not, referred for treatment are increased.[59] As these youth continue to be followed, evidence will build to address long-term safety and efficacy of multidisciplinary treatment on their health and wellbeing.

Internalizing Disorders and Gender Dysphoria

Data from nationally representative samples of students,[60] and also clinic-based studies of youth seeking medical treatment for GD[34,51,61,62] reveal marked increases in depression among transgender youth compared with their cisgender counterparts. Clinically significant anxiety is also common.[58] In contrast, children with GD who socially transition with the support of their family exhibit levels of depression that are no different, and anxiety levels that are only mildly elevated, from age-matched population norms.[63] Additional evidence that support of others is important to maintain good mental health for gender nonconforming youth are associations between poor peer relations (i.e., gets teased, not liked by others) and

emotional problems.[64] Thus internalizing disorders, such as depression and anxiety are not necessarily a comorbidity of GD per se. Rather, psychological distress is likely caused by social ostracism and maltreatment by others.

Suicidality and Nonlethal Self-Harm

Transgender youth are more likely to think about suicide, attempt suicide, and inflict nonlethal self-harm (i.e., cutting, burning, or hitting) than cisgender youth.[58,62] Self-harm in youth with GD is most common among assigned females and those impacted by psychologic symptoms, such as anxiety and depression.[65] A report from Ontario, Canada, found that transgender adolescents and young adults were more likely to have greater self-esteem and life satisfaction, as well as decreased depression, suicidal ideation, and suicide attempts if their parents were supportive of their gender identity, in comparison to those individuals whose parents were "somewhat to not at all supportive."[66] Further investigations of the impact of social support and of gender-affirming multidisciplinary care warrant greater resources and effort, as studies of transgender youth continue to expand in pediatric medicine.

Eating Disorders

In the largest survey study of transgender youth to date, a higher rate of eating disorders was observed compared with cisgender women.[67] Furthermore, assigned females are at particular risk.[68] A smaller study reported high rates of overweight and obesity among transgender youth.[51] For these youth, having too little or too much body fat may be a way to hide undesired physical characteristics. Thus it is recommended to screen for eating disorders in gender nonconforming children and adolescents.[68]

Traits of Autism Spectrum Disorder

There is growing evidence from parent and teacher ratings, as well as review of medical records, that traits of autism spectrum disorder (ASD) and GD cooccur in some youth and adults.[36,69–72] Although ASD is more prevalent in boys than in girls, in gender conforming individuals,[73] the association between ASD and GD is similar for both natal males and females.[70,72] Although there are no clinical guidelines for the delivery of care to children and adolescents with cooccurring GD and ASD traits, initial consensus guidelines for assessment and care are available.[74]

NATURAL HISTORY OF GENDER DYSPHORIA

Information about the natural history of GD is limited. This is in part because medical treatment has been inaccessible to many because of expense and/or stigmatization surrounding this condition. In addition, much of what is known about GD focuses on adults. Thus basic understanding about the natural history of GD in youth is only now being elucidated. Here we review what is currently understood about remission versus persistence of GD in children and adolescents, and also the impact of family support and medical treatment on mental health status of young people whose gender identity is incongruent with their natal sex.

Desistence Versus Persistence

Historically, the majority of children who presented for treatment of GD experienced remission (desisters) by late childhood or early adolescence.[54] Studies of desisters, and also those who continue to experience GD into later adolescence and adulthood (persisters), are beginning to reveal factors that distinguish between these groups. Specifically, natal females, those with more intense GD in childhood and adolescence, and those who experience greater dissatisfaction with their primary and secondary sex characteristics are more likely to be persisters. Persisters are also more likely to be sexually attracted to members of their natal sex.[53] In addition, when asked if they are a boy or a girl, children whose GD persists are more likely to report that they believe themselves to be the sex opposite their natal sex, whereas desisters are more likely to report that they wished they were the other sex.[54] The possibility of remission of GD in later childhood or early adolescence, coupled with the ability to use the onset of puberty, as a diagnostic tool for persistence of GD, motivate recommendations for delaying pubertal suppression (see "Medical Treatment," later) until after transyouth enter the first stages of puberty (Tanner stages 2–3).[3,75]

Impact of Family Support and Treatment

Among prepubertal children with GD who have the support of their families and who have socially transitioned, depression is no different from population averages and anxiety is only mildly elevated.[63] Later in development, puberty suppression is associated with improved psychosocial functioning in adolescents whose GD persists.[76] Among older adolescents and young adults with GD who received puberty suppression, cross-sex hormone treatment, and in some cases gender reassignment surgery—psychological function was comparable with the general population.[64] In all of these studies, mental health support was part of multidisciplinary care delivered by experienced healthcare teams. Thus many of the mental health comorbidities of GD discussed earlier are ameliorated when family support is coupled with access to multidisciplinary care for children and adolescents of various developmental stages.

ROLE OF MENTAL HEALTH IN MULTIDISCIPLINARY CARE

The Standards of Care of the World Professional Association for Transgender Health (WPATH) (WPATH, 7th Version) and the Endocrine Society Clinical Practice Guideline for Gender-Dysphoric/Gender-Incongruent Persons[2,3] promote several approaches for the psychological support of youth with GD and their families. It is recommended that youth receive mental healthcare before, during, and after their social and medical transition. Roles for mental healthcare providers include[1]: the ability to assess GD/GI in children and adolescents and appropriately use the DSM and International Classification of Diseases for diagnosing these conditions[2]; provide counseling and supportive psychotherapy to youth and their families[3]; diagnose and treat other psychiatric conditions apart from GD[4]; refer for pubertal suppression, cross-sex hormone therapy; and gender reassignment surgery when appropriate, including assessment of comprehension of the risks and benefits of these treatments[5]; refer patients and families to peer support; and[6] educate and advocate on behalf of patients and their families.

Both the WPATH and the Endocrine Society outline competency requirements for mental health professionals who provide services to children and adolescents with GD. These include[1] training in child/adolescent gender development (including gender nonconforming identities and roles) and child/adolescent psychopathology, with a minimum of a Master's degree in clinical psychology from an accredited program and relevant licensing,[2] and supervised training and competency in psychotherapy or counseling, including treatment of GD, as well as continued education in these areas.[2,3]

Social Transition

Some children benefit from a social (nonmedical) transition to help determine if their GD will remit or persist. Reversible changes that allow a child to live according to the gender they identify with at home and school (such as hair length, clothing, and name change) are associated with improved mental health among this group.[63] Children who undergo social transition are less likely to experience remission of their GD,[53] and it is unclear if this is because only those with stronger GD initiate social transition, or if social transition itself impacts the evolution of GD in youth. Because current understanding of the effects of childhood social transition on GD is limited, mental health professionals may work with families to determine if this option is best for their child. For example, social transition may be considered exploratory (as opposed to finite) and may be first attempted while families vacation or in the privacy of the home.[2]

BOX 19.2 Baseline and Follow-Up Protocol During Suppression of Puberty

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

Every 6–12 mo
- Laboratory: LH, FSH, E2/T, 25OH vitamin D

Every 1–2 y
- Bone density using DEXA
- Bone age on x-ray of the left hand (if clinically indicated)

DEXA, Dual-energy x-ray absorptiometry; *E2*, estradiol; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *T*, testosterone.
(From Hembree, W.C. et al. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrine Metab, 102 (11), 1–35; by permission of the Endocrine Society.)

MEDICAL TREATMENT

Current Treatment Models

GD that either emerges or worsens with the onset of physical puberty is highly predictive of a transgender identity during adulthood.[77] This observation is central to the rationale for medical intervention in eligible transgender adolescents. Medical care of transgender youth has been primarily informed by Clinical Practice Guidelines from the Endocrine Society[3] and cosponsoring organizations and by Standards of Care from WPATH.[2] These documents endorse the use of gonadotropin-releasing hormone (GnRH) agonists at Tanner Stage 2 of pubertal development (testicular volume $\geq$4 mL for assigned males at birth or initial stages of breast budding for assigned females at birth) in adolescents who meet the criteria for GD (optimally determined by a qualified mental health gender specialist) that has either emerged or worsened with the onset of puberty. Additional criteria for initiation of pubertal suppression with GnRH agonists include the following: the adolescent has requested treatment and has provided informed assent and the parents or legal guardians have provided informed consent, and any coexisting medical or psychosocial concerns that could interfere with treatment have been addressed.[3] GnRH agonists should not be used in prepubertal gender dysphoric children to block the initiation of puberty.[3]

Considered fully reversible, GnRH agonists, by pausing puberty, provide additional time for gender identity exploration, without the pressure of continued pubertal progression, and prevent irreversible development of secondary sex characteristics associated with the puberty that is not aligned with the person's affirmed gender identity.[3] Such undesired physical changes include breast development, female body habitus, and potentially short stature in assigned females at birth, and Adam's apple, lowered voice, male bone configuration, and potentially tall stature in assigned males at birth.[22] A protocol for baseline and follow-up monitoring of physical examination, and laboratory testing during pubertal suppression with GnRH agonists is outlined in Box 19.2. GnRH agonists, while the preferred option for pubertal suppression, are costly and often inaccessible. Alternatives for pubertal suppression include depot and oral progestins.[3]

Adolescents who have undergone pubertal suppression at early puberty and continue to meet the criteria for GD may request phenotypic transition with sex steroids. Age-specific recommendations for initiation of gender-affirming sex steroids in gender dysphoric adolescents are not delineated in the WPATH Standards of Care seventh version.[2] The most recent version of the Endocrine Society Clinical Practice Guidelines recommends initiating treatment "using a gradually increasing dose schedule after a multidisciplinary team of medical and mental health professionals has confirmed the presence of GD/GI, and sufficient mental health capacity to give informed consent, which most individuals have by age 16 years."[3] In addition, the most recent version of the Endocrine Society Clinical Practice Guidelines acknowledges that there may be compelling reasons to initiate sex hormone treatment before 16 years of age in some gender dysphoric adolescents. In gender dysphoric adolescents whose puberty is blocked at Tanner stage 2, delaying gender-affirming sex hormone treatment until 16 years of age could be detrimental to bone health; furthermore, keeping someone suspended in a prepubertal state until the age of 16 years could have detrimental mental health effects.[3] A protocol for induction of puberty in gender dysphoric adolescents, and recommendations for baseline and follow-up physical examination and laboratory monitoring during pubertal induction are provided in Boxes 19.3 and 19.4, respectively.

During pubertal induction with gradually increasing doses of estrogen or testosterone, initial sex steroid levels will not be sufficient to suppress endogenous sex steroid secretion. In transgender females, even when adult levels of estrogen are reached, it is recommended that GnRH agonist treatment (or another antiandrogen) be continued until gonadectomy.[3] Given that some transgender adults may not choose to have gonadectomy, long-term studies are needed to assess potential risks of prolonged GnRH agonist treatment. GnRH agonist treatment can typically be stopped in transgender males, once adult levels of testosterone have been achieved.[3]

It is not uncommon for some transgender adolescents to initially present for care when they have either virtually completed puberty or are already postpubertal. In such cases, transgender females are treated with estrogen, as well as an agent that blocks testosterone secretion and/or action, using protocols typical for transgender adults. With respect to estrogen treatment, 17 β-estradiol (transdermal, oral, or parental) is preferred to conjugated (e.g., premarin) or synthetic estrogens (e.g., ethinyl estradiol) because conjugated and synthetic estrogen levels cannot be monitored in the serum and ethinyl estradiol is associated with increased risk for venous thromboembolic disease and death from cardiovascular causes in studies of adults.[3] Postpubertal transgender male adolescents can be treated with testosterone alone, following protocols typical for transgender adults. Although testosterone typically induces amenorrhea within a few months, a progestin or other agent may be used if uterine bleeding persists.[78]

BOX 19.3 Protocol Induction of Puberty

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

Induction of female puberty with transdermal 17β-estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 day):
- 6.25–12.5 mcg/24 hour (cut 25-mcg patch into quarters, then halves)
- 25 mcg/24 hour
- 37.5 mcg/24 hour
- Adult dose 50–200 mcg/24 hour
- *Adjust maintenance dose to mimic physiological estradiol levels.*

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

IM, Intramuscularly; *SC*, subcutaneously.
(From Hembree, W.C. et al. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrine Metab, 102 (11), 1–35; by permission of the Endocrine Society.)

BOX 19.4 Baseline and Follow-up Protocol During Induction of Puberty

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

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

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

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).

BMD, Bone mineral density; *DEXA*, dual-energy X-ray absorptiometry.
(From Hembree, W.C. et al. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrine Metab, 102 (11), 1–35; by permission of the Endocrine Society.)

With respect to surgery, some transgender adolescents seek such procedures to bring their bodies into closer alignment with their gender identity. It is recommended that gender-affirming genital surgery involving gonadectomy and/or hysterectomy not take place until the individual has reached at least 18 years of age, or the age of legal majority in their country.[3] For transgender males seeking breast reduction surgery, the Endocrine Society Guidelines acknowledge that some adolescents may consider this procedure before 18 years of age, but note there is insufficient evidence to recommend a specific age requirement.[3] These guidelines suggest that clinicians should consider the physical and mental health status of the individual patient, when determining the timing of this procedure.

Outcomes and Potential Adverse Effects

Limited outcomes data are available based on current treatment models. As noted earlier, one published study has thus far evaluated mental health in transgender adolescents/young adults before and after GnRH agonist treatment, following gender-affirming sex steroid treatment, and 1 year after "gender reassignment surgery."[64] At the completion of the observation period, GD was resolved, general psychological functioning had improved, and a sense of "wellbeing" was observed to be equal or greater to that found in age-matched controls. In addition, none of the 55 study participants regretted treatment.[64]

Potential adverse effects of pubertal suppression with GnRH agonists in transgender youth, as recently reviewed, include impaired bone mineral density (BMD) and compromised fertility. In addition, there are unclear effects on brain development, body mass index (BMI), and body composition.[79]

With respect to skeletal health, a 6-year longitudinal study (that spanned the period of pubertal suppression, gender-affirming sex hormone treatment, and gonadectomy), observed a significant decrease in lumbar spine areal BMD z-scores (relative to natal sex) in transgender females, with a similar decrease, following pubertal suppression in transgender males.[80] Potential study limitations, as acknowledged by the authors, included a relatively small number of study participants, relatively low doses of sex hormones, and lack of information regarding other factors that can influence BMD, including vitamin D status, dietary calcium intake, and weight-bearing exercise.[80] During pubertal suppression with GnRH agonists in early pubertal transgender adolescents, it is recommended to monitor vitamin D status and supplement if necessary, and to encourage adequate dietary calcium intake and weight-bearing exercise.[22] In a separate study, bone turnover markers and bone mineral apparent density (BMAD) z-scores decreased, following GnRH agonist treatment in younger transgender adolescents, whereas an increase in BMAD was observed after 2 years of gender-affirming sex hormone treatment, in both younger and older transgender adolescents.[81] A 22-year follow-up study of a gender dysphoric adolescent, treated initially with GnRH agonist and subsequently with gender-affirming sex hormones, found that BMD was in the normal range for both sexes when evaluated at 35 years of age.[82]

A discussion about implications for fertility must precede any treatment of gender dysphoric adolescents with either GnRH agonists or gender-affirming sex hormones. Transgender adolescents may wish to preserve fertility, which will likely be compromised if puberty is suppressed at an early stage, and the individual subsequently transitions with gender-affirming sex hormones. In vitro maturation of human germ cells has not yet been achieved, although some families elect to freeze a section of prepubertal gonadal tissue for potential future use.[83] Cryopreservation of mature sperm or eggs is an option for late pubertal/ fully pubertal adolescents. However, recent reports indicate that even when provided with counseling regarding

potential impact of sex hormone treatment on fertility and options for fertility preservation, only a small percentage of such adolescents opted to pursue fertility preservation.[84,85] Questionnaires to assess fertility and fertility preservation attitudes in transgender youth and their parents have been recently developed.[86,87]

With respect to brain function, few studies have thus far evaluated potential adverse effects of GnRH agonists in transgender adolescents. When comparing small groups of GnRH agonist-treated versus untreated transgender adolescents (both male-to female and female-to male), there was no significant compromise of executive functioning, a developmental milestone typically achieved during puberty.[88] A 28-month longitudinal study in one transgender adolescent, undergoing treatment with GnRH agonist, showed lack of expected variation in white matter fractional anisotropy, a measure of brain maturation thought to normally occur during puberty, as well as a 9-point drop in operational memory testing after 22 months of pubertal suppression.[89] Given this relative lack of data, further longitudinal studies are needed to assess the impact of GnRH agonist treatment on brain development and function in transgender adolescents.

Studies assessing the impact of GnRH agonist treatment on BMI and body composition have also been carried out. Although variable results have been observed with respect to BMI,[80,90] an increase in fat percentage and a decrease in lean body mass percentage, after 1 year of treatment with GnRH agonist, have been reported in both transgender male and female adolescents.[90] In a separate study, significant weight gain was reported in one of 27 transgender adolescents treated with GnRH agonist, although this individual's BMI was noted to be greater than the 85th percentile before treatment.[91]

A small number of short-term studies have thus far evaluated potential adverse effects of gender-affirming sex hormones in transgender adolescents. No change in blood pressure, BMI standard deviation score, lean body mass percentage, or fat percentage were observed in a study from the Netherlands of 28 transgender females treated for 1 to 3 years, primarily with gradually increasing doses of 17 β-estradiol.[92] In addition, no abnormalities were observed with liver enzymes or creatinine, and there was no change in hematocrit or hemoglobin A1c. Hyperprolactinemia was observed in one individual who had received high-dose ethinyl estradiol treatment to limit statural growth.[92]

Two studies from the United States have assessed potential adverse effects of gender-affirming sex hormones in transgender adolescents and young adults. Following treatment with 17 β-estradiol in 44 transgender females, no abnormalities were seen in blood pressure, BMI, hemoglobin/hematocrit, lipids, renal and liver function studies, or in prolactin.[93] Following treatment with testosterone in 72 transgender males, there was an increase in BMI and in hemoglobin/hematocrit (supraphysiologic hematocrit levels were seen in 4% of the individuals) and a decrease in high-density lipoprotein cholesterol levels; no abnormalities were seen in blood pressure, renal and liver function studies, or in hemoglobin A1c.[93] A separate prospective study, after 21 to 31 months of treatment with gender-affirming hormones in 25 transfeminine and 34 transmasculine individuals, showed no clinically significant adverse effects in a variety of metabolic parameters.[94]

CHALLENGES TO DELIVERY OF CARE

Multidisciplinary care for transgender youth represents a relatively new focus of clinical service and research. Although there have been significant advances, beginning with pioneering work from the Netherlands, there are only limited safety and efficacy studies, with virtually no published data on the use of GnRH agonists to suppress puberty in gender dysphoric youth younger than 12 years of age, or cross-sex hormones in transgender adolescents younger than 16 years of age. Randomized controlled trials are often considered the gold standard; however, this approach to study hormonal interventions in gender dysphoric youth has not been considered feasible or ethical.[95,96] Although an increasing number of clinical programs have emerged around the world in recent years, there are many geographic areas where no such services exist, requiring patients and their families to travel long distances. In addition, there are significant limitations to access for medical treatments, given that all hormonal interventions for gender dysphoric youth are considered "off-label" in the United States, are expensive (GnRH agonists, in particular), and are often denied by insurance companies. Furthermore, lack of formalized training of providers and prejudice and misunderstanding on the part of family, community, and both medical and mental health providers limit access to optimal care.[97]

There are additional challenges to providing optimal care for transgender youth. Whereas almost all published research has been conducted in the context of a binary gender model, there are increasing numbers of youth seeking care that identify as gender nonbinary.[98] Another limitation to the delivery of evidence-based care is that most studies of children, adolescents, and young adults with GD include only those with early-onset GD. A phenomenon known as *rapid-onset gender dysphoria* (ROGD), in which GD is first expressed by older youth during or after the completion of puberty, is poorly understood at this time.[99] Methodological concerns have been raised regarding the ROGD report (calling into question the existence of ROGD, itself), including the fact that only parents (recruited from websites) and none of the gender dysphoric youth participated in the study, and that parents were not recruited from websites supportive of transgender youth.[100] More research is needed to better understand those youth who have been described to have ROGD to optimally provide safe and effective care for these individuals.

CONCLUSIONS

Significant advances in our understanding of transgender/gender nonconforming youth have been achieved, although significant gaps in knowledge remain. Compelling studies have emerged supporting the concept that gender identity is not simply a psychosocial construct, but reflects a complex interplay of biological, environmental, and cultural factors. The removal of the term "gender identity disorder," replacing it with "gender dysphoria" in the DSM-*V*, underscores that a transgender identity, in and of itself, is no longer considered pathological, and that clinical concern should focus on GD that may be present, along with concomitant mental health challenges. The first long-term study, based on current models of care, indicates that mental health comorbidities in gender dysphoric youth either significantly diminish or resolve, when such individuals are provided with gender-affirming care, optimally delivered in a multidisciplinary clinical setting.[64] Further prospective, long-term outcome studies are needed to optimize care for transgender/gender nonconforming youth.

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