Hormone Therapy

Introduction

Transgender and gender diverse (TGD) persons may request gender-affirming hormone therapy (GAHT) to achieve changes consistent with their embodiment goals and/or gender identity. Ever since the first WPATH SOC published in 1979 and in subsequent updates of the SOC, including SOC version 7, gender-affirming hormone therapy has been accepted as medically necessary (Coleman et al., 2012). WPATH endorsed the Endocrine Society's guidelines for GAHT for TGD persons in 2009 and 2017(Hembree et al., 2009; Hembree et al., 2017). The European Society for Sexual Medicine has also published a position statement on hormone management in adolescent and adult TGD people (T'Sjoen et al., 2020). When provided under medical supervision, GAHT in adults is safe (Tangpricha and den Heijer, 2017; Safer and Tangpricha, 2019). However, there are some potential long-term risks, and careful monitoring and screening is required to reduce adverse events (Hembree et al., 2017; Tangpricha et al., 2019; Rosenthal, 2021).

The approach to GAHT differs and depends on the developmental stage of the individual at the time of initiation of hormone therapy as well as their treatment goals. Hormone therapy is not recommended for children who have not begun endogenous puberty. In eligible youth (as per the adolescent chapter) who have reached the early stages of puberty, the focus is usually to delay further pubertal progression with gonadotropin releasing hormone agonists (GnRHas) until an appropriate time when GAHT can be introduced. Eligible adults may initiate GAHT if they fulfill the criteria as per the assessment chapter. In addition, health care providers should discuss fertility goals and fertility preservation options prior to initiating GAHT (see chapter on Reproductive Health).

Gender affirming hormone therapy with feminine embodiment goals typically consists of estrogen and an androgen lowering medication (Hembree et al., 2017). Although there are anecdotal reports of progesterone use for breast development and mood management, there is currently insufficient evidence that potential benefits of progesterone administration outweighs the potential risks (Iwamoto et al., 2019). Masculinizing GAHT typically consists of testosterone. Both WPATH and the Endocrine Society recommend monitoring levels of sex hormones. While GAHT is customized to meet the individual needs of the TGD person, typically hormone levels are a maintained at a concentration sufficient to support good bone health and not supraphysiologic (Hembree et al., 2017; Rosen et al., 2019).

In most cases, GAHT is maintained throughout life. It is not known if doses of GAHT should be reduced in older TGD people. Discontinuation of hormone therapy may result in bone loss in both trans feminine and trans masculine individuals and definitely in those whose gonads have been removed (Wiepjes et al., 2020). Routine primary care should also be performed (see chapter on Primary Care). Epidemiology studies have reported an increased incidence of cardiovascular disease and venous thromboembolism (VTE) in TGD people receiving estrogen, most notably in older women and with different preparations of GAHT (Maraka et al., 2017; Irwig, 2018). TGD individuals treated with testosterone may also have increased adverse cardiovascular risks and events, such as increased myocardial infarction, blood pressure, decreased HDL-cholesterol, and excess weight (Alzahrani et al., 2019; Cocchetti et al., 2021; Irwig, 2018; Kyinn et al., 2021). Health professionals (HPs) should discuss lifestyle and pharmacologic therapy with patients who are at the highest risk of developing

cardiovascular disease (see chapter on Primary Care. Polycythemia is another disorder that may present in TGD people taking testosterone (Antun et al., 2020). Therefore, it is important to continuously monitor for the development of conditions that can be exacerbated by GAHT throughout life (Hembree et al., 2017).

Summary of Recommendations

Statement 1: We recommend health professionals should begin pubertal hormone suppression in eligible transgender and gender diverse adolescents after they first exhibit physical changes of puberty (Tanner stage 2).

Statement 2: We recommend health professionals use GnRH agonists to suppress endogenous sex hormones in transgender and gender diverse patients where puberty blocking is indicated.

Statement 3: We suggest health professionals prescribe progestins (oral or injectable depot) for pubertal suspension in transgender youth when GnRH agonists are either not available or are cost prohibitive.

Statement 4: We suggest health professionals prescribe GnRH agonists for suppression of sex steroids without concomitant sex steroid hormone replacement in adolescents seeking such intervention and who are well into or have completed pubertal development (past Tanner stage 3) but are either unsure about or do not want to begin sex steroid hormone therapy.

Statement 5: We suggest health professionals prescribe sex hormone treatment regimens as part of gender-affirming treatment in eligible adolescents who are at least Tanner stage 2, preferably* with parental/guardian consent, and that treatment decisions be made with the participation of the adolescent, parents/guardians, and treatment team*.

Statement 6: We recommend health professionals measure hormone levels during gender-affirming treatment to ensure that endogenous sex steroids are lowered and administered sex steroids are maintained at levels appropriate to the treatment goals of transgender and gender diverse patients according to the Tanner stage.

Statement 7: We recommend health professionals prescribe progestogens or a GnRH agonist in transgender adolescents with a uterus to reduce dysphoria caused by their menstrual cycle when gender-affirming testosterone use is not yet indicated.

Statement 8: We suggest healthcare providers involve professionals from multiple disciplines who are experts in transgender health and the management of the care required for transgender and gender diverse adolescents.

Statement 9: We recommend health professionals institute regular clinical evaluations for physical changes and potential adverse reactions to sex steroid hormones, including laboratory monitoring of sex steroid hormone every 3 months during the first year of hormone therapy or with dose changes until stable adult dosing is reached followed by clinical and laboratory testing once or twice a year once an adult maintenance dose is attained.

Statement 10: We recommend health professionals inform and counsel all individuals seeking gender-affirming medical treatment about the options available for fertility preservation prior to initiating puberty suppression and prior to treating with hormonal therapy.

Statement 11: We recommend health professionals evaluate and address medical conditions that can be exacerbated by lowered endogenous sex hormone concentrations and treatment with exogenous sex hormones before beginning treatment for transgender and gender diverse people.

Statement 12: We recommend health professionals educate transgender and gender diverse patients undergoing gender-affirming treatment about the onset and time course of the physical changes induced by sex hormone treatment.

Statement 13: We recommend health professionals not prescribe ethinyl estradiol for transgender youth and adults as part of a gender-affirming hormone treatment.

Statement 14: We suggest health professionals prescribe transdermal estrogen for transgender youth and adults at higher risk of developing venous thromboembolism based on age > 45 years or a previous history of venous thromboembolism, when it is recommended, they receive gender-affirming estrogen treatment.

Statement 15: We suggest health professionals not prescribe conjugated estrogens in transgender youth and adults when estradiol is available as a component of gender-affirming hormone treatment.

Statement 16: We recommend health professionals prescribe testosterone-lowering medications (either cyproterone acetate, spironolactone, or GnRH agonists) for transgender youth and adults with testes who are taking estrogen as part of a hormone treatment plan if the individual's goal is to approximate circulating sex hormone concentrations of cisgender women.

Statement 17: We recommend health professionals monitor hematocrit (or hemoglobin) in transgender youth and adults treated with testosterone.

Statement 18: We suggest health professionals collaborate with surgeons regarding hormone use before and after gender affirmation surgery.

Statement 19: We suggest health professionals counsel patients about the various options available for gender affirmation surgery for transgender and gender diverse patients unless surgery is not desired or is medically contraindicated.

Statement 20: We recommend health professionals initiate and continue gender-affirming hormone therapy in transgender youth and adults who desire this treatment due to demonstrated improvement in psychosocial functioning and quality of life.

Statement 21: We recommend health professionals maintain existing hormone therapy for transgender youth and adults in the event of a deterioration in mental health and assess the reason for the deterioration.

** this statement should be read in conjunction with the statement that indicates the meaning of "preferably" in the Adolescent Chapter, "We recommend that when gender- affirming medical or surgical treatments are indicated for adolescents, health professionals working with transgender and gender diverse adolescents involve parent(s)/guardian(s) in the assessment and treatment process, unless their involvement is determined to be harmful or unnecessary to the adolescent".*

Gender-Affirming Hormone Therapy in Youth

The following sections will discuss hormone therapy in TGD youth. Depending on the developmental stage of the youth, this hormone therapy generally comprises two phases, namely pubertal suppression followed by the addition of GAHT. During the first phase, pubertal development is halted to allow the youth to explore their gender identity and embodiment goals to prepare for the next phase, which may include GAHT. This section will discuss the recommendations for the use of GnRHas as well as alternate approaches to pubertal suppression and will be followed by recommendations for gender-affirming hormone treatment. Sections that are applicable to youth and adults will follow in the next section.

Statement 1:
We recommend health professionals begin pubertal hormone suppression in eligible transgender and gender diverse adolescents only after they first exhibit physical changes of puberty (Tanner stage 2).

In general, the goal of GnRHa administration in TGD adolescents is to prevent further unwanted development of the endogenous secondary sex characteristics corresponding to the sex designated at birth. Since this treatment is fully reversible, it is regarded as an extended time for adolescents to explore their gender identity by means of an early social transition (Ashley, 2019). Treatment with GnRHas also has therapeutic benefit since it often results in a vast reduction in the level of distress stemming from unwanted physical changes that occur when endogenous puberty begins (Rosenthal, 2014; Turban et al., 2020).

In addition, the suppression of the development of secondary sex characteristics is most effective when sex hormone treatment is initiated in early to mid-puberty as compared to when sex hormone treatment is initiated after puberty is completed (Bangalore-Krisha et al., 2019). Correspondingly, for adolescents who have already completed endogenous puberty and are considering starting GAHT, GnRHas can be used to inhibit unwanted physical functions, such as menses or erections, and can serve as a bridge until the adolescent, guardian(s) (if the adolescent is not able to consent independently), and treatment team reach a decision (Bangalore-Krishna et al., 2019; Rosenthal, 2021).

The onset of puberty occurs through reactivation of the hypothalamic-pituitary-gonadal axis. Clinical assessment of the stages of puberty is based on physical features that reflect that reactivation. In individuals with functioning ovaries, Tanner stage 2 is characterized by the budding of the mammary gland. The development of the mammary gland occurs from exposure to estrogen produced by the ovaries. In individuals with functioning testes, Tanner stage 2 is characterized by an increase in testicular volume (typically greater than 4 ml). The growth of the testes is mediated through the gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH). In the later stages, the testes produce enough testosterone to induce virilization of the body (Palmert et al., 2021).

Statement 2:
We recommend health professionals use GnRH agonists to suppress endogenous sex hormones in transgender and gender diverse patients in whom puberty blocking is indicated.

Statement 3:
We suggest health professionals prescribe progestins (oral or injectable depot) for pubertal suspension in transgender youth when GnRH agonists are not available or are cost prohibitive.

Statement 4:
We suggest health professionals prescribe GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in adolescents seeking such intervention who are well into or have completed pubertal development (past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy.

GnRHas reduce gonadotrophin and sex steroid concentrations in TGD adolescents and thus halt the further development of secondary sex characteristics (Schagen et al., 2016). Their use is generally safe with the development of hypertension being the only short-term adverse event reported in the literature (Delemarre-van de Waal & Cohen-Kettenis, 2006; Klink et al., 2015). GnRHas prevent the pituitary gland from secreting LH and FSH (Gava et al., 2020). When the gonadotropins decrease, the gonad is no longer stimulated to produce sex hormones (estrogens or androgens), and the sex hormone levels in the blood decrease to prepubertal levels. GnRHa treatment leads to partial regression of the initial stages of the already developed secondary sex characteristics (Bangalore et al., 2019). TGD adolescents with functioning ovaries will experience diminished growth of breast tissue, and if treatment is started at Tanner Stage 2, the breast tissue may disappear completely (Shmer et al., 2016). Menarche can be prevented or discontinued following the administration of GnRHas in adolescents with a uterus. In TGD adolescents with functioning testes, testicular volume will regress to a lower volume.

When GnRHa treatment is started in adolescents at the later phases of pubertal development, some physical changes of pubertal development, such as late-stage breast development in TGD adolescents with functioning ovaries and a lower voice and growth of facial hair in TGD adolescents with functioning testes, will not regress completely, although any further progression will be stopped (Delemarre-van de Waal & Cohen-Kettenis, 2006). GnRHas have been used since 1981 for the treatment of central precocious puberty (Comite et al., 1981; Laron et al., 1981), and their benefits are well established (please also see the Adolescent Chapter Statements). The use of GnRHas in individuals with central precocious puberty is regarded as both safe and effective, with no known long-term adverse effects (Carel et al., 2009). However, the use of GnRHas in TGD adolescents is considered off-label because they were not initially developed for this purpose. Nonetheless, data from adolescents prescribed GnRHas in a similar dose and fashion demonstrate effectiveness in delaying the onset of puberty although the long-term effects on bone mass have not been well established (Klink et al., 2014). Although long-term data are more limited in TGD adolescents than in adolescents with precocious puberty, data collection specifically in this population are ongoing (Klaver et al., 2020; Lee et al., 2020; Millington et al., 2020; Olson-Kennedy et al., 2019).

We recognize GnRHas may not be available for eligible adolescents because it is not covered by health insurance plans or may be cost-prohibitive. Therefore, other approaches should be considered in these cases, such as oral or injectable progestin formulations. In addition, in adolescents older than 14 years, there are currently no data to inform health professionals whether GnRHas can be administered as monotherapy (and for what duration) without posing a significant risk to skeletal health. This is because the skeleton will not have any exposure to adequate levels of sex steroid hormones (Rosenthal, 2021).

Prolonged hypogonadal state in adolescence, whether due to medical conditions such as hypergonadotropic hypogonadism, iatrogenic causes such as GnRHa monotherapy or physiological conditions such as conditional delay of growth and development, often is associated with an increased risk of poor bone health later in life (Finkelstein et al., 1996, Bertelloni et al., 1998). However, bone mass accrual is a multifactorial process that involves a complex interplay between endocrine, genetic, and lifestyle factors (Anai et al., 2001). When deciding on the duration of GnRHa monotherapy, all contributing factors should be considered, including factors such as pretreatment bone mass, bone age, and pubertal stage from an endocrine perspective and height gain, as well as psychosocial factors such as mental maturity and developmental stage relative to one's adolescent cohort and the adolescent's individual treatment goals (Rosenthal, 2021). For these reasons, a multidisciplinary team and an ongoing clinical relationship with the adolescent and the family should be maintained when initiating GnRHa treatment (see Adolescent Chapter statements 8, 9, and 12). The clinical course of the treatment, e.g., the development of bone mass during GnRHa treatment and the adolescent's response to treatment, can help to determine the length of GnRHa monotherapy.

Statement 5:
We suggest health providers prescribe sex hormone treatment regimens as part of gender-affirming treatment in eligible adolescents who are at least Tanner stage 2, preferably* with parental/guardian consent, and treatment decisions should be made with the participation of the adolescent, parents/guardians, and treatment team*.
(this statement should be read in conjunction with the statement that indicates the meaning of "preferably" in the Adolescent Chapter, "We recommend that when gender- affirming medical or surgical treatments are indicated for adolescents, health professionals working with transgender and gender diverse adolescents involve parent(s)/guardian(s) in the assessment and treatment process, unless their involvement is determined to be harmful to the adolescent or unnecessary.")*

Statement 6:
We recommend health professionals measure hormone levels during gender- affirming treatment to ensure endogenous sex steroids are lowered and administered sex steroids are maintained at a level appropriate for the treatment goals of transgender and gender diverse patients according to the Tanner stage.

Sex steroid hormone therapy generally comprises two treatment regimens, depending on the timing of the GnRHa treatment. When GnRHa treatment is started in the early stages of endogenous pubertal development, puberty corresponding with gender identity or embodiment goals is induced with doses of sex steroid hormones similar to those used in peripubertal hypogonadal adolescents. In this context, adult doses of sex steroid hormones are typically reached over approximately a 2-year period (Chantrapanichkul et al., 2021). When GnRHa treatment is started in late- or post-pubertal transgender adolescents, sex steroid hormones can

be given at a higher starting dose and increased more rapidly until a maintenance dose is achieved, resembling treatment protocols used in transgender adults (Hembree et al., 2017). An additional advantage of GnRHa treatment is that sex steroid hormones do not have to be administered in supraphysiological doses, which would otherwise be needed to suppress endogenous sex steroid production (Safer & Tangpricha, 2019). For TGD individuals with functioning testes, GnRHa treatment (or another testosterone-blocking medication) should be continued until such time as the transgender adolescent/young adult ultimately undergoes gonadectomy, if this surgical procedure is chosen as part of their gender-affirming care. Once adult levels of testosterone are reached in TGD individuals with functioning ovaries who have been initially suppressed with GnRHa's, testosterone alone at physiological doses is typically sufficient to lower ovarian estrogen secretion, and GnRHas can be discontinued as discussed below (Hembree et al., 2017). For TGD adolescents with functioning ovaries who are new to care, transition can be accomplished with physiological doses of testosterone alone, without the need for concomitant GnRHa administration (Hembree et al., 2017).

Gender-affirming sex steroid hormone therapy induces the development of secondary sex characteristics of the gender identity. Also, the rate of bone mineralization, which decreases during treatment with GnRHa's, rapidly recovers (Klink et al., 2014). During GnRHa treatment in early-pubertal TGD adolescents, the bone epiphyseal plates are still unfused (Kvist et al., 2020, Schagen et al., 2020). Following the initiation of sex steroid hormone treatment, a growth spurt can occur, and bone maturation continues (Vlot et al., 2017). In postpubertal transgender adolescents, sex steroid hormone treatment will not affect height since the epiphyseal plates have fused, and bone maturation is complete (Vlot et al., 2017).

In TGD adolescents with functioning testes, the use of 17-ß-estradiol for pubertal induction is preferred over that of synthetic estrogens, such as the more thrombogenic ethinyl estradiol (see Recommendations for Sex Steroid Hormones in Transgender Adults) (Asscheman et al., 2015). It is still necessary to either continue GnRHa's to suppress endogenous testosterone production or transition to another medication that suppresses endogenous testosterone production (see Recommendations for Sex Hormones in Transgender Adults) (Rosenthal et al., 2016). Breast development and a female fat distribution are among a number of physical changes that occur in response to estrogen treatment (Table 1).

For TGD adolescents seeking masculinizing treatment, androgens are available as injectable preparations, transdermal formulations, and subcutaneous pellets. For pubertal induction, the use of testosterone-ester injection is generally recommended by most experts initially because of cost, availability and experience (Shumer et al., 2016). It is advised to continue GnRHa's at least until a maintenance level of testosterone is reached. In response to androgen treatment, virilization of the body occurs, including a lowering of the voice, more muscular development particularly in the upper body, growth of facial and body hair, and clitoral enlargement (Rosenthal et al., 2016) (Table 1).

In almost all situations, parental/caregiver consent should be obtained. Exceptions to this recommendation, in particular when caregiver or parental involvement is determined to be harmful to the adolescent, are described in more detail in the Adolescent Chapter (see Statement 11), where the rationale for involving parents/caregivers in the consent process is also described.

Statement 7:

We suggest health professionals prescribe progestogens or GnRH agonists to reduce dysphoria caused by their menstrual cycle for transgender adolescents with a uterus, when androgen therapy is not yet indicated.

Menstrual suppression is a treatment option commonly requested by TGD individuals who experience distress related to menses or the anticipation of menarche. Statement 7 in the Adolescent Assessment Chapter describes this in more detail. To achieve amenorrhea, menstrual suppression can be initiated as a solo option before initiating testosterone or alongside testosterone therapy (Carswell & Roberts, 2017). Some youth, who are not ready for testosterone therapy or are not yet at an appropriate pubertal/developmental stage to begin such treatment, express an interest in induction of amenorrhea (Olson-Kennedy et al., 2018). Adolescents who experience an exacerbation of dysphoria related to the onset of puberty may elect to be treated with GnRHas for pubertal suppression (also see the Adolescent Chapter).

Progestogens may be effective in adolescents whose goal is solely menstrual suppression. Continuous administration of progestin-only oral pills (including the contraceptive and noncontraceptive options), medroxyprogesterone injections, or levonorgestrel intrauterine device can be used for induction of amenorrhea (Pradhan & Gomez-Lobo, 2019). TGD individuals with functioning ovaries who start testosterone therapy may have 1-5 menstrual cycles before amenorrhea is achieved (Taub et al., 2020). Once amenorrhea is achieved, some TGD individuals with functioning ovaries may also choose to continue progestin treatment for birth control if relevant to their sexual practices.

TGD individuals with functioning ovaries and a uterus should be counseled about the potential for breakthrough menstrual bleeding in the first few months after initiating menstrual suppression. With GnRHa therapy, breakthrough bleeding may occur 2-3 weeks after initiation of the medication. For individuals seeking contraception or for those who continue to experience menstrual bleeding on progestin therapy, an estrogen combination with progestin may be considered for the maintenance of amenorrhea (Schwartz et al., 2019).

Statement 8:
We suggest healthcare providers involve professionals from multiple disciplines who are experts in transgender health and the management of the care of transgender and gender diverse adolescents.

As with the care of adolescents, we suggest where possible a multidisciplinary expert team of medical and mental health professionals be assembled to manage this treatment. In adolescents who request sex steroid hormone treatment (given this is a partly irreversible treatment), we suggest initiating treatment using a schedule of gradually increasing doses after a multidisciplinary team of medical and mental health professionals has confirmed the persistence of GD/gender incongruence and has established the individual possesses the mental capacity to give informed consent (Hembree et al., 2017). Specific aspects concerning the assessment of adolescents and the involvement of their caregivers and a multidisciplinary team are described in more detail in the Adolescent Assessment Chapter (statements 3, 8, 11, and 12).

If possible, TGD adolescents should have access to experts in pediatric transgender health from multiple disciplines including primary care, endocrinology, fertility, mental health, voice, social work, spiritual support, and surgery (Chen et al., 2016; Eisenberg et al., 2020; Keo-Meier & Ehrensaft, 2018). Individual providers are encouraged to form collaborative working

relationships with providers from other disciplines to facilitate referrals as needed for the individual youth and their family (Tishelman et al., 2015). However, the lack of available experts and resources should not constitute a barrier to care (Rider et al., 2019). Helpful support for adolescents includes access to accurate, culturally informed information related to gender and sexual identities, transition options, the impact of family support, and connections to others with similar experiences and with TGD adults through online and in person support groups for adolescents and their family members (Rider et al., 2019)

Many TGD adolescents have been found to experience mental health disparities, initial mental health screening (e.g., PHQ-2, GAD) can be employed as indicated (Rider et al., 2019). Providers should keep in mind that being transgender or questioning one's gender does not constitute pathology or a disorder. Therefore, individuals should not be referred for mental health treatment exclusively on the basis of a transgender identity. HPs and mental health professionals (MHPs) who treat these youths and make referrals should, at a minimum, be familiar with the impact of trauma, gender dysphoria, and gender minority stressors on any potential mental health symptomatology, such as disordered eating, suicidal ideation, social anxiety, etc. These healthcare providers should also be knowledgeable about the level of readiness of inpatient mental health services in their region to provide competent, gender-affirming care to TGD youth (Barrow & Apostle, 2018; Kuper et al., 2018; Kuper et al., 2019; Tishelman & Neumann-Mascis, 2018). The Adolescent Chapter Statements 3, 4, and 12 D address this in more detail. Because parents of these youth commonly experience high levels of anxiety immediately after learning their youth is TGD, and their response to their child predicts that child's long-term physical and mental health outcomes, appropriate referrals for mental health support of the parents can be of great utility (Coolhart et al., 2017; Pullen Sansfaçon et al., 2015; Taliaferro et al., 2018).

Statement 9:

We recommend health professionals organize regular clinical evaluations for physical changes and potential adverse reactions to sex steroid hormones, including laboratory monitoring of sex steroid hormone every 3 months during the first year of hormone therapy or with dose changes until a stable adult dosing is reached followed by clinical and laboratory testing once or twice a year once an adult maintenance dose is attained.

Sex steroid hormone therapy is associated with a broad array of physical and psychological changes (Irwig, 2017; Tangpricha & den Heijer, 2017) (**Table 1**). After sex steroid hormone therapy has been initiated, the HP should regularly assess the progress and response of the individual to the treatment (also see Adolescent Chapter). This evaluation should assess the presence of any physical changes as well as the impact of treatment on gender dysphoria (if present) and psychological well-being (**Table 1**). Clinical visits provide important opportunities for HPs to educate patients about the typical time course required for physical changes to manifest and encourage realistic expectations. During the first year of hormone therapy, sex steroid hormone doses are often increased. A major factor guiding the dose is the serum levels of the corresponding sex steroid hormone. In general, the goal is to target serum levels of the sex steroids to match the levels associated with the individual's gender identity, although optimal target ranges have not been established (Hembree et al., 2017).

In addition to assessing the positive changes associated with sex steroid hormone therapy, the HP should regularly assess whether the treatment has caused any adverse effects (**Table 2).** Examples of adverse signs and symptoms include androgenic acne or bothersome sexual dysfunction (Braun et al., 2021, Kerckhof et al., 2019). Gender-affirming hormone treatment also

has the potential to adversely influence several laboratory tests. For example, spironolactone may cause hyperkalemia, although it is an uncommon and transient phenomenon (Millington et al., 2019). Testosterone increases the red blood cell count (hematocrit), which may occasionally cause erythrocytosis (Antun et al., 2020) (see Recommendation on Monitoring Transgender Individuals Receiving Testosterone Therapy) (Hembree et al., 2017). Both estrogen and testosterone can alter lipid parameters, such as high-density protein lipoprotein (HDL) cholesterol and triglycerides (Maraka et al., 2017). See tablets 3 and 4 for more information regarding Gender-affirming hormone treatment).

The frequency of clinical evaluations should be individualized and guided by the individual's response to treatment. We suggest clinical assessments be performed approximately every 3 months during the first year of hormone therapy in patients who are stable and are not experiencing significant adverse effects (**Table 5**). We suggest rather than recommend testing be carried out every 3 months in the first year to allow some flexibility on the timing of these tests as there is no strong evidence or evidence from published studies supporting specific testing intervals. If an individual does experience an adverse effect, more frequent laboratory testing and/or clinical visits are often needed. Given the potential harm associated with sex hormone levels that exceed expected ranges in humans, we strongly recommend regular testing be performed as a standard practice when initiating GAHT in TGD individuals. Once a person has reached a stable adult dose of sex steroid hormone with no significant adverse effects, the frequency of clinic visits can be reduced to one to two per year (Hembree et al., 2017).

Statement 10:
We recommend health professionals inform and counsel all individuals seeking gender-affirming medical treatment about options for fertility preservation prior to initiating puberty suppression and prior to administering hormone therapy.

Pubertal suppression and hormone treatment with sex steroid hormones may have potential adverse effects on a person's future fertility (Cheng et al., 2019) (see Adolescent and Reproductive Chapters). Although some TGD people may not have given much thought to their future reproductive potential at the time of their initial assessment to begin medical therapy, the potential implications of the treatment and fertility preservation options should be reviewed by the hormone prescriber and discussed with the person seeking these therapies (Ethics Committee of the American Society for Reproductive Medicine et al., 2015; De Roo et al., 2016).

Individuals with testes should be advised that prolonged treatment with estrogen often causes testicular atrophy and a reduction in sperm count and other semen parameters (Adeleye et al., 2019). Nonetheless, there are major gaps in knowledge, and findings regarding the fertility of trans feminine people who take estrogen and antiandrogens are inconsistent (Cheng et al., 2019). In one study, heterogeneity in testicular histology was evident whether patients discontinued or continued therapy prior to elective orchiectomies (Schneider et al., 2015). For example, the discontinuation of estrogen and antiandrogens for six weeks resulted in complete spermatogenesis in 45% of individuals with the remainder showing meiotic arrest or spermatogonial arrest (Schneider et al., 2015). However, serum testosterone levels confirmed to be within female reference ranges leads to complete suppression of spermatogenesis in most transgender women (Vereecke et al., 2020). The principal fertility preservation option for patients with functioning testes is sperm cryopreservation, also known as sperm banking

(Mattawanon et al., 2018). For prepubertal patients, suppression of puberty with GnRHas pauses the maturation of sperm (Finlayson et al., 2016).

Individuals with functioning ovaries should be advised that testosterone therapy usually results in cessation of menses and ovulation, often within a few months of initiation (Taub et al., 2020). There are also major gaps in knowledge regarding the potential effects of testosterone on oocytes and subsequent fertility of TGD patients (Eisenberg et al., 2020, Stuyver et al., 2020). One study found that testosterone treatment may be associated with polycystic ovarian morphology, whereas other studies reported no metabolic (Chan et al., 2018) or histologic (De Roo et al., 2017; Grynberg et al., 2010) evidence of polycystic ovary syndrome (PCOS) following treatment with testosterone. TGD patients with an intact uterus and ovaries often regain their fertility potential if testosterone therapy is discontinued (Light et al., 2014). Indeed, a live birth after assisted reproductive technology has been reported following hormone-stimulated egg retrieval from a TGD individual who did not discontinue testosterone therapy (Greenwald et al, 2021; Safer and Tangpricha, 2019). Other fertility preservation options for TGD patients with ovaries are oocyte cryopreservation and embryo cryopreservation with sperm from a partner or donor. The above options require hormonal stimulation for egg retrieval and the use of assisted reproductive technology. For early pubertal transgender youth, suppression of puberty with GnRHa's pauses the maturation of germ cells, though a recent report noted ovarian stimulation of a TGD adolescent treated with a GnRHa's in early puberty (and continued during ovarian stimulation) resulted in a small number of mature oocytes that were cryopreserved (Rothenberg et al., 2019). Treating an TGD adolescent with functioning tests in the early stages of puberty with a GnRHa's not only pauses maturation of germ cells but will also keep the penis at a prepubertal size. This will likely impact surgical considerations if that person eventually desires a penile-inversion vaginoplasty as there will be less penile tissue to work with. In these cases there is an increased likelihood that a vaginoplasty will require a more complex surgical procedure--e.g. intestinal vaginoplasty (Dy et al., 2021; van de Grift et al., 2020). Such considerations should be included in any discussions with patients and families considering use of pubertal blockers in early pubertal with functioning testes.

Statement 11:

We recommend health professionals evaluate and address medical conditions that can be exacerbated by lowered endogenous sex hormone concentrations and treatment with exogenous sex hormones before beginning treatment in transgender and gender diverse people.

TGD people seeking virilization must be informed about the possibilities, consequences, limitations, and risks associated with testosterone treatment. Testosterone therapy is contraindicated during pregnancy or while attempting to become pregnant given its potential iatrogenic effects on the fetus. Relative contraindications to testosterone therapy include severe hypertension, sleep apnea, and polycythemia since these conditions can be exacerbated by testosterone. Monitoring blood pressure and lipid profiles should be performed before and after the onset of testosterone therapy. The increase in blood pressure typically occurs within 2 to 4 months following the initiation of testosterone therapy (Banks et al., 2021). Patients who develop hypercholesterolemia and/or hypertriglyceridemia may require treatment with dietary modifications and/or medication. TGD people seeking feminizing treatment with a history of thromboembolic events, such as deep vein thrombosis and pulmonary embolism, should undergo evaluation and treatment prior to the initiation of hormone therapy. This is because estrogen therapy is strongly associated with an increased risk of thromboembolism, a potentially life-threatening complication. In addition, risk factors that can increase the risk of

thromboembolic conditions, such as smoking, obesity, and sedentary lifestyle, should be modified. In patients with nonmodifiable risk factors such as known thrombophilia, a past history of thrombosis, or a strong family history of thromboembolism, treatment with transdermal estrogen and/or concomitant with anticoagulants may decrease the risk of thromboembolism. However, there are limited data to guide treatment decisions. The presence of a disease at baseline such as a hormone sensitive cancer, coronary artery disease, cerebrovascular disease, hyperprolactinemia, hypertriglyceridemia, and cholelithiasis should be evaluated prior to the initiation of gender affirming hormone therapy as relative risks may be shifted in association with exogenous hormone treatment. (Hembree et al., 2017; Safer, 2021)

Statement 12:
We recommend health professionals educate transgender and gender diverse patients undergoing gender-affirming treatment about the onset and time course of physical changes induced by sex hormone treatment.

The effects of testosterone treatment are multiple and may include the appearance of increased body and facial hair, male pattern baldness, increased muscle mass and strength, decreased fat mass, deepening of the voice, interruption of menses (if still present), increased prevalence and severity of acne, clitoral enlargement, and increased sexual desire (Defreyne et al., 2020; Fisher et al., 2016; Giltay & Gooren, 2000; G. T'Sjoen et al., 2019; Yeung et al., 2020) (**Table 1**). Other testosterone-associated changes include increased lean body mass, skin oiliness, (de Blok et al., 2020; Hembree et al., 2017; Kuper et al., 2018; Kuper et al., 2019; Taliaferro et al., 2018; Tishelman & Neumann-Mascis, 2018) (**Table 1**).

Estrogen treatment induces breast development. However, fewer than 20% of individuals reach Tanner breast stage 4-5 after 2 years of treatment (de Blok et al., 2021). Additional changes include decreases in testicular volume, lean body mass, skin oiliness, sexual desire, spontaneous erections, facial hair, and body hair along with increased subcutaneous body fat (**Table 1**). In adult patients, estrogen does not alter a person's voice or height (Iwamoto et al., 2019; Wiepes et al., 2019).).

The time course and extent of physical changes vary among individuals and are related to factors such as genetics, age of initiation, and overall state of health (Deutsch et al., 2015; van Dijk et al., 2019). Knowledge of the extent and timing of sex hormone–induced changes, if available, may prevent the potential harm and expense of unnecessary treatment changes, dosage increases, and premature surgical procedures (Dekker et al., 2016).

Statement 13:
We recommend against the use of ethinyl estradiol and conjugated estrogens in transgender women as part of a gender-affirming hormone regimen.

Statement 14:
We recommend the use of transdermal estrogen in transgender women who are at higher risk of venous thromboembolism based on age >45 years or a previous history of venous thromboembolism.

Statement 15:

We suggest health professionals not prescribe conjugated estrogens in transgender youth and adults when estradiol is available as part of a gender- affirming hormone treatment.

Determining the safest and most efficacious estrogen compound and route of administration for TGD people is an important topic. The recommended estrogen-based regimens are presented in **Table 4**. The Free University Hospital in Amsterdam first reported 45 events of VTE occurring in 816 transgender women, notably an expected incidence ratio of VTE 20-fold higher than that reported in a reference population (van Kesteren et al., 1997). Following this report, the Free University Gender Clinic recommended the use of transdermal estradiol for transgender women older than 40 years of age, which subsequently lowered the incidence of VTE (Nota et al., 2019; Toorians et al., 2003). Other studies suggested ethinyl estradiol was associated with a higher risk of blood clotting due to an increased resistance to the anticoagulating effects of activated protein C (APC) and elevated concentrations of the clotting factors protein C and protein S (Toorians et al., 2013). Other studies published within the past 15 years from other clinics reported transgender women taking other forms of estrogen had lower rates of VTE than transgender women taking ethinyl estradiol (Asscheman et al., 2013). Furthermore a 2019 systematic review concluded that ethinyl estradiol administration was associated with the highest risk of VTE in transgender women, while an association between progesterone use and VTE was also identified (Goldstein et al., 2019).

The 2017 Endocrine Society guidelines did not recommend conjugated equine estrogens (CEEs) as a treatment option because blood levels of conjugated estrogens cannot be measured in transgender women, making it difficult to prevent supraphysiologic dosing of estrogen thereby increasing the potential risk of VTE (Hembree et al., 2017). A retrospective study from the UK examined the risks of oral CEE versus oral estradiol valerate versus oral ethinyl estradiol and found up to a 7-fold increase in the percentage of transgender women in the oral CEE group who developed VTE compared with transgender women using other forms of estrogen (Seal et al., 2012). In a nested, case-control study, over 80,000 cisgender women aged 40-79 who developed a VTE were matched to approximately 390,000 cisgender women without VTE; the results showed oral estradiol use had a lower risk of VTE than conjugated estrogens, and transdermal estrogen was not associated with an increased risk of VTE (Vinogradova et al., 2019).

Our commissioned systematic review evaluated several formulations of estrogen and identified a retrospective and a cross-sectional study that made head-to-head comparisons of the risks associated with different formulations (Wierckx et al., 2013; Wierckx et al., 2012). There were no identified studies that evaluated the risk of different formulations of estrogen that employed a prospective interventional design. The retrospective study examined 214 transgender women taking transdermal estradiol (17β-estradiol gel 1.5 mg/d or estradiol patch 50 mcg/d) or a daily intake of oral estrogens (estradiol 2 mg/d, estriol 2 mg/d, ethinyl estradiol 50 mcg/day, or ethinyl estradiol 30-50 mcg in an oral contraceptive) (Wierckx et al., 2013). Within a 10-year observation period, 5% of the cohort developed a VTE, 1.4% (3 out of 214) experienced a myocardial infarction (MI), and 2.3% (5 out of 214) a transient ischemic attack or cerebrovascular accident (TIA/CVA). The prevalence of VTE, MI and TIA/CVA was increased following the initiation of estrogen therapy. However, the authors did not report differences between regimens of estrogen in terms of these endpoints.

The same group of investigators conducted the cross-sectional study that examined 50 transgender women (mean age 43 ± 10) taking oral estrogen (estradiol valerate 2mg/d, estriol 2 mg/d or ethinyl estradiol 50-120 mcg/day) or using transdermal estradiol (17β-estradiol 1.5

mg/day or estradiol 50 mcg/day) over a follow-up duration of 9.2 years (Wierckx et al., 2012). Twelve percent (n=6) developed either a VTE, MI, or a TIA/CVA. Two of the participants were taking conjugated estrogen 0.625 mg/d (one person in combination with cyproterone acetate), 2 participants were taking ethinyl estradiol 20-50 mcg/d, 1 was taking cyproterone acetate 50 mg/d, while the estrogen regimen used by the sixth participant was not defined. None of the subjects taking oral estradiol or transdermal estradiol developed a VTE, MI, or TIA/CVA.

One prospective study examined the route of estrogen administration in 53 transgender women in a multicenter study carried out throughout Europe. Transgender women younger than 45 years of age (n=40) received estradiol valerate 4 mg/d in combination with cyproterone acetate (CPA) 50 mg/d and transgender women older than 45 years of age (n=13) received transdermal 17β-estradiol, also with CPA. No VTE, MI, or TIA/CVA was reported after a 1 year of follow-up in either the oral or transdermal estrogen group. An additional retrospective study from Vienna found no occurrences of VTE among 162 transgender women using transdermal estradiol who were followed for a mean of 5 years (Ott et al., 2010).

We are strongly confident in our recommendation against the use of ethinyl estradiol based on historical data from the Amsterdam clinic demonstrating a reduction in the incidence of VTE after discontinuing the use of ethinyl estradiol and the recent systematic review demonstrating an increased risk of VTE in transgender women taking ethinyl estradiol (Weinand & Safer, 2015). We are confident in our recommendation against the use of CEE based on the 2012 study by Seal et al. demonstrating an increased risk of VTE in transgender women taking CEE compared with other formulations of estrogen and with data from cisgender women on hormone replacement therapy (Canonico et al., 2007; Seal et al., 2012). Prospective and retrospective studies in transgender women have reported occurrences of VTE/MI/CVA only in those taking CEE or ethinyl estradiol. Since estradiol is inexpensive, more widely available, and appears safer than CEE in limited studies, the committee recommends against using CEE when estradiol is an available treatment option. The quality of studies may be limited to prospective, cohort or cross-sectional study designs; however, the stronger level of recommendation is based on the consistent evidence supporting the association between the use of ethinyl estradiol and CEE and a greater risk of VTE/MI/CVA in transgender women.

We are also confident in our recommendation for the administration of transdermal preparations of estrogen in older transgender women (age >45 years) or those with previous history of VTE. The confidence in our recommendation is based on the decreased incidence of VTE reported from the Amsterdam clinic when transgender women are switched to using transdermal preparations after age 40 (van Kesteren PJ, et al., 1997). Furthermore, the prospective, multicenter cohort study ENIGI found no incidence of VTE/MI/CVA in transgender women who are routinely switched to transdermal estrogen at age 45 (Dekker et al., 2016). In addition, a study by Ott et al. demonstrated no incidence of VTE in 162 transgender women treated with estradiol patches (Ott et al., 2010).

Statement 16:

We recommend health professionals prescribe testosterone-lowering medications (either cyproterone acetate, spironolactone, or GnRH agonists) for transgender youth and adults with testes taking estrogen as part of a hormone treatment plan if their individual goal is to approximate levels of circulating sex hormone of cisgender women.

Most gender clinics in the United States and Europe prescribe estrogen combined with a testosterone-lowering medication (Mamoojee et al., 2017) (**Table 5).** In the United States,

spironolactone is the most commonly prescribed testosterone lowering medication, GnRHas are commonly used in the UK, and cyproterone acetate are most often prescribed in the rest of Europe (Angus et al., 2021; Kuijpers et al., 2021). The rationale for adding a testosterone-lowering medication is two-fold: (1) to lower testosterone levels to within the reference range of cisgender females, and (2) to reduce the amount of estrogen needed to achieve adequate physical effects. Each testosterone-lowering medication has a different side effect profile. Spironolactone is an antihypertensive and potassium-sparing diuretic, and thus may lead to hyperkalemia, increased frequency of urination, and a reduction in blood pressure (Lin et al., 2021). Cyproterone acetate has been associated with the development of meningioma and hyperprolactinemia (Nota et al., 2018). GnRHa's, while very effective in lowering testosterone levels, can result in osteoporosis if doses of estrogen given concurrently are insufficient (Klink et al., 2014).

One systematic review identified one study that reported findings from a head-to-head comparison of the testosterone-lowering medications cyproterone acetate and leuprolide (Gava et al., 2016). Two studies compared a group of transgender women taking estrogen plus testosterone-lowering medications with a group who received only estrogen. The systematic review did not provide sufficient evidence to suggest any of the three testosterone-lowering medications had a better safety profile in terms of improved outcomes in bone health, testosterone levels, potassium levels, or in the incidence of hyperprolactinemia or meningiomas (Wilson et al., 2020). Therefore, no recommendation can be given. The review did report spironolactone-based regimens were associated with a 45% increase in prolactin levels, whereas cyproterone-based regimens increased prolactin levels by more than 100%. However, the clinical significance of elevated prolactin levels is not clear because the rates of prolactinomas were not significantly elevated in either the spironolactone- or CPA-treated groups (Wilson et al., 2020). One retrospective, cohort study from a single center in the United States reported no clinically significant increases in prolactin levels in 100 transgender women treated with estrogen plus spironolactone (Bisson et al., 2018). A retrospective study from the Netherlands of 2,555 transgender women taking primarily CPA with various formulations of estrogen reported an increased standardized incidence ratio of meningiomas in patients who used cyproterone acetate after gonadectomy for many years when compared with the general Dutch population (Nota et al., 2018). Furthermore, in a shorter study in Belgium, 107 transgender women had transient elevations in prolactin levels following treatment with cyproterone acetate, which declined to normal after discontinuation (Defreyne et al., 2017). A recent publication, not included in the systematic review, examined 126 transgender women taking spironolactone, GnRHas, or cyproterone and concluded cyproterone was associated with higher prolactin levels and a worse lipid profile than spironolactone or GnRHas (Sofer et al., 2020). After balancing the costs and accessibility of measuring prolactin levels against the clinical significance of an elevated level, a decision was made not to make a recommendation for or against monitoring prolactin levels at this time. HPs should therefore make individualized clinical decisions about the necessity to measure prolactin levels based on the type of hormone regimen and/or the presence of symptoms of hyperprolactinemia or a pituitary tumor (e.g., galactorrhea, visual field changes).

Cyproterone has also been linked to meningiomas. Nine cases of meningioma have been reported in the literature among transgender women primarily taking cyproterone acetate (Mancini et al., 2018). This increased risk has also been identified in cisgender populations. In 2020, the European Medicines Agency published a report recommending cyproterone products with daily doses of 10 mg or more should be restricted because of the risk of developing meningioma (European Medicines Agency). Most likely this association is a specific effect of cyproterone acetate and has not been extrapolated to include other testosterone-lowering

drugs. In the United States, where cyproterone acetate is not available, the North American Association of Central Cancer Registries (NAACCRs) database did not identify an increased risk of brain tumors (not specific to meningiomas) among transgender women (Nash et al., 2018). Furthermore, there was not an increase in the hazard ratio of brain tumors in the Kaiser cohort of 2,791 transgender women compared with cisgender controls (Silverberg et al., 2017). No long-term studies have reported on the risk of meningiomas and prolactinomas in transgender women taking GnRHa's.

Our strong recommendation for the use of testosterone-lowering medications as part of a hormone regimen for transgender individuals with testes is based on the global practice of using these medications in addition to estrogen therapies as well as the relatively minimal risk associated these therapies. However, we are not able to make a recommendation favoring one testosterone-lowering medication over another at this time. The published data thus far raises some concerns about the risk of meningiomas with the prolonged use (>2 years) and higher doses (>10mg daily) of cyproterone acetate (Weill et al, 2021, Nota et al, 2018, Ter Wengel et al, 2016).

Statement 17:
We recommend health professionals monitor hematocrit (or hemoglobin) levels in transgender youth and adults treated with testosterone.

There are good quality data suggesting a rise in hematocrit (or hemoglobin) is associated with transgender persons treated with testosterone (Defreyne et al., 2018). The testosterone regimens in the systematic review included testosterone esters ranging from the equivalent of 25- 250 mg SC/IM weekly, testosterone undecanoate 1000 mg every 12 weeks, or testosterone gel 50 mg applied daily to the skin (Defreyne et al., 2018; Gava et al., 2018; Giltay et al., 2000; Meriggiola et al., 2008; Pelusi et al., 2014; T'Sjoen et al., 2005; Wierckx et al., 2014; Wierckx et al., 2014) . The expected rise should be consistent with reference ranges in cisgender males.

Statement 18:
We suggest health professionals collaborate with surgeons regarding hormone use before and after gender affirmation surgery.

Statement 19:
We suggest health professionals counsel patients about the various options for genital gender affirmation surgery for transgender and gender diverse patients, unless surgery is either not desired or is medically contraindicated.

Despite the absence of evidence, perioperative clinical standards for gender affirmation surgeries have included cessation of hormone therapy for 1-4 weeks before and after surgery, most commonly genital surgeries (Hembree et al., 2009). Such practice was meant to mitigate the risk of VTE associated with exogenous estrogen administration (Hembree et al., 2009). Estrogen and testosterone could then be resumed at some point postoperatively.

After careful examination, investigators have found no perioperative increase in the rate of VTE among transgender individuals undergoing surgery while being maintained on sex steroid treatment throughout when compared with that among patients whose sex steroid treatment was discontinued preoperatively (Gaither et al., 2018; Hembree et al., 2009; Prince & Safer,

2020, Kozato et al 2021). Sex steroid treatment is especially important after gonadectomy to avoid the sequelae of hypogonadism, the risk of developing osteoporosis, and for the maintenance of mental health and quality of life (Fisher et al., 2016; Rosen et al., 2019). Thus, hormone providers and surgeons should educate patients about the necessity for continuous exogenous hormone therapy after gonadectomy.

To be able to educate patients and serve as clinical advocates, HPs should be knowledgeable about the risks/benefits of gender affirmation surgeries and should also be cognizant of the performance measures and surgical outcomes of the surgeons to whom they might refer patients (Beek, Kreukels et al., 2015; Colebunders et al., 2017; Wiepjes et al., 2018). In general, most surgeries can be thought of as involving three regions: the face, chest/breasts, and genitalia (internal and external). Additional procedures include body contouring and voice surgery.

Multiple options are available for facial gender-affirming surgery for trans feminine individuals including, but not limited to, chondrolanryngoplasty, rhinoplasty, contouring or augmentation of the jaw, chin, and forehead, facelift, and hair transplantation. Options available for chest/breast surgery include breast augmentation, double mastectomy with nipple grafts, periareolar mastectomy, and liposuction. The most common gender affirmation surgery for TGD individuals with endogenous breast development is masculinizing chest surgery (mastectomy) (Horbach et al., 2015; Kailas et al., 2017).

Internal genital surgery options include orchiectomy, hysterectomy, salpingo-oophorectomy, vaginoplasty, and colpectomy/vaginectomy (Horbach et al., 2015; Jiang et al., 2018). The inner lining in vaginoplasty is typically constructed from penile skin, skin grafts, a combination of both, or a bowel segment. Removal of the uterus/ovaries can be performed individually or all at once (hysterectomy, salpingo-oophorectomy, and colpectomy). If colpectomy is performed, a hysterectomy must also be performed. The ovaries may remain in situ, upon patient request. A potential benefit of leaving one or both ovaries is fertility preservation, while the downside is the potential for the development of ovarian pathology, including cancer (De Roo et al., 2017)

External genital surgery options include vulvoplasty, metoidioplasty, and phalloplasty (Djordjevic et al., 2008; Frey et al., 2016). Hair removal may be necessary before performing external genital procedures (Marks et al., 2019). Vulvoplasty can include the creation of the mons, labia, clitoris, and urethral opening. Urethral lengthening is an option for both metoidioplasty and phalloplasty but is associated with a greatly increased complication rate (Schechter & Safa, 2018). Wound care and physical therapy are necessary for managing wounds resulting from the donor sites for phalloplasty (van Caenegem et al., 2013). Pelvic physical therapy can also be an important adjunct intervention after surgery for managing voiding and sexual function (Jiang et al., 2019). Dialogue, mutual understanding, and clear communication in a common language between patients, HPs, and surgeons will contribute to well-considered choices about the available surgical options.

Statement 20:
We recommend health professionals initiate and continue gender-affirming hormone therapy in transgender youth and adults who wish this treatment due to demonstrated improvement in psychosocial functioning and quality of life.

Statement 21:

We recommend health professionals maintain existing hormone therapy if TGD individual's mental health deteriorates and assess the reason for the deterioration, unless contraindicated.

Several mental health disparities have been documented in the transgender population including depression, suicidality, anxiety, decreased self-esteem, and post-traumatic stress disorder (Arcelus et al., 2016; Becerra-Culqui et al, 2018; Bouman et al., 2017; Eisenberg et al., 2017; Heylens et al., 2014; Witcomb et al., 2018). The gender minority stress model provides evidence of several mediators and moderators of these disparities (Hendricks & Testa, 2012). Mediators and moderators of mental health disparities unique to transgender people include experiences of discrimination, victimization, misgendering, family rejection, and internalized transphobia (Hendricks & Testa, 2012). Factors that have a positive effect on mental health include family acceptance, supportive social and romantic relationships, transgender community connectedness, protection by affirming and inclusive policies, policies of affirmation and inclusion, possession of updated legal name/gender documentation, and achievement of physical gender transition based on individualized embodiment goals (Bauer et al., 2015; Bockting et al., 2013; Bouman et al., 2016; de Vries et al., 2014; Du Bois et al., 2018; Gower et al., 2018; Hendricks & Testa, 2012; Keo-Meier et al., 2015; Meier et al., 2013; Pflum et al., 2015; Smith et al., 2018; Ryan et al., 2010).

Hormone therapy has been found to positively impact the mental health and quality of life of TGD youth and adults who embark this treatment (Aldridge et al., 2020; Allen et al., 2019; Bauer et al., 2015; Nobili et al., 2018; Russell et al., 2018; Ryan, 2009). In many cases, hormone therapy is considered a lifesaving intervention (Allen et al., 2019; Grossman & d'Augelli, 2006; Moody et al., 2015). Several studies have found associations between the initiation of hormone therapy and improved mental health in youth and adults (Aldridge et al., 2020; Costa et al., 2016; de Vries et al., 2014; Kuper et al., 2020; Nguyen et al., 2018; White Hughto & Reisner, 2016), including improvements in quality of life (Gorin-Lazard et al., 2012; Gorin-Lazard et al., 2013; Murad et al., 2010; Newfield et al., 2006; Nobili et al., 2018; White et al., 2016), a reduction in anxiety and depression (Aldridge et al., 2020; Colizzi et al., 2014; Davis & Meier, 2014; de Vries et al., 2011; Gómez-Gil et al., 2012; Rowniak et al., 2019), decreased stress (Meier et al., 2011), and decreased paranoia (Keo-Meier & Fitzgerald, 2017). A prospective, controlled trial using the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) demonstrated significant improvement in multiple domains of psychological functioning in transgender men after only 3 months of testosterone treatment (Keo-Meier et al., 2015). Although there are higher rates of autism symptoms in the transgender population, these symptoms have not been found to increase after the initiation of hormone therapy (Nobili et al., 2020).

Because a reduction in depressive symptoms may correlate with a decrease in the risk of suicide, withholding hormone therapy based on the presence of depression or suicidality may cause harm (Keo-Meier et al., 2015; Levy et al., 2003). Turban (2020) found a decrease in the odds of lifetime suicidal ideation in adolescents who desired pubertal suppression and had access to this treatment compared with those with a similar desire with no such access (Turban et al., 2020). A recent systematic review found pubertal suppression in TGD adolescents was associated with an improved social life, decreased suicidality in adulthood, improved psychological functioning, and quality of life (Rew et al., 2020). Because evidence suggests hormone therapy is directly linked to decreased symptoms of depression and anxiety, the practice of withholding hormone therapy until these symptoms are treated with traditional psychiatry is considered to have iatrogenic effects (Keo-Meier et al., 2015). If psychiatric treatment is indicated, it can be started or adjusted concurrently without discontinuing hormone therapy.

Table 1 Expected Time Course of Physical Changes in Response to Gender- Affirming Hormone Therapy

Testosterone Based Regimen

Effect	Onset	Maximum
Skin Oiliness/acne	1-6 months	1-2 years
Facial/body hair growth	6-12 months	>5 years
Scalp hair loss	6-12 months	>5 years
Increased muscle mass/strength	6-12 months	2-5 years
Fat redistribution	1-6 months	2-5 years
Cessation of menses	1-6 months	1-2 years
Clitoral enlargement	1-6 months	1-2 years
Vaginal atrophy	1-6 months	1-2 years
Deepening of voice	1-6 months	1-2 years

Estrogen and Testosterone-Lowering Based Regimens

Effect	Onset	Maximum
Redistribution of body fat	3-6 months	2-5 years
Decrease in muscle mass and strength	3-6 months	1-2 years
Softening of skin/decreased oiliness	3-6 months	Unknown
Decreased sexual desire	1-3 months	Unknown
Decreased spontaneous erections	1-3 months	3-6 months
Decreased sperm production	Unknown	2 years
Breast growth	3-6 months	2-5 years
Decreased testicular volume	3-6 months	Variable
Decreased terminal hair growth	6-12 months	>3 years
Increased scalp hair	Variable	Variable
Voice changes	None	

Data for testosterone-based regimens from (Ahmad & Leinung, 2017; Irwig, Childs, & Hancock, 2017; Klaver et al., 2018; Park, Carter, & Larson, 2019; Schönauer et al., 2020; Stoffers, de Vries, & Hannema, 2019; Taub et al., 2020; Van Caenegem et al., 2015; Yeung et al., 2020)
Data for estrogen and testosterone-lowering based regimens from (de Blok et al., 2018; Matoso et al., 2018; Reisman, Goldstein, & Safer, 2019; Stevenson, Wixon, & Safer, 2016)

TABLE 2 RISKS ASSOCIATED WITH SEX STEROID HORMONE THERAPY, BOLDED ITEMS ARE CLINICALLY SIGNIFICANT (Updated from SOC-7)

RISK LEVEL	Estrogen-based regimens	Testosterone-based regimens
Likely increased risk	**Venous Thromboembolism** **Infertility** **Hyperkalemia[s]** Hypertrigyceridemia Weight Gain	**Polycythemia** **Infertility** Acne Androgenic Alopecia Hypertension Sleep Apnea Weight Gain Decreased HDL Cholesterol and increased LDL Cholesterol
Likely increased risk with presence of additional risk factors	Cardiovascular Disease Cerebrovascular Disease Meningioma[c] Polyuria/Dehydration[s] Cholelithiasis	Cardiovascular Disease Hypertriglyceridemia
Possible increased risk	Hypertension Erectile Dysfunction	
Possible increased risk with presence of additional risk factors	Type 2 Diabetes Low Bone Mass/Osteoporosis Hyperprolactinemia	Type 2 Diabetes Cardiovascular Disease
No increased risk or inconclusive	Breast and Prostate Cancer	Low Bone Mass/Osteoporosis Breast, Cervical, Ovarian, Uterine Cancer

[C] cyproterone-based regimen
[S] spironolactone-based regimen

TABLE 3 GENDER-AFFIRMING HORMONE REGIMENS IN TRANSGENDER AND GENDER DIVERSE YOUTH (Adapted from the Endocrine Society Guidelines)

Induction of female puberty (estrogen based regimen) with oral 17ß-estradiol
Initiate at 5µg/kg/d and increase every 6 months by 5 µg/kg/d up to 20 µg/kg/d according to estradiol levels
Adult dose = 2-6 mg/day

In postpubertal transgender adolescents, the dose of 17ß-estradiol can be increased more rapidly:
1 mg/d for 6 months followed by 2 mg/d and up according to estradiol levels

Induction of female puberty (estrogen based regimen) with transdermal 17ß-estradiol
Initial dose 6.25-12.5 µg/24 h (cutting 24 g patch to ¼ then ½)
Titrate up by every 6 months by 12.5 µg/24 h according to estradiol levels
Adult dose = 50-200 µg/24 hours
For alternatives once at adult dose (Table 4)

Induction of male puberty (testosterone based regimen) with testosterone esters
25 mg/m^2/2 weeks (or alternatively half this dose weekly)
Increase by 25 mg/m^2/2 weeks every 6 months until adult dose and target testosterone levels achieved. See alternatives for testosterones (Table 4)

TABLE 4 HORMONE REGIMENS IN TRANSGENDER AND GENDER DIVERSE ADULTS*

Estrogen Based Regimen (Transfeminine)

Estrogen	
Oral or sublingual	
Estradiol	2.0-6.0 mg/day
Transdermal	
Estradiol transdermal patch	0.025-0.2 mg/day
Estradiol gel various	‡ daily to skin
Parenteral	
Estradiol valerate or cypionate	5-30 mg IM every 2 weeks
	2-10 IM every week
Anti-Androgens	
Spironolactone	100 – 400 mg/day
Cyproterone acetate	10 mg/day
GnRH agonist	3.75- 7.50 mg SQ monthly
GnRH agonist depot formulation	11.25/22.5 mg SQ 3/6 monthly

‡ Amount applied varies to formulation and strength

Testosterone Based Regimen (Transmasculine)

Transgender males

Testosterone	
Parenteral	
Testosterone enanthate/cypionate	50 - 100 IM/SQ weekly or
	100 – 200 IM every 2 weeks
Testosterone undecanoate	1000 mg IM every 12 weeks
Transdermal testosterone	
Testosterone gel 1.6%	50-100 mg/day
Testosterone transdermal patch	2.5 – 7.5 mg/day

**Doses are titrated up or down until sex steroid hormone levels are in the therapeutic range*

Table 5 Hormone Monitoring of Transgender and Gender Diverse People Receiving Gender Affirming Hormone Therapy (adapted from the Endocrine Society Guidelines)

Transgender male or transmasculine embodiment goals

1. Evaluate patient approximately every 3 months (with dose changes) in the first year and 1 to 2 times per year to monitor for appropriate physical changes in response to testosterone.
2. Measure serum total testosterone every 3 months (with dose changes) until levels are at goal
    a. For parenteral testosterone, the serum total testosterone should be measured midway between injections. The target level is 400-700 ng/dL. Alternatively, measure peak and trough peaks to ensure levels remain in the range of reference men.
    b. For parenteral testosterone undecanoate, testosterone should be measured just before injection. If the level is <400 ng/dL, adjust the dosing interval.
    c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 week of daily application (at least 2 hours after application of product).
3. Measure hematocrit or hemoglobin concentrations at baseline and approximately 3 months (with dose changes) for the first year and then one to two times a year.

Transgender Female or transfeminine embodiment goals

1. Evaluate patient approximately every 3 months (with dose changes) in the first year and one to two times per year to monitor for appropriate physical changes in response to estrogen.
    a. Serum testosterone levels should be less than 50 ng/dL.
    b. Serum estradiol should be in the range of 100-200 pg/mL.
2. For individuals receiving spironolactone, serum electrolytes, in particular potassium, and kidney function, in particular creatinine, should be monitored.
3. Follow primary care screening per primary care chapter recommendations

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