Endocrinology of Transgender Medicine

Guy T'Sjoen,[1,2] Jon Arcelus,[3,4] Louis Gooren,[5] Daniel T. Klink,[6] and Vin Tangpricha[7]

[1]Department of Endocrinology, Ghent University Hospital, 9000 Ghent, Belgium; [2]Center for Sexology and Gender, Ghent University Hospital, 9000 Ghent, Belgium; [3]Institute of Mental Health, Jubilee Campus, University of Nottingham, Nottingham NG7 2TU, United Kingdom; [4]Nottingham Centre for Transgender Health, Nottingham NG1 3AL, United Kingdom; [5]University Hospital, Vrije Universiteit of Amsterdam, 1081 HV Amsterdam, Netherlands; [6]ZNA Queen Paola Children's Hospital, 2020 Antwerp, Belgium; and [7]Division of Endocrinology, Metabolism, and Lipids, Department of Medicine, Emory University, Atlanta, Georgia 30322

ORCiD numbers: 0000-0003-0457-9673 (G. T'Sjoen); 0000-0002-3805-0180 (J. Arcelus); 0000-0002-4021-5853 (V. Tangpricha).

ABSTRACT Gender-affirming treatment of transgender people requires a multidisciplinary approach in which endocrinologists play a crucial role. The aim of this paper is to review recent data on hormonal treatment of this population and its effect on physical, psychological, and mental health. The Endocrine Society guidelines for transgender women include estrogens in combination with androgen-lowering medications. Feminizing treatment with estrogens and antiandrogens has desired physical changes, such as enhanced breast growth, reduction of facial and body hair growth, and fat redistribution in a female pattern. Possible side effects should be discussed with patients, particularly those at risk for venous thromboembolism. The Endocrine Society guidelines for transgender men include testosterone therapy for virilization with deepening of the voice, cessation of menses, and increases of muscle mass and facial and body hair. Owing to the lack of evidence, treatment of gender nonbinary people should be individualized. Young people may receive pubertal suspension, consisting of GnRH analogs, later followed by sex steroids. Options for fertility preservation should be discussed before any hormonal intervention. Morbidity and cardiovascular risk with cross-sex hormones is unchanged among transgender men and unclear among transgender women. Sex steroid–related malignancies can occur but are rare. Mental health problems such as depression and anxiety have been found to reduce considerably following hormonal treatment. Future studies should aim to explore the long-term outcome of hormonal treatment in transgender people and provide evidence as to the effect of gender-affirming treatment in the nonbinary population. ***(Endocrine Reviews 40: 97 – 117, 2019)***

The acceptance by society, reflected in the media, that gender identity may not always match the assigned sex at birth has provided the option and permission for individuals to question their gender identity more freely. Consequently, in some countries, transgender health services have expanded and developed so that gender-diverse people wanting physical change are able to access gender-affirming medical interventions. Hormone treatment, pivotal for those who wish to transition into their affirmed gender that differs from their sex that is assigned at birth, is ideally prescribed under the supervision of endocrinologists. However, many endocrinologists may feel uneasy and unskilled when working with the transgender population because the field of transgender medicine is relatively new. This review aims to summarize the endocrine treatment of transgender people wishing to undergo gender-affirmation therapies. The review first describes the terminology used in the field of transgender medicine, followed by a critical review of the diagnostic criteria currently in use, and it summarizes the mental health difficulties that transgender people may present with and the benefits of gender-affirming treatment on well-being. Finally, the major focus of this paper is to provide a critical review of the published literature on the hormonal treatment and long-term monitoring for transgender children and adults.

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ESSENTIAL POINTS

- Transgender people before gender-affirming treatment present with higher levels of mental health problems, particularly depression, anxiety, and self-harm, than do cisgender people
- Gender-affirming treatment has been found to reduce mental health problems in transgender people
- Long-term estrogen and androgen-lowering medications may be associated with increased risk of thromboembolism, which can be mitigated by changing the formulation and route of estrogen therapy
- Testosterone treatment in transgender men is seen as safe regarding cardiovascular and oncological disease in the short-term and mid-term, but long-term effects need to be elucidated
- The endocrine treatment of adolescents with gender dysphoria consists of two phases, first pubertal suppression followed by the addition of hormones
- The few somatic data available in adolescents are favorable and hitherto support the fact that the proven psychological benefits of early medical intervention outweigh the potential medical risks
- In well-informed transgender people regrets of gender-confirming treatment are very rare

Terminology

The term "gender nonconforming" is used to describe individuals whose gender identity, role, or expression differs from what is normative for their assigned sex at birth in a given culture and historical period (1). Transgender is used as an umbrella term to describe individuals whose gender identity differs from the assigned sex at birth. Transgender males are people assigned female at birth but who self-identify as male. Transgender females are people assigned male at birth, but who self-identify as female. When a person's identity matches the sex assigned at birth, the term "cisgender" is used. The term "nonbinary" describes people whose gender identity, role, or expression does not conform to the binary understanding of gender (male or female). This can be used as an umbrella term to include people with no gender (agender), two genders (bigender), multiple genders (pangender), or with a fluid gender (gender fluid) (2, 3), among others. Nonbinary people prefer for people to use the pronouns of "they" and "them" when addressing them (3).

Terminology changes all the time, and terms used in the past may become outdated and can be perceived as pejorative. For example, the term transsexual, which has been used since 1949 (4), is largely now confined to the legal and medical literature. The 10th edition of the International Classification of Diseases and Related Health Problems (ICD-10) (5) still uses the term "transsexualism" as a diagnostic term to describe individuals whose sex assigned at birth does not match their gender identity and want gender-affirming treatment. This term is likely to change to "gender incongruence" in the forthcoming 11th edition of the ICD (ICD-11) (6). Other terms still used but considered outdated (although they can still be found in the literature) are "FtM" (female to male) to describe transgender men or "MtF" (male to female) to describe transgender women.

Gender dysphoria refers to a profound distress or discomfort caused by the discrepancy between a person's assigned sex at birth and gender identity (1). Not every transgender person suffers from gender dysphoria, and the urgency for medical intervention among transgender people may vary (1). For some people, social change may be enough without the need for further physical intervention. For others, owing to their personal circumstances, physical intervention may not be opportune or appropriate. Many, however, will access transgender health services to obtain gender-affirming treatment whether in the form of hormone treatment and/or through gender-affirming surgery. Research in the field of transgender medicine has primarily focused on transgender people accessing transgender health services (7). Owing to the requirement in certain countries to provide funded health services only to those with a medical diagnosis, terms describing the gender-related suffering of transgender people have remained part of current diagnostic criteria (5, 8). In this review, the term transgender is used throughout to describe individuals who seek access to medical treatment in order for their bodies to become more congruent to their identified gender. A summary of some of the terms used in transgender health can be found in Table 1.

Methodology

Eligibility criteria

Studies were selected only when participants were described as transgender (whether self-identified or diagnosed by health professionals) and they had empirical data relating to the hormonal treatment in

Table 1. Terminology Used in Transgender Health

Terms and Definitions
Cisgender: A person whose identity matches the sex assigned at birth.
Gender-affirming treatment: Physical treatment that some transgender people access in order for their bodies to be adapted to the bodies of their experienced gender or gender identity by means of hormones and/or surgery.
Gender dysphoria: A profound distress or discomfort caused by the discrepancy between assigned sex at birth and gender identity. This is the same term as the current diagnostic term of the DSM-5.
Gender expression: The external manifestations of someone's gender, which can include name, pronouns, clothing, haircut, behavior, voice, or body characteristics.
Gender identity disorder: Diagnostic term used in previous versions of the DSM. The term is still used for the child diagnosis in the ICD-10, but the proposed name for ICD-11 is gender incongruence of childhood. Currently this term is not preferred given the term "disorder."
Gender identity/experienced gender: A person's internal sense of gender. Unlike gender expression, gender identity is not visible to others.
Gender incongruence: The proposed diagnostic term to be used in the new edition of the ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek gender-affirming treatment.
Gender reassignment: Previously used term to describe what is known now as gender-affirming treatment.
Gender role: The behaviors, attitudes, and personality traits that a society, in a historical period, designates as masculine or feminine.
Natal sex: The term "sex assigned at birth," which is usually based on genital anatomy, is more appropriate.
Sex: Attributes that characterize biological maleness or femaleness. They can 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: An individual's 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), or be bisexual, asexual, pansexual, and so forth.
Transgender *(adj.):* An umbrella term to describe individuals whose gender identity differs from the sex assigned at birth based on their sexual characteristics.
Transgender female: A person who self-identifies as female, but whose sex was assigned male at birth.
Transgender male: A person whose sex was assigned female at birth (based on sexual characteristics) but self-identifies as male.
Transition: The process during which transgender people change their physical, social, and/or legal characteristics consistent with their gender identity.
Transsexual *(adj.):* A diagnostic term used in the ICD-10. The term is currently used in some of the medical literature when discussing diagnoses. The term transgender should now be used instead except when referring to the current ICD-10 diagnosis.

this population. Only studies in English published in peer-reviewed journals and with >10 participants were selected. This is a critical review with a focus on recent and original data. This paper describes and reviews the available literature since the last published review study by one of the coauthors of the current review (9).

Information sources and search

An electronic literature search included the period between January 1999 and November 2017 used Medline/PubMed, PsycINFO, and Embase. Additionally, reference sections of identified articles and Google Scholar were examined for further relevant publications. The search used keywords for terms referring to transgender people (transsexualism, transgender, gender dysphoria, gender identity disorder, trans*) or hormonal treatment (cross-sex hormones, testosterone, estrogen, blockers, GnRH agonist). Every term used for transgender people was combined using the "OR" and "AND" operators with every term used for hormonal treatment. Articles of interest were those that included the transgender population and had empirical data relating to hormonal treatment within this population. Articles describing the effects of treatment, side effects, risk, and long-term outcome were also collected and reviewed to help with the discussion in this review. If information was only to be retrieved from case reports, such as oncology, both the case reports and recent reviews on the specific topic were examined. The results of the present review are presented by describing the treatment in adults

(transgender women and men) first, followed by the treatment in adolescents.

Diagnosis

Currently the ICD-10 includes the diagnosis of transsexualism as part of the diagnostic category of "gender identity disorders" (F64). It is expected that the new edition of the ICD (ICD-11) will change this term and move it out of the mental health chapter. It is likely that the new term to be used will be "gender incongruence of adolescence and adulthood" (or GIAA) (6, 10, 11).

The desire to de-pathologize being transgender and the importance of securing access to health care has been a dilemma in both the development of the current edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and the ICD-11. The American Psychiatric Association's diagnosis in the DSM-5 addresses the distress caused by the incongruence between assigned sex at birth and experienced gender as gender dysphoria. This diagnosis aims to classify the symptoms (dysphoria) and not the individual. For an individual to fulfill the diagnostic criteria for gender dysphoria they need to present with a marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration (8).

If reaching a consensus to develop terms to classify transgender adults has been complicated, creating criteria for children has been even more complex. The ICD-11 is proposing the diagnosis of gender incongruence in children (10) whereas the DSM-5 uses the diagnosis of gender dysphoria in children.

Prevalence

More than 20 studies have sought to investigate prevalence rates of transgender people. Although more recently prevalence rates of transgender identities have been reported using population studies, most of the available literature has extrapolated prevalence rates from people attending transgender health clinics (7).

Some of the first epidemiological studies, which focused on individuals seeking services to undergo gender-affirming genital surgery (12), found prevalence rates of 0.40 per 100,000 people. The ratio between male assigned at birth and female assigned at birth was found to be 4 to 1 (11). Other European studies, based on people attending transgender health services, provide different prevalence rates over time: 1.22 per 100,000 (1976 to 1980), 1.58 per 100,000 (1976 to 1983), and 2.77 per 100,000 (1976 to 1986) (13). Once again, rates of male assigned at birth transgender people have been found to be higher than female assigned at birth transgender people at a ratio of 3 to 1. Studies looking at more recent periods (between 1972 and 1996) provide higher prevalence rates of 3.42 per 100,000 with ratios between birth-assigned females and males being more similar (1.4 to 1) (14).

Studies have also examined the number of people who have petitioned governmental agencies to change their gender status legally. Those studies have described prevalence rates ranging from 2.1 (15) to 16.6 (16) per 100,000 people. A recent meta-analysis found an overall prevalence for transsexualism (as this is the diagnosis and term used in the published papers) of 4.6 in 100,000 individuals: 6.8 for transgender women and 2.6 for transgender men, with an increase in reported prevalence during the last 50 years (7).

However, not every transgender person wants and/or seeks medical care to affirm gender (1). To identify the overall prevalence of transgender people (including those not accessing services) population studies may be more representative of the transgender community. Population-based studies have found a considerably higher prevalence rate than those reported in clinical studies. For example, a study asking a sample of community participants in the United States (28,045 aged 18 to 64 years) as to whether they considered themselves transgender found a prevalence rate of 0.5% (17). Studies from the Netherlands and Belgium described that 0.7% (18) and 1.1% (19) of people assigned male at birth and 0.6% (18) and 0.8% (19) of people assigned female at birth reported an incongruent gender identity.

Most of the epidemiological studies have been conducted in Western countries, particularly in Europe and the United States. Societies that are more egalitarian and open will facilitate the expression of gender diversity, and hence prevalence rates in those countries may be reported higher than in more restrictive societies. Low prevalence rates in certain societies may need to be regarded with caution, as they may reflect a symptom of repression. A ban on gender identity expression for personal, cultural, or religious reasons may manifest itself as distress and profound unhappiness and may lead to the development of mental health problems (20).

Mental Health in Transgender People and the Effect of Hormonal Treatment

Overall prevalence of mental health diagnoses

Studies investigating rates of mental health diagnoses in the transgender population, once again, have focused on those attending transgender health services (21). Most of the studies have been cross-sectional and report high rates of affective disorders (38%) (22) such as depression (23) and adjustment disorders (24), as well as anxiety disorders (17%) (25, 26). Rates of nonsuicidal self-injuries have also been found to be very high, particularly among young people (46%) as well as suicide attempts (27–29). The few studies that compared their findings to the general cisgender population (controlled by age and sex) found certain mental health diagnoses, such as anxiety disorders, are

threefold more prevalent among transgender people compared with cisgender people (25).

Differences in prevalence according to gender

There are some discrepancies as to whether mental health diagnoses are more common among transgender men or among transgender women. Some studies have found that mental health diagnoses were not related to assigned or identified gender (30, 31), whereas other studies have demonstrated higher rates of mood disorders (23, 32), anxiety disorders (32), adjustment disorders (18), and substance abuse (24) among transgender women than among transgender men. Most of those studies are biased by not controlling for factors known to influence mental health diagnoses, particularly hormone treatment. This means that people have been recruited for studies independently as to whether they are on hormone treatment or not, although research has confirmed that such treatment reduces mental health problems. Interestingly, more recent large controlled studies involving only transgender people not on treatment have found that anxiety disorders were more prevalent among transgender men than among transgender women (25). A similar study also found levels of self-harm were also higher among the same group (28).

Predictors of mental health problems

Several factors have been found to predict mental health issues among the transgender population attending transgender health services, such as experiences of victimization (or transphobic experiences), low self-esteem (27), and interpersonal problems (28, 33). Lack of hormone treatment of those wanting physical change has been found to be the strongest predictor of mental health diagnoses (21, 25, 31).

The role of hormone treatment in mental health

A number of longitudinal studies have explored the role of hormonal treatment in mental health and quality of life among transgender people wanting gender-affirmation treatment. These studies, which have mainly been conducted in Europe [Sweden (34), Italy (35), Belgium (36), and Germany (37)], have all demonstrated that people's mental health (levels of depression and anxiety) significantly improved following hormone treatment. Long-term follow-up studies and studies involving large groups of people are needed to evaluate whether these improvements remain. Hence, hormone treatment of those wanting physical change needs to be accessible, as this will reduce morbidity and improve quality of life of transgender people.

Posttreatment regrets

The literature on posttreatment regret is complex to interpret. Overall satisfaction after gender-affirming treatment is high. A study from >20 years ago found 2% of transgender women and 1% of transgender men later regretted their decision to undergo hormonal and/or surgical treatment (38). There are many causes of regret. Frequently dissatisfaction following gender-affirming surgery has been interpreted as regret regarding social and medical transition. To distinguish those people who express dissatisfaction following gender-affirming treatment from those who wish to detransition and return to their sex assigned at birth, Pfäfflin (39) in 1992 differentiated minor from major regrets. In one of the largest gender clinics (Amsterdam), 2034 individuals received treatment between 1975 and 1998. Ten of these people subsequently indicated that they regretted their decision to have undergone the treatment (nine transgender women and one transgender man) (39). The reason for those regrets varied from identifying with the sex assigned at birth and wanting detransition (n = 6) (classified as major regrets) to dissatisfaction of the outcome of surgery or loss of support following gender-affirming treatment (n = 4) (minor regrets). Upon review in 2005, the number of major and minor regrets increased by 5 out of a total of 3090 subjects. In 2015 the total number of subjects treated had risen to 6793, but there was no further increase in those expressing regret. The fact that fewer people have been having doubts about their treatment decisions over time may reflect the much-improved understanding of gender incongruence both by transgender people themselves and by the medical profession, as well as much greater acceptance of transgender people in society (39).

"The medical professional provides a more patient-centered approach to care and understands the needs of the person rather than making a diagnosis of the patient."

Summary

Mental health diagnoses are common in the transgender population, possibly owing to negative societal values, but they do improve once gender-affirming treatment is initiated. This highlights the importance of hormone treatment and access to adequate transgender health care. Although state-funded health services, which are primarily available in Europe, may develop services where the needs of the transgender population can be provided for, including assessment, psychological support (when needed), hormonal treatment, and gender-affirming surgery, other health care systems may not be so fortunate and transgender people may find themselves searching for professionals who are able to confidently prescribe and monitor hormone treatment.

Results

Hormonal treatment in transgender women

Initial evaluation of transgender women

Transgender women seek hormone therapy to change their physical appearance to better match their gender identity and expression (40, 41). Furthermore,

transgender women experience improved quality of life and a decrease in gender dysphoria upon initiation of hormone therapy (42, 43). In the United States, Canada, and most of Europe, transgender women must seek medical professionals for hormone therapy because these medications are available only by prescription, but there is a black market also particularly for oral contraceptives. For non-Western countries, hormone therapy is often self-prescribed without supervision by a medical professional. Available evidence from the United States and Europe suggests that hormone therapy initiated and monitored under the supervision of a medical professional is associated with very low rates of adverse events (44, 45).

The Endocrine Society guidelines recommend that a medical professional confirm the diagnosis of gender dysphoria and/or gender incongruence in transgender women prior to the initiation of hormone therapy. Medical professionals should document that the gender dysphoria has been persistent and that the individual is able to make an informed decision and consent for treatment (40). However, there are no validated psychological tests or imaging studies that have been clinically useful to diagnose gender dysphoria (46), which is likely because people with gender nonconforming expression and behaviors represent a very large and heterogeneous population. There is no demonstrable biological substrate for gender incongruence. In this regard, medical professionals have been moving toward a more gender-affirmative model whereby the medical professional provides a more patient-centered approach to care and understands the needs of the person rather than making a diagnosis of the patient (47, 48).

Screening for conditions prior to initiation of hormone therapy

Medical professionals should evaluate transgender women for conditions that can be exacerbated by hormone therapy. Patients with a history of thromboembolic diseases such as deep vein thrombosis and pulmonary embolism should undergo evaluation and treatment prior to the initiation of hormone therapy (40). Additionally, risk factors that can increase the risk of thromboembolic conditions should be modified such as smoking, obesity, and sedentary lifestyle. In patients with modifiable risk factors such as known thrombophilia, past history of thrombosis, or a strong family history of thromboembolism, treatment with transdermal estrogen and/or concomitant treatment with anticoagulation therapy may need to be considered, although there are limited data to guide treatment decisions (49, 50). Other diseases such as hormone-sensitive cancers, coronary artery disease, cerebrovascular disease, hyperprolactinemia, hypertriglyceridemia, and cholelithiasis should be evaluated prior to the initiation of estrogen therapy, as these conditions can be exacerbated by estrogen.

Modalities of hormonal therapy in transgender women

There are two main classes of medications used in transgender women: (1) estrogen therapies and (2) androgen-lowering hormone therapies.

Estrogen therapies. The synthetic estrogen ethinyl estradiol was a widely used estrogen in Europe prior to 2003. However, given recent safety concerns about its prothrombotic potential and its potential role in cardiovascular disease, most clinics have now switched to oral, cutaneous, or IM estradiol (51). A few commonly used estrogen regimens in transgender women have been reported [see appendix B of Ref. (40)]; however, there are very few head-to-head studies comparing the efficacy and safety of estrogen regimens. In a large multinational cohort study (titled European Network for the Investigation of Gender Incongruence) of four European countries (Belgium, Netherlands, Italy, and Norway), >300 transgender women were prescribed oral estradiol valerate at 4 mg daily or estradiol valerate at 20 mg IM every 2 weeks or an estradiol patch (100 μg daily), each with cyproterone acetate (CPA) at 50 mg daily (52). In the short term (<5 years), these regimens are associated with mild elevations of prolactin (53) and improvements in bone mineral density (BMD) after 1 year of therapy (54). No short-term or long-term adverse events have been published from this cohort using this hormone regimen.

In a German cohort, transgender women were treated with a regimen of estradiol valerate at 10 mg IM every 10 days. The authors also reported short-term gains in bone density after 24 months of therapy along with higher body mass index (BMI) with an increase of fat mass and decrease of lean body mass (55).

In the United Kingdom, transgender women were previously prescribed ethinyl estradiol or conjugated equine estrogen, but they are now changed to oral estradiol at a dose of ~4 mg daily (56). In a retrospective review of transgender women in the United Kingdom, transgender women prescribed oral conjugated equine estrogens had increased risk of thromboembolism compared with transgender women taking oral estradiol valerate or ethinyl estradiol. In this cohort, 4.4% of transgender women on oral conjugated equine estrogen experienced a thromboembolic event compared with <1% in transgender women on estradiol or ethinyl estradiol ($P = 0.026$).

In the United States, estrogen therapy can be prescribed as oral tablets, IM injections, and transcutaneous preparations (41). Most commonly published in the United States is the prescription of oral estradiol at 4 to 5 mg daily (57, 58). Studies that compare the long-term safety and effectiveness among the different formulations of estrogen are lacking. The Endocrine Society guidelines recommend that the

doses of estradiol be titrated to serum estradiol levels at ~200 pg/mL (734 pmol/L) (40).

Androgen-lowering therapies. Transgender women will often require the addition of a medication to lower testosterone levels into the female range (59). In most European countries, the most commonly prescribed androgen-lowering medication is oral CPA 50 mg daily (44, 52, 60). Cyproterone acts primarily as an androgen receptor blocker but also has some progesterone-like activity (61). However, given reports of increased risk of meningiomas (62–64), association with depression (56), and increased risk of hyperprolactinemia (53) with CPA use, in the United Kingdom, transgender women are now prescribed GnRH agonists to lower testosterone concentrations (65). In contrast to the rest of Europe and the United States, GnRH agonists are provided free of charge to transgender women by the National Health Service in the United Kingdom (56).

Spironolactone is the most commonly prescribed testosterone-lowering medication in the United States (57, 58). Spironolactone is classically known as an antagonist of the mineralocorticoid receptor and a potassium sparing diuretic. It also has antiandrogen properties by directly lowering testosterone synthesis and testosterone action at the androgen receptor (40). One US cohort of ~100 transgender women found estrogen therapy in combination with oral spironolactone at 200 mg daily was effective in lowering serum testosterone levels to the cisgender female range for serum testosterone after ~1 year of therapy (66).

Peripheral androgen receptor blockers such as flutamide or dutasteride have not been recommended for use in transgender women because these agents do not lower serum testosterone levels and there are limited published studies in this population (40).

Other second-line hormonal therapies. Progesterone: Progesterone therapies such as medroxyprogesterone have been used as a second agent to lower testosterone concentrations in transgender girls and women (57). Some transgender women may request progesterone to enhance breast development; however, there are no clinical studies to support a positive effect of progesterone on breast development (67). Furthermore, there are concerns regarding potential increased risk of thromboembolism and stroke found in cisgender women taking progesterone (68, 69). Therefore, progesterone therapy is not a routinely used medication in transgender women.

5α-Reductase inhibitors: Some transgender women may experience male pattern hair loss and may seek treatments to arrest hair loss and/or restore hair. In general, lowering serum testosterone levels into the cisgender female range is often adequate to arrest hair loss in most transgender women; however, there are still some transgender women who experience hair loss despite lowered serum testosterone levels. A few case series in transgender women with androgenetic alopecia have demonstrated finasteride therapy to be effective to improve hair loss without significant side effects (70, 71). The routine use of 5α-reductase inhibitors has been limited over previous concerns of long-term sexual dysfunction and depression reported to be found in cisgender men (72, 73).

Feminization in transgender women

Treatment with estrogen and testosterone-lowering medications will induce feminine and reduce masculine physical characteristics Fig. 1 (41). The most studied physical change in transgender women is the development of breast tissue. An Italian cohort study found increases in breast size were the only physical feature that was significantly associated with improvement in body uneasiness scores (43). However, <20% of transgender women reach Tanner breast stage 4 to 5 after 24 months of hormone therapy and thus often seek mammoplasty. Early studies in transgender women indicated breast development reached a maximum size by 2 years (74). However, a more recent study of 229 transgender women participating in the European Network for the Investigation of Gender Incongruence cohort found that breast development reached a plateau within the first 6 months of therapy and half of the transgender women had a AAA cup size or less (75). Fisher *et al.* (43) also found that testicular volume decreased by ~60% after 24 months of transfeminine hormone therapy.

"All transgender women should be aware of the potential fertility preservation options such as sperm cryopreservation."

Body composition. In a meta-analysis of studies published prior to 2015, transfeminine hormone therapy was associated with increased body fat and a decrease in lean body mass in 171 transgender women (76). More recent studies from Europe have documented that BMI increases in transgender women after transfeminine hormone therapy (43, 77). Klaver *et al.* (78) also demonstrated increases in body weight in 179 transgender women, and transfeminine hormone therapy was associated with an increase in body fat, specifically in the android, leg, and gynoid regions. However, recent studies from the United States have demonstrated that important changes in BMI in transgender girls and women do not occur during a short term (<6 months) (56, 79).

Voice. Transgender women will have an improved self-perceived feminine quality in their voice after the initiation of hormone therapy (80). However, many transgender women still have difficulty with their voice quality and are misperceived in the wrong gender by others (81). Transgender women may undergo voice training exercises to improve their voice quality (82). Laryngeal surgical treatment has been described as an option for transgender women to improve voice quality; however, a meta-analysis failed to demonstrate a significant benefit of surgical techniques to improve the quality of the voice (83).

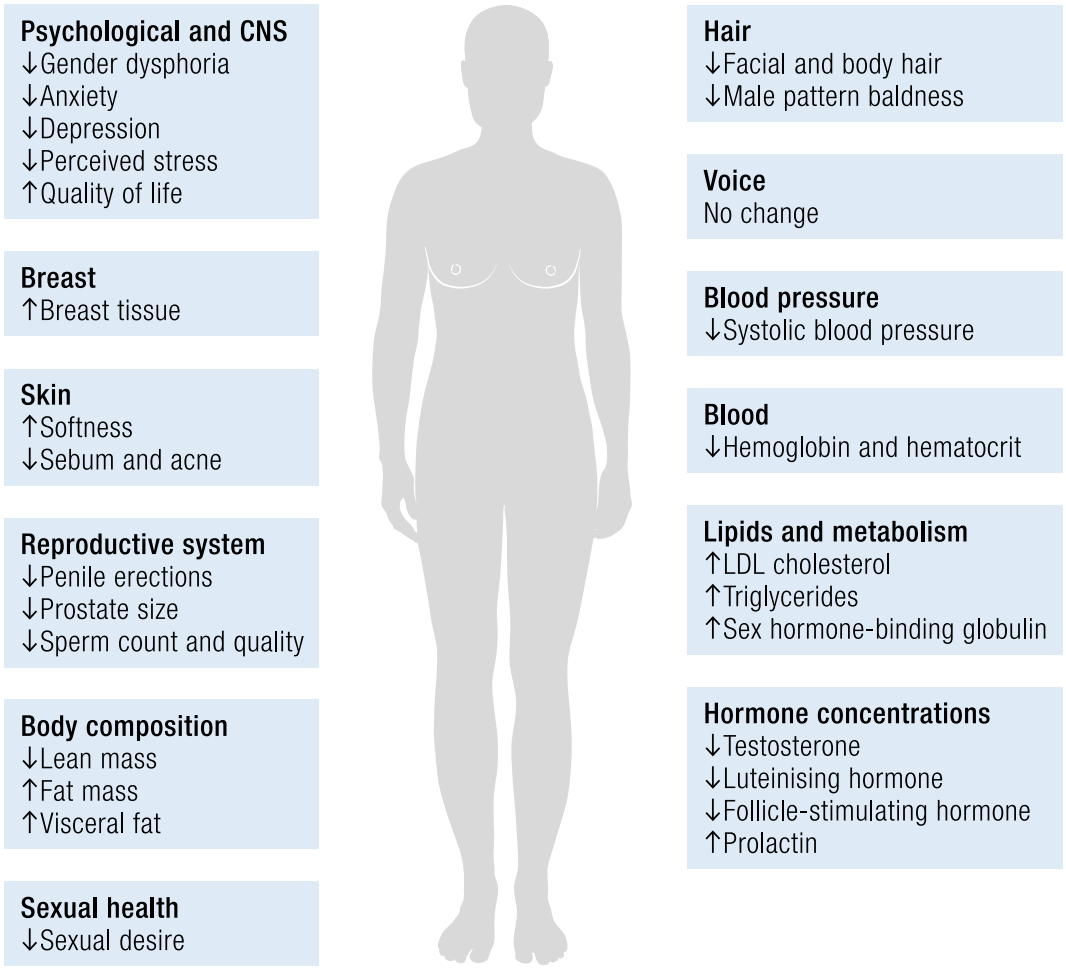

Figure 1. Effects of estrogen and antiandrogen treatment in transgender women. [Reproduced with permission from Tangpricha V, den Heijer M. Estrogen and antiandrogen therapy for transgender women. Lancet Diabetes Endocrinol 2017;5:291–300. (41); ©2019 Illustration Presentation ENDOCRINE SOCIETY].

Skin and hair. Transgender women will also experience reduction in facial hair after transfeminine hormone therapy. Fisher *et al.* (43) reported that Ferriman–Gallwey scores improved after 2 years of transfeminine hormone therapy. Transfeminine hormone therapy may arrest male pattern hair loss (71). A survey of transgender women reported interest in having facial hair removal procedures; however, few data on the effectiveness of such procedures have been published (84).

Safety data specific to transgender women

Cardiovascular and thromboembolic safety. There have been some concerns about long-term effects of transfeminine hormone therapy on cardiovascular outcomes. A single-center study of >200 transgender women from Belgium reported increased rates of myocardial infarction, venous thrombosis, and cerebrovascular disease compared with cisgender men and women (85). A recently commissioned systematic review and meta-analysis of cardiovascular outcomes in transgender individuals did not find an increased risk of myocardial infarction, stroke, or venous thrombosis in transgender women owing to lack of reported outcomes from 29 eligible studies (86). This systematic review also found that transfeminine hormone therapy was associated with increased serum triglyceride levels of 31.9 mg/dL (95% CI, 3.9 to 59.9) in transgender women treated for >24 months with no changes in serum low-density lipoprotein or high-density lipoprotein. Thrombosis risk in transgender women is likely increased given the known prothrombotic actions of estrogen. However, under medical supervision, the risks of transfeminine hormone therapy appear to be safer than self-prescribed transfeminine hormone therapy (45). A large study conducted in 162 transgender women treated with transdermal estrogen in Austria found that only 19 had a genetic mutation associated with venous thrombosis (1 with protein C deficiency and 18 with activated protein C resistance) and none developed a thrombotic event, suggesting that estrogens that avoid the hepatic first-pass effect may have less prothrombotic risk (87). Furthermore, given the low frequency of genetic mutations associated with thrombosis (19 out of 162), the authors do not recommend routine screening for thrombophilia. There have been reports of transgender women who developed

a thrombotic event and were successfully treated with anticoagulation therapy (50, 88). However, there are no long-term studies to guide treatment of transgender women following a thrombotic event.

Bone health. The fracture rate associated with transfeminine hormone therapy is unknown. Estrogen is critically important for preserving BMD in postmenopausal women and in men who lack estrogen action at the bone (*e.g.*, mutations in the estrogen receptor or aromatase enzyme) (89, 90). A recent meta-analysis of 392 transgender women found a significant increase in lumbar spine BMD but no changes in hip BMD. The rates of fracture were found to be low, with no fractures found in 53 transgender women after 12 months in this review (91). A recent multicenter study of 231 transgender women in Europe treated with transfeminine hormone therapy found a 3.67% increase in lumbar spine bone density and a 0.97% and 1.86% increase in total hip and femoral neck bone density, respectively, after 1 year of therapy (54).

Transgender women have been found to have lower BMD even prior to the start of hormone therapy (92). Van Caenegem *et al.* (92) found that 16% of transgender women had T-scores at the lumbar spine below −2.5 and approximately one third had T-scores between −1 and −2.5 at the lumbar spine or total hip. The reasons why transgender women had lower bone density than expected for age are not clear, but the authors hypothesized decreased outdoor physical activity as an explanation, as vitamin D status was found to be low in 72% of the cohort.

Oncological data and mortality. The prevalence of hormone-sensitive cancers such as breast and prostate cancer appears to be low among transgender women. Initial studies from a cohort of >2000 transgender women reported no increase in breast cancer incidence compared with the expected rate of breast cancer in cisgender women (93). A large cohort of >5000 transgender military veterans in the United States reported only nine cases of breast cancer in transgender veterans, two in transgender women, and seven in transgender men (94). All of the transgender women presented with late-stage breast cancer that proved to be fatal, whereas the transgender men before or after breast ablation presented with earlier disease (95). One the largest studies examining cancer risk in transgender women in the United States used data from one large health care system (Kaiser Permanente: Georgia and Northern and Southern California (96). Using an electronic database method to identify transgender women in this cohort, they identified 2791 transgender women subjects. Based on ICD-9 codes, the investigators found no increased risk of breast cancer or any cancer when comparing transgender women to matched cisgender women. However, there was an increased risk of breast cancer and endocrine gland cancers in transgender women compared with matched cisgender men. Furthermore, there was a decreased risk of prostate cancer compared with matched cisgender men. Other studies have reported a low risk of prostate cancer in transgender women. A recent review of literature of prostate cancer in transgender women only found 10 cases reported (97).

Other considerations. Fertility: All transgender women should be aware of the potential fertility preservation options such as sperm cryopreservation. Transgender women report that they are interested in having their own biologic children but very few transgender women use fertility preservation technologies (98, 99), possibly due to the lack of funding for fertility preservation in many countries. Because sperm production will decline after the initiation of hormone therapy, the Endocrine Society guidelines recommend that all transgender women discuss fertility options with their health care team prior to the initiation of hormone therapy (40).

Monitoring of feminizing hormone therapy: Transgender women who take hormone therapy under medical supervision experience very low rates of complications (44, 45). Transgender women should maintain serum estradiol and testosterone concentrations within the expected physiologic female range (40). The Endocrine Society recommends hormone measurements every 3 months in the first year of initiating hormone therapy until the hormone concentrations reach the desired concentrations. Once the hormone dose is achieved, the hormone concentrations of both testosterone and estrogen can be measured once yearly or when there is a dose change to ensure that levels remain in the range expected for cisgender females (40). Transgender women taking spironolactone should have measurement of potassium and kidney function on a regular basis. Following surgery, transgender women can have a final measurement of serum testosterone to confirm that levels in the male range are eliminated.

Measurement of prolactin levels during the course of gender-affirming hormone therapy has been suggested by the Endocrine Society guidelines. However, recent reports indicate that elevated prolactin levels seem to occur in transgender women on CPA and not on spironolactone. Defreyne *et al.* (53) demonstrated that prolactin levels increased in transgender women receiving cyproterone but decreased after discontinuation. Furthermore, a recent study by Fung *et al.* (100) demonstrated that transgender women treated with cyproterone had significantly higher prolactin levels compared with those treated with spironolactone (41).

Hormonal treatment in transgender men

Initial evaluation of transgender men

During the first outpatient consultation, the same principles apply as described for transgender women above.

Screening for conditions prior to initiation of hormone therapy

Transgender men must be informed of the possibilities, consequences, limitations, and risks of testosterone treatment. Fertility preservation options are to be discussed before starting a medical intervention. Pregnancy is an absolute contraindication for testosterone therapy, and relative contraindications include severe hypertension, sleep apnea, and polycythemia (40). Conditions that can be exacerbated by testosterone therapy are presence of erythrocytosis, baseline high hematocrit levels (*e.g.*, secondary to smoking or chronic obstructive pulmonary disease), sleep apnea, and congestive heart failure. Knowledge on the presence of menstruation problems prior to initiation of testosterone treatment and on sexual practices will guide the need for follow-up procedures such as pelvic ultrasounds and pap smears.

Modalities of hormonal treatment in transgender men

Testosterone. The principal hormonal treatment used to induce virilization is testosterone. Under medical supervision, testosterone therapy is safe based on short-term and longer-term safety studies (44, 101, 102). Different testosterone formulations may be available depending on geographical location. Most commonly prescribed are injectable testosterone esters (40). More recently, subcutaneous administration of testosterone was shown to be effective and preferred by transgender men at a median dosage 75 mg weekly in 63 transgender men (103, 104), confirming an earlier intervention study (104). Long-acting testosterone undecanoate is also being used for treatment of transgender men (105). However, in the United States, the prescription of testosterone undecanoate is limited owing to the potential risk of oil pulmonary embolus, and both patient and provider must undergo Risk Evaluation and Mitigation Strategy training to receive this therapy. Other intervention studies [see appendix A of Ref. (40)] have also used topical androgen gel or transdermal patches. The use of oral testosterone (testosterone undecanoate), axillary solutions, patches, nasal sprays, buccal tablets, or pellets is rarely reported for treatment in transgender men. In one study the effects of three different testosterone formulations were evaluated at baseline and after 12 months of treatment and no differences were found regarding short-term safety, compliance, body composition, metabolic parameters, and general life satisfaction (106). Androgen therapy will need to be continued lifelong to maintain the achieved virilization and to avoid symptoms of hypogonadism such as vasomotor symptoms or osteoporosis.

Progestational agents. If menstrual bleeding does not stop after initiation of testosterone, a progestational agent, such as oral lynestrenol at 5 to 10 mg daily or medroxyprogesterone at 5 to 10 mg, might be considered. This occurs frequently with the use of transdermal or oral testosterone undecanoate, which are both associated with lower testosterone levels compared with injectable testosterone. GnRH analogs to halt menses are theoretically possible, but they are rarely reported in adults given the costs of therapy. If ovariectomy is performed, the progestational medication can be discontinued (107–109).

Virilization in transgender men

Treatment in transgender men is intended to induce virilization. This includes cessation of menses, development of male physical contours, a deepening of the voice, clitoral growth, increased sexual desire, and increased facial and body hair (Fig. 2) (108, 110, 111). Male pattern baldness may also occur. Changes in body composition, with redistribution of body fat and increased muscle mass and strength, have been described extensively (40, 44, 112). The time period before cessation of menses may vary from 1 to 12 months after testosterone initiation, sometimes requiring the addition of a progestational agent (40, 113). Mean clitoral length may reach 3.83 ± 0.42 cm after 2 years of testosterone therapy (43)

It is important that transgender men understand the possibilities but also the limitations of testosterone treatment. Height and bone structure (broader hips) and the larger degree of subcutaneous fat remain largely unchanged when therapy is started after puberty (108). Most of the published guidelines have been developed with the white transgender person in mind, but ethnic differences may warrant tailoring of standard doses (114). Recommendations based on clinical experience are in favor of continuing testosterone treatment of elderly transgender men (115).

Body composition. Testosterone therapy will enhance a more masculine musculature, body shape, and body fat distribution. Testosterone therapy will result in changes in body composition. A meta-analysis of 10 studies examining body composition changes in response to testosterone during 12 months found body weight increased by 1.7 kg (0.7 to 2.7), body fat decreased by 2.6 kg (−3.9 to −1.4), and lean body mass increased by 3.9 kg (3.2 to 4.5) (76). Another systematic review, focusing among other parameters on BMI, revealed an increase in BMI from 1.3% to 11.4% (116). Grip strength increased with 18% in a study with 23 participants and 1-year parenteral testosterone undecanoate treatment (92).

Voice. Testosterone therapy at doses in the physiological range for men will induce acoustic changes occurring from effects on the larynx (117). In a cross-sectional study of 38 transgender men, acoustic voice variables and voice quality were similar between the transgender men and cisgender controls. However, 10% of the transgender men experienced issues with pitch quality, needing voice therapy and sometimes pitch-lowering surgery (118). Transgender

Figure 2. Effects of testosterone treatment in transgender men. [Reproduced with permission from Irwig MS. Testosterone therapy for transgender men. *Lancet* Diabetes Endocrinol 2017;5: 301–311. (110); ©2019 Illustration Presentation ENDOCRINE SOCIETY].

men (n = 77) whose voices sounded more congruent with their experienced gender reported greater well-being than did those with less gender-congruent voices (119). There are very few prospective data on the voice changes in transgender men upon testosterone treatment. Seven transgender men on IM testosterone esters all reached a cisgender male mean fundamental frequency within 6 months of testosterone therapy. A mean decrease of 49 Hz was measured (120). In the largest longitudinal study to date (n = 50, with 36 having data for baseline and 12-months follow-up), acoustic analysis of fundamental frequency of the habitual voice showed a significant decrease after 3 months (−37 Hz), up to 12 months (−67 Hz), with group data congruent with cisgender male reference data. In 24% of participants additional voice therapy was necessary. When using an adapted version of the Transsexual Voice Questionnaire (121) for transgender men looking at self-perception of voice prospectively during IM testosterone undecanoate therapy in 80 participants, improvements during the first 3 months were attributed to the hormonal intervention (80).

Skin and hair. Both androgens and estrogens are known to affect the pilosebaceous unit of the skin, as in the sebocytes and hair follicle dermal papilla androgen and estrogen receptors are expressed. In a study of 17 transgender men, IM testosterone therapy was associated with increases in the Ferriman–Gallwey hirsutism scores (122). After 12 months, facial and abdominal hair had not yet reached diameters found in cisgender males. An increase in acne on the face and back was present in 94% and 88%, respectively, after 4 months. Data on both the shorter-term and longer-term dermatological effects of IM testosterone undecanoate were available from a prospective intervention study in 20 hormone-naive transgender men, combined with a cross-sectional part with 50 transgender men with an average of 10 years on various testosterone treatments (101). The Ferriman–Gallwey

score (in cisgender women usually <8) increased in a time-dependent manner from a median of 0.5 to 12 after 1 year, whereas long-term testosterone treatment resulted in a median score of 24. The presence and severity of acne based on the Gradual Acne Grading Scale increased during the first year and peaked at 6 months; facial acne was present in 82%, and back acne was present in 88%. Long-term data from this study showed that 94% of transgender men had no to mild acne. In a study with 45 transgender men, 16% developed troublesome acne when treated with testosterone undecanoate for 2 years (123).

In a retrospective, observational study, 81 transgender men treated with testosterone esters or testosterone undecanoate self-assessed the degree of male pattern baldness using a five-point scale [*i.e.*, type I (no hair loss) to type V (complete hair loss)]. The authors found that 38% of transgender men had male pattern baldness types II to V. Thinning of hair was related to the duration of androgen administration and present in half of the transgender men after 13 years (124). Wierckx *et al.* (44) reported that 17% of participants developed androgenic alopecia based on the Norwood–Hamilton classification after 1 year of treatment. Longer-term (10 years on average) testosterone treatment was associated with 32% of mild frontotemporal hair loss and 31% moderate to severe androgenetic alopecia (101). In 10 transgender men with androgenetic alopecia, treatment with oral finasteride at 1 mg daily for 12 months induced improvement with one grade on the Norwood–Hamilton scale after a mean of 5.5 months since the start of treatment (70).

Safety data specified for transgender men

Cardiovascular safety. Adult cisgender men have higher cardiovascular mortality rates than do women, which has been attributed to differences in sex hormone levels. However, the available cardiovascular outcome data in transgender men show that testosterone treatment does not result in adverse cardiovascular outcomes (125). Four different recent review papers (86, 116, 126, 127) summarized the effects of testosterone on surrogate risk factors of cardiovascular disease. These reviews demonstrated that despite a perceived negative impact on a number of risk factors, including an increase in hematocrit, a decrease in high-density lipoprotein cholesterol, an increase in triglycerides, low-density lipoprotein cholesterol levels, and inflammation parameters (128), a small increase in systolic blood pressure (44, 123), and a decrease in adiponectin and leptin (129), no significant increase in cardiovascular outcomes was found (77). Furthermore, there have been no elevated rates of cardiovascular deaths when compared with cisgender men and women at short and medium follow-up in the larger studies [except for one study (30)]. However, data on cardiovascular outcomes in older (65+ years of age) transgender men are mostly lacking (86). In a cross-sectional study of 50 transgender men on testosterone treatment of an average of 10 years, no subject had experienced myocardial infarction, stroke, or deep venous thrombosis (130). In a similar case-control study, 138 transgender men on testosterone therapy for an average of 7.4 years showed a low cardiovascular morbidity (85). In a prospective study with 43 transgender men who were treated with testosterone esters every 3 weeks, there was an increased incidence of previously absent metabolic syndrome after 1 (16.3%) and 2 years (18.6%), especially in those with psychiatric comorbidity (131). Furthermore, most studies in transgender men report no adverse impact of testosterone treatment on fasting glucose or insulin sensitivity (44, 106, 129, 131).

Many studies report an association between testosterone therapy and increased Hb (range, +4.9% to 12.5%) and hematocrit (range, +4.4%–17.6%) during the first year of treatment, which then plateaus after the initial year of treatment (105, 123). Clinically significant erythrocytosis has been reported but is likely very uncommon (116). In such cases, practitioners sometimes advise change of the testosterone route of administration or reduction of dosage, despite the absence of outcome data showing risk reduction of thrombotic events. In one study, use of testosterone gel showed smaller increases in Hb (+4%) and hematocrit (+2%) compared with injectable testosterone (106).

A prospective study of 89 transgender men treated with parenteral testosterone undecanoate and lynestrenol for ~4 years found no cases of venous thromboembolic disease despite five subjects who had the activated protein C mutation. The authors concluded that general screening for thrombophilic defects is not recommended (87). In a similar study, 50 transgender men followed for ~10 years found no cases of venous thromboembolism (130)

Importantly, note that most transgender men are still relatively young, at an age when the risk of cardiovascular events is low. Long-term data and data from older transgender men are needed.

Bone health. Sex steroid hormones play important roles in bone growth and maintenance. Men develop larger, longer, and stronger bones during puberty, explained through the combination of sex steroids and mechanical loading. Testosterone therapy in transgender men preserves bone density with adequate dosing due to aromatization of testosterone to estradiol (132). There are very limited data on the risk of osteoporotic fractures in transgender men (91). Transgender men have similar BMD compared with cisgender females prior to testosterone therapy (92, 133, 134).

Following ovariectomy, testosterone substitution therapy appears to prevent short-term (<2 years) (54, 92, 106, 123, 133, 135–137) and long-term (10+ years) (138–141) bone loss due to estrogen deficiency.

Transgender men had larger cortical bone size compared with cisgender females in a cross-sectional study (140). An additional study confirmed the higher cortical thickness by histomorphometric bone biopsy study (142) and higher areal BMD at cortical sites (136, 139). This reflects the effect of androgens on the periosteal circumference of cortical bone. The androgen-induced higher muscle mass also induces a higher mechanical load on the bone, possibly stimulating bone formation according to the mechanostat theory (143). Higher bone formation was observed in transgender men on testosterone (92, 133, 138, 140), and both muscle mass and strength were positively associated with trabecular and cortical parameters and bone size. Nearly all studies reported a maintained areal BMD, which argues against bone loss (91). However, in transgender men who underwent ovariectomy, bone loss has been described when they irregularly used or stopped androgen therapy or when dosage was inadequate (134, 135, 138).

Oncological data and mortality. Both practitioners and transgender men express concern around carcinogenicity of long-term hormonal therapy, although these concerns are not supported by the available data. Recently, the published cancer case reports in transgender men were summarized (144): one vaginal, one cervical, seven breast, one endometrial, and three ovarian cancers have been described to date. The association to risk factors such as smoking and alcohol use, sexually transmitted infections, and lack of adequate access to screening programs has to be acknowledged and included in future research (144). In transgender men on testosterone treatment and not undergoing surgical interventions, breast and cervical cancer screening protocols are advised, but timing and frequency of monitoring of female internal organs in transgender men are a matter of debate.

The available data on cancer mortality are limited and based on studies on four different populations (Belgium, Sweden, Netherlands, and United States). Despite low statistical power, these reviews demonstrate very few cancer events in the population of transgender men (30, 85, 93, 102, 130, 145, 146). The data on overall mortality in transgender men, specifically related to testosterone treatment, are scarce, and the few available studies are underpowered (30). A study from the Dutch cohort with 122 transgender men (145), with a later follow-up on 293 (146) and 364 transgender men (102), reported mortality to be similar to those of the general population. The lack of cancer outcome data underlines the need for studies of a large and inclusive sample size and long-term follow-up from multiple specialized centers.

Other considerations. Fertility: There is a clear need to discuss reproductive options with transgender men before starting testosterone treatment (98). From a study based on a questionnaire, 54% of the transgender men desired to have children and 37% would have banked oocytes had this been possible (147). Genital reconstructive surgery results in an irreversible loss of natural reproductive capacities, whereas testosterone therapy has an important but partially reversible impact on fertility. In theory, embryo and oocyte cryopreservation as established techniques, and ovarian tissue cryopreservation more experimentally can be mentioned as examples of fertility preservation options (148). The necessary hormonal stimulations with multiple endovaginal ultrasound monitoring are likely to be perceived as physically and emotionally difficult, making oocyte cryopreservation not the preferred fertility preservation technique in this group, and some wish to postpone this toward the time of hysterectomy and oophorectomy. A strong suppression of anti-Müllerian hormone has been described in 22 transgender men treated with a GnRH agonist, combined with testosterone gel and an aromatase inhibitor (149). Reassuringly, androgen treatment did not deplete the primordial follicles in the ovarian cortex strips, and a normal distribution of cortical follicles in the ovaries remained intact in 40 transgender men after >1 year of testosterone treatment (150). However, the use of *in vitro* maturation without the use of xenotransplantation is far from implementation in a clinical setting (151). Once a mature oocyte is obtained, the use of partner sperm or donor sperm and a recipient uterus upon thawing of the oocytes, or a female partner or surrogate mother, will enable conception.

"Treatment can generally start when the adolescent is in Tanner stages 2 to 3."

Based on an online survey in 41 transgender men who had been pregnant, of which 25 had used testosterone, 80% reported resuming menstruation within 6 months upon interrupting testosterone treatment, whereas 20% experienced no menses before pregnancy. Of note, exogenous testosterone is not an adequate means of birth control. Testosterone has teratogen effects on the fetus; therefore, transgender men should avoid pregnancy while on testosterone therapy. This is included in preconception counseling that addresses stopping testosterone while trying to conceive and during pregnancy, with the possibility of increasing gender dysphoria during and after the pregnancy. Postpartum, the options for breast feeding and when to reinitiate testosterone have to be discussed (152).

Monitoring of virilizing hormone therapy: Monitoring is advised three to four times in the first year of treatment and once or twice per year thereafter, according to the Endocrine Society guidelines (40). Aiming at testosterone levels in the physiologic normal male range and measuring hematocrit or Hb to avoid erythrocytosis are the most important parameters. Bone densitometry in transgender men should be performed when risk factors (smoking, excessive alcohol use, family history of osteoporosis, history of fracture, use of glucocorticoids, anorexia nervosa) for

osteoporosis exist, and more specifically in those who stop or temporarily interrupt hormone therapy after gonadectomy. Screening for breast and cervical cancer in transgender men who do not undergo surgical interventions is advised (40).

Hormonal treatment in adolescents

The endocrine treatment of transgender adolescents consists of two phases: pubertal suspension or gonadal suppression followed by the addition of hormones. During the first phase, pubertal development is halted and adolescents can further explore their gender identity and prepare for the next phase.

Gonadal suppression in adolescents

Gonadal suppression using GnRH analogs. To achieve gonadal suppression generally, GnRHa analogs (GnRHas) are used (153). GnRHas have been used since 1981 in the treatment of central precocious puberty (154, 155), and their benefits are well established and the use of GnRHa is regarded as both safe and effective, with no long-term adverse effects (156).

Treatment can generally start when the adolescent is in Tanner stages 2 to 3. In clinical practice, transgender boys usually can start when in Tanner breast stage 2 and transgender girls when they have a testicular volume of 6 to 8 mL. Also, adolescents who have already physically matured can use GnRHas to inhibit unwanted pubertal development, such as breast formation and menses in girls or further male phenotype development and erections in boys, until the adolescent's gender identity is more stable (40).

The general safety and efficacy of GnRHas have been studied (157, 158). Anthropometry and body development, hormonal status, and metabolic parameters were followed prospectively in 49 transgender girls (median age at start, 13.6 years; Tanner genital stage 4) and 67 transgender boys (median age, 14.2 years; Tanner breast stage 4) during 12 months of GnRHa monotherapy. Puberty was adequately suppressed with a decrease of testicular volume from 13.9 (±6.5) mL to 8.6 (±4.7) mL in 33 transgender girls. In transgender boys who initiated GnRHas early in puberty at Tanner breast stage 2 and early menarche, breast tissue fully regressed to stage 1 (n = 4) and menses ceased. Effective gonadal suppression was also reflected in a decrease in gonadotropin levels after a period of 3 months to nearly undetectable levels and a coinciding decrease in sex hormones. Testosterone decreased from 262 ng/dL (9.1 nmol/L) to <29 ng/dL (1.0 nmol/L) in transgender girls. In transgender boys, estradiol decreased from a median of 123 pmol/L to 29 pmol/L. As for anthropometry, height velocity decreased in both transgender boys and transgender girls whereas BMI SD score calculated for sex assigned at birth increased significantly. Body composition and the lean body mass percentage decreased and fat percentage increased significantly. Regarding safety monitoring, glutamyl transferase, aspartate aminotransferase, alanine aminotransferase, and creatinine levels did not significantly change from baseline to 12 months of treatment, but alkaline phosphatase decreased, most likely reflecting the decrease in growth velocity (157).

GnRHas are generally well tolerated with the exception of hot flushes early in treatment (158). However, hypertension in transgender adolescents under triptorelin treatment was reported in three transgender boys in a cohort of 138 subjects. Hypertension was reversible upon cessation of triptorelin, but in one case increased intracranial pressure occurred, requiring the temporary use of acetazolamide (159). GnRHa-induced hypertension is an uncommon side effect and has only been reported incidentally in children (160, 161).

Gonadal suppression in adolescents using other regimes. When resources cannot provide for GnRHa alternative treatment, regimens should be considered such as progestagens in transgender boys or CPA in transgender girls (40). Similar to transgender women, endogenous androgen production can be suppressed using antiandrogens such as CPA or spironolactone in late pubertal girls. The effects of prolonged CPA monotherapy were studied retrospectively in 27 transgender girls who were in Tanner genital stage 4. After 6 months of CPA at 50 mg once daily, testosterone decreased from 432 ng/dL (15.8 nmol/L) to 248 ng/dL (8.6 nmol/L) and remained stable at 226 ng/dL (7.8 nmol/L). LH and FSH, however, were not suppressed at 5.0 IU/L and 5.1 IU/L during this period. Prolactin increased from 318.2 pmol/L to 760.8 pmol/L, but none developed galactorrhea. Clinically more than half of the subjects reported reduced shaving frequency and approximately one third had breast development (Tanner breast stages 2 to 3). There was no increase in BMI SD scores. Fatigue was the only reported side effect. As for safety monitoring, only a transient increase of liver enzymes was seen in 15% of the study subjects. The levels remained under the threshold of three times the upper limit and therefore treatment was not stopped. Metabolic parameters such as lipid profile and glucose homeostasis were not negatively affected (162).

In postmenarche adolescent transgender boys an alternative for GnRHas to stop or decrease menses frequency may be the use of progestagens. A cohort of 42 transgender boys (mean age of 15 years and in Tanner breast stage 4) was retrospectively studied during 11.6 months of lynestrenol monotherapy. After 6 months, metrorrhagia occurred in 50% but reduced to 18% in the following 6 months. Subjects reported headache (12%) and hot flushes (10%). Serum LH decreased from 7.56 IU/L to 2.58 IU/L, but levels of FSH and estradiol remained unchanged. Weight increased during the first 6 months but returned to baseline value after 12 months. Regarding safety

monitoring, Hb and hematocrit increased but remained in the normal male range. Liver enzymes, lipid profile, and glucose homeostasis were not negatively affected (163).

The addition of gender-affirming hormones to GnRHa monotherapy

Hormone therapy in adolescents generally has two treatment regimes. In the case when GnRHa treatment is initiated in the early stages of pubertal development, the "new" puberty is induced with a dosage scheme that is also common in hypogonadal patients. Alternatively, when GnRHa treatment is initiated in late puberty and thus the duration of the hypogonadal state was limited, hormones can be given at a higher initial dose and more rapidly increased until the expected adult dose. An additional advantage of GnRHa treatment is that hormones do not have to be administered in supraphysiological dosages, which would otherwise be needed to suppress endogenous sex steroid production (40).

The timing of starting sex hormones in transgender adolescents continues to be an issue of debate. The recommended age of 16 years (40) is based on local jurisdiction, and not on cognitive maturation or pubertal development. In most countries at age 16 one is considered to be legally adult and one can make medical decisions. Indeed, when the first studied cohort was started in the Netherlands the age of 16 was chosen for this very reason. As a consequence there are few data available on starting GnRHa at an earlier age. The Endocrine Society guidelines make a recommendation to allow hormone therapy to be initiated at ages younger than 16 when the transgender child is evaluated by a multispecialty team with expertise in gender identity development in children. However, the need for re-evaluating the recommended age for starting GnRHa may shift in the future (1).

Transgender girls. For a pubertal induction, it is recommended to start 17β-estradiol at a dosage of 5 mg/kg/d, followed by six monthly increments of 5 mg/kg until a maintenance dosage of 2 mg is reached. The second treatment regimen is more suitable for transgender girls who initiated gender-affirming treatment when at least 15.5 years old. After a period of gonadal suppression varying from 3 to 6 months, estrogens can be given at a daily start dosage of 1 mg and increased to 2 mg after 6 months (40).

The effects of the addition of 17β-estradiol were studied prospectively in 28 transgender girls (155). Estrogen treatment was started at a median age of 16.0 years after a median duration of 24.8 months of GnRHa monotherapy. Breast development had started within 3 months, and after 1 year median Tanner breast stage was 3 progressing to 5 after 3 years (n = 16) with a variability of all breast stages. With respect to body shape, hip circumference increased and waist circumference decreased. Although BMI increased, BMI SD scores did not. When bone age was $<$15 years at the start of estradiol, median height gain was 6.8 cm after 3 years of estrogen therapy. Overall final height was 182.7 cm, corresponding to +1.9 SD for Dutch adult women. When the adult dose of 2 mg of estradiol daily was used during a median duration of 2 years, the median serum estradiol was 27 pg/mL (100 pmol/L) [range, 6.5 to 103 pg/mL (24 to 380 pmol/L)]. A change in prolactin levels was not seen. Additionally, Hb, hematocrit, HbA1c, liver enzymes, and creatine remained unchanged (164).

Transgender boys. For pubertal induction the use of testosterone ester injections is recommended. The initial dose is 25 mg/m^2 every 2 weeks IM and is increased with 25 mg/m^2 every 6 months. The maintenance dosages vary from 200 mg per 2 weeks for testosterone monoesters, such as testosterone enanthate, to 250 mg per 3 to 4 weeks for testosterone ester mixtures. For transgender boys who started treatment in late puberty, testosterone can be started at 75 mg IM every 2 weeks, followed by the maintenance dosage after 6 months (40). It is advised to continue GnRHa at least until maintenance dosage of testosterone is reached and preferred to continue until gonadectomy. With androgens, virilization of the body occurs, including lowering of the voice, more muscular development, particularly in the upper body, facial and body hair growth, and clitoral growth (40, 158).

Other considerations. Bone health in transgender adolescents: During puberty, the bone mass increases and peak bone mass is only achieved at the age of 20 to 30 years (165, 166). Bone mass accrual is regulated by genetic factors, gonadal hormones, and environmental factors such as physical activity and adequate supply of nutrients (calcium, vitamin D). During the hypogonadal state induced by GnRHa monotherapy, BMD is affected (167, 168). In transgender girls BMD of the lumbar spine remained stable but z score decreased during 1.5 to 2 years of gonadal suppression. In the femoral region, BMD and z score decreased but not significantly. In contrast, in transgender boys the BMD of lumbar spine and femoral region decreased together with the corresponding z scores (168).

When sex steroids are added, bone mass accrual reassumes. In transgender girls, absolute BMD and z scores in the lumbar spine but not the hip increased (167, 168), but after 2 years of estrogen their z scores were still below those of age- and sex assigned–matched norms (168). In transgender boys (150, 151), the bone density and z scores of the lumbar spine and the femoral region increased (n = 42) after 2 years of testosterone therapy but were still not at pretreatment levels (168).

When BMD development was assessed until young adulthood, however, it was found that the loss in z score was still partially present at the age of 22

"GnRHa treatment in adolescents is both clinically and biochemically effective in suppressing the hypothalamic-pituitary-gonadal axis and appears to be well tolerated and safe."

implying a possible delay in or loss of peak bone mass (167). To this date only one case report has been published on long term BMD development and it was shown that absolute BMD and *z* scores of a transgender man, treated with GnRHa in his adolescence was in the normal range at age 35. However pretreatment data were not provided (169).

The addition of gender-affirming hormones to other methods of gonadal suppression: For transgender girls, two retrospective studies reported on the addition of estrogens to antiandrogen therapies in transgender adolescents. In one study the subjects received CPA (163), and in the other study spironolactone (79) was used. The addition of estrogens to CPA monotherapy in transgender girls resulted in either the initiation or further progression of breast development. Oral 17β-estradiol was started at 0.5 mg daily and increased to 0.75 mg after 6 months. After 12 months of estrogen therapy, 66.7% reached Tanner breast stage 3 and 9.5% reached Tanner breast stage 4. After 12 months, both testosterone and LH decreased significantly to 168 ng/dL (5.8 pmol/L) and 3.2 IU/L, respectively, and FSH demonstrated a declining trend to 2.8 IU/L. The mean 17β-estradiol level was 33 pg/mL (121.1 pmol/L). The most common adverse event reported by the transgender girls was fatigue but resolved in almost all. BMI SD scores remained stable. In addition metabolic parameters, lipid profile and glucose homeostasis did not change (162).

In a study of 44 transgender girls (mean age, 18 years; range, 14 to 25 years) of whom 38 received spironolactone (dosage, 50 to 200 mg daily), oral estrogen was added in three routes: oral (dosage between 1 and 8 mg daily), IM (dosage 20 to 80 mg monthly), or transdermal (dosage 0.025 to 0.200 mg weekly). There were no changes reported in BMI, metabolic parameters, lipid profile, and prolactin and there were no differences in the methods of administration. Among the 38 subjects taking spironolactone, potassium levels did not change (79).

For transgender boys, testosterone can be added to progestagens as previously described (40) The clinical effects and effects on metabolic parameters in adolescent transgender boys have been investigated retrospectively in two studies, one single-center study (n = 42) (163) and one multicenter study center (n = 72) (79); however, in the latter study, seven subjects had received GnRHas prior to the testosterone therapy. Only the single-center study reported on side effects, which were fatigue and acne. Clinically, there was a weight gain as both BMI (79) and BMI SD scores increased (163). Although testosterone preparation and dosing differed, both studies reported an increase in both Hb and hematocrit. With a testosterone ester mixture on a biweekly frequency, values remained within the normal male range (163), whereas when treated with testosterone ester on a weekly base, hematocrit increased to supraphysiological levels of >50% in 3% of the cohort (two cases) with no adverse events reported (79). Alanine aminotransferase, aspartate aminotransferase, and creatinine increased but remained in the normal range. Lipid profile was more unfavorable with an increase of cholesterol and low-density lipoprotein and a decrease of high-density lipoprotein. Glucose homeostasis parameters HbA1c (79, 163) and insulin, glucose, or homeostatic model assessment index (154) were not affected.

Final considerations. Knowledge regarding the treatment of gender dysphoria and nonconforming has steadily advanced during the past 10 years (170). Although the psychological benefits of gender-affirming treatment of young adolescents with gender dysphoria using GnRHas have been established (171, 172), data on long-term health outcome are still sparse. GnRHa treatment in adolescents is both clinically and biochemically effective in suppressing the hypothalamic–pituitary–gonadal axis and appears to be well tolerated and safe (157). However, transgender boys may be more susceptible to the development of arterial hypertension (159). Studies regarding treatment with estrogen on pubertal development and short-term safety demonstrate feminization of the body without adverse events (164). In transgender boys, data on combined GnRHas and androgens is lacking. Retrospective reports on BMD development demonstrated a loss of *z* scores in transgender boys and transgender girls during gonadal suppression, followed by an increase after the addition of hormones, but at the age of 22 years *z* scores were still under pretreatment levels. Other long-term follow-up data are not available. Also, the aforementioned studies mainly describe a relatively older and mature group, mid-teens and Tanner stage 4 and up, which coincides with a relatively shorter duration of an induced hypogonadal state. There are currently no publications available focusing on treatment of the young and less matured (Tanner stages 2 or 3) adolescents with gender dysphoria, and therefore the effects of prolonged gonadal suppression (*i.e.*, 3 to 4 years) for the short term or long term are unknown. There needs to be investigation when the initiation of sex steroid hormones before the recommended age of 16 may prevent the negative sequelae of hypogonadism on the skeleton. Finally, when GnRHas are not available, alternative methods to suppress puberty can be used in the more sexually matured adolescent. Short-term data on the uses of antiandrogens in transgender girls and progestagens in transgender boys demonstrated their efficacy and safety (162, 163).

Key Conclusions and Recommendations for Future Clinical Research

The current available research is based mostly on cross-sectional studies, with limited longitudinal data.

There is also a paucity of information on diverse ethnic and socioeconomic populations and studies on treatment outcome in adolescents. The current literature comes from mostly Western European and from higher income countries, where many participants undergo surgical procedures, and has at best intermediate duration follow-up. Limited data exist on hormonal treatment in gender nonbinary persons. For specific analyses such as outcome or mortality, no single center has a sufficiently large patient base to study the population with statistical rigor.

An important barrier to better care is the diversity of training and practice across providers. Health care professionals continue to face challenges in providing optimal care for the transgender population, also due to a lack of education on the topic. The improvement of formal transgender education in medical schools and among health care providers in the broadest sense is timely (173). Professionals working in health services need to understand that patient gender identity is important and needs to be considered during any consultation. Treating people with respect requires a good understanding of people's identity regarding their gender. Transgender health care has to be included in national and international conferences of all involved specialties. We feel strongly about the fact that involving the transgender community at all stages of research is vital. This patient-centered research will progressively lead toward more studies where transgender community involvement is crucial in identifying research priorities, research design, helping recruitment, and dissemination of study results. Patient-centered outcome priorities in endocrinology are breast development in transgender women, time to menstrual cessation in transgender men, dose-related responses to hormonal interventions, and effect on sexual function and fertility, among many others (174).

Transgender medicine research is finally moving away from case reports and small series. Many efforts have gone into summarizing available data in numerous recent systematic reviews, from which we have to internalize the findings, avoid repeating the same research, and take the investigations further. The collection and reporting of original good quality data through networks has to be higher on the agenda. Innovative and patient-centered long-term research with randomized controlled trials if possible, to advance of the safety and efficacy of hormonal interventions, is a priority. In doing so, clinicians and academics must listen to the voices of transgender people, recognizing and respecting the internal diversity within the transgender community.

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Acknowledgments

Correspondence and Reprint Requests: Guy T'Sjoen, MD, PhD, Ghent University Hospital, Department of Endocrinology and Center for Sexology and Gender, 9 K 12 IE, Corneel Heymanslaan 10, 9000 Gent, Belgium. E-mail: guy.tsjoen@ugent.be.

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Abbreviations

BMD, bone mineral density; BMI, body mass index; CPA, cyproterone acetate; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; GnRHa, gonadotropin releasing hormone analog; ICD, International Classification of Diseases and Related Health Problems. .