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Update in Adult Transgender Medicine

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Abstract

Transgender people often face barriers in health care due to lack of access to care, lack of knowledgeable healthcare professionals, discrimination, and gaps in medical and mental health research. Existing research on transgender health has focused heavily on mental health, HIV/AIDS, sexually transmitted diseases/infections, and substance abuse. Gender-affirming hormone therapy and/or surgery allows for some alignment of biology and gender identity. Gender-affirming care may offer quality-of-life benefits, which may outweigh modest concerns related to exogenous hormone therapy. The Endocrine Society treatment guidelines were revised in 2017, and this article reviews recent data that might inform a future guideline revision. Future longitudinal research is needed to close the gap in knowledge in the field of transgender medicine.

INTRODUCTION

The revised Endocrine Society 2017 treatment guidelines include the following broad themes: Providers involved in the care of transgender and gender-diverse (TGD) patients should be knowledgeable and have sufficient training; TGD patients should receive safe, effective hormone regimens targeting the typical hormone ranges associated with their gender identities; and all patients seeking gender-affirming medical treatment should receive information and counseling for fertility preservation (1). This article reviews data published since 2017 that might inform a future guideline revision.

In a 2016 national survey, 1.4 million individuals were TGD, making up 0.6% of the US adult population. Many data sources related to this population are cross sectional with passive evaluation of collected data for clinical uses (2–3). Furthermore, in such population-based surveys, people may underreport gender identity, and the number of TGD adults may be higher (2). TGD individuals experience unique healthcare disparities that stem from lack of access to health care, lack of knowledgeable healthcare professionals, discrimination, and gaps in medical and mental health research (3–5). The existing research on TGD individuals is primarily focused on HIV/AIDS, sexually transmitted diseases/infections, and substance abuse (3–4).

Understanding the current terminology pertaining to TGD medicine is critical. "Transgender" is an umbrella term used to categorize individuals whose gender identity does not match the sex recorded on their original birth certificate. "Gender identity" is the term used to describe one's inner sense of self in terms of female, male, neither, or a combination (3). "Gender expression" indicates how an individual presents their gender identity—masculine, feminine, neither, or both. Transgender (or trans) men typically have a male gender identity, and trans women typically have a female gender identity. "Gender-nonbinary" individuals are those whose gender identity does not align with the typical gender binary of male or female. Gender-nonbinary individuals may identify as all genders, neither gender, or a combination of both (3). "Cisgender" (cis) refers to individuals who are not TGD. "Gender dysphoria" describes the psychological discomfort experienced by some TGD people (3).

Although the term gender dysphoria is recognized by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), expressions of gender identity are not a mental health condition per se. The use of gender dysphoria by the World Health Organization's International Classification of Diseases (ICD) for the diagnosis of transgender individuals has resulted in the practice of healthcare providers and companies using the term for billing and reimbursement for medical interventions. As such, this term has been used to label TGD people in medical records when they seek gender-affirming care. The next edition of the ICD will discard the term gender dysphoria and replace it with the term gender incongruence in a new chapter on sexual health (6).

HORMONE TREATMENT FOR TRANSGENDER WOMEN/TRANSFEMININE PEOPLE

A trans woman/transfeminine individual may elect to undergo gender-affirming hormone treatment (GAHT) to align gender identity with physical appearance (3, 7). Typically, trans women will take an antiandrogen regimen to bring their testosterone levels to <50 ng/dL (the female range). The typical regimen includes estrogen and an adjunct antiandrogen to enable lower doses of the estrogen to be used. Spironolactone, cyproterone acetate, and gonadotropin-releasing hormone are among the most popular adjunctive androgen-lowering/-inhibiting agents (3). Lower testosterone levels in the setting of adult levels of estradiol can produce typically feminine physical attributes (i.e., increased breast development, decreased facial/body hair, and feminized body shape/composition) (7–10). Estrogens can be taken through oral, transdermal, or parenteral

Table 1 Selected studies on changes in body composition

Title (reference)	Design, cohort, and measurement	Findings
Muscle Strength, Size, and Composition Following 12 Months of Gender-Affirming Treatment in Transgender Individuals (11)	Design: single-center observational study Cohort: 11 trans women, 12 trans men Measurement: changes in muscle mass, volume, and strength levels	Thigh muscle volume decreased by 5% and quadriceps CSA decreased by 4% in trans women. No alterations in radiological density were reported Thigh muscle volume increased by 15% and quadriceps CSA increased by 6% in trans men Trans men increased muscle strength levels by 12%; trans women retained strength levels
How Does Hormone Transition in Transgender Women Change Body Composition, Muscle Strength and Haemoglobin? Systematic Review with a Focus on the Implications for Sport Participation (12)	Design: systematic review Cohort: 24 studies Measurement: changes in body composition, muscle strength, and hemoglobin	Lean body mass decreased by 3.0% to 5.0% Muscle CSA decreased after 12–36 months; however, trans women still had greater CSA than cis women GAHT in trans women led to a significant decrease in hemoglobin
Sustained Breast Development and Breast Anthropometric Changes in 3 Years of Gender-Affirming Hormone Treatment (14)	Design: prospective cohort study Cohort: 69 adult trans women Measurement: breast development	1% of trans women had a bra cup size less than A, 9% had an A, 16% had a B, and 1% had an E Breast development was sustained during the first three years of GAHT Breast size and development may extend beyond the time course noted in the Endocrine Society guidelines

Abbreviations: CSA, cross-sectional area; GAHT, gender-affirming hormone treatment.

methods; however, the route of estrogen administration has not been shown to influence clinical outcomes in trans women (10).

Estrogen can alter body composition, decreasing lean body mass and increasing body fat (9, 11–12). One study (11) measuring the effects of feminizing GAHT on muscle size, function, and composition reported decreases in muscle volume and quadriceps cross-sectional area (CSA) by 5% and 4%, respectively. In a systematic review, Harper et al. (12) reported seven studies with 3.0% to 5.5% reduction in lean body mass among transfeminine people and eight studies reporting an increase in total body fat in trans women. The same study (12) reported that GAHT led to a significant decrease in hemoglobin and a decrease in muscle CSA; however, trans women still retained a greater CSA than their cis women counterparts (see **Table 1**).

Many trans women and transfeminine patients consider breast development essential (9–10, 13–14). One study (9) reported that breast size was the sole source of body comfort in trans women. Research surrounding breast development in trans women is conflicting (9, 14). T'Sjoen et al.'s review (9) reports one study showing that breast size reached a maximum after 2 years and another concluding that breast development plateaued after 6 months. De Blok et al. (14) reported that breast development and growth were sustained during the first 3 years of gender-affirming care (see **Table 1**).

Progestins are often sought out by trans people for reported impact on feminization and breast development (9). Progestin therapies such as medroxyprogesterone acetate can suppress testosterone levels via central feedback (3, 9). Progestins are not recommended by the Endocrine Society

Table 2 Selected reviews on risk factors associated with gender-affirming care

Title (reference)	Risk factors
Endocrinology of Transgender Medicine (9)	Thrombosis risk in transgender women due to prothrombic effects of estrogen Decrease of sperm production in trans women; trans men may experience a decrease in fertility and adverse pregnancy outcomes due to teratogenic effects of testosterone Rise in testosterone levels in trans men may unmask erythrocytosis
Research Gaps in Medical Treatment of Transgender/Nonbinary People (3)	Increased risk of cardiovascular risk factors and breast cancer when progestins are combined with estrogens in trans women Inadequate dosing of testosterone may have a negative impact on bone density in trans men Trans women undergoing GAHT are at increased risk of VTE
Cardiovascular Health Maintenance in Aging Individuals: The Implications for Transgender Men and Women on Hormone Therapy (17)	One year of GAHT had undesirable effects on lipid profiles in trans men A three-fold increase in death due to unfavorable cardiovascular outcomes in trans women Increased risk of VTE in trans women, increases with age. Ethinyl estradiol may lead to a higher VTE risk

Abbreviations: GAHT, gender-affirming hormone treatment; VTE, venous thromboembolism.

due to the risk of breast cancer, thromboembolism, and stroke in postmenopausal women (3, 9, 15). Additionally, Igo & Visram (16), in a retrospective review, concluded that trans women did not appear to derive benefit from progesterone, with some patients discontinuing use either due to absence of any measurable effects or due to poor mood.

Previous research has reported that transfeminine people undergoing GAHT have an increased risk of venous thromboembolism (VTE) (due to the prothrombic effects of estrogen) and risk to cardiometabolic health (8, 17–19). It is not clear if risk relates to hormone dose, route of administration, duration of hormone therapy, or other factors (3, 8, 18). However, a literature review by Slack & Safer (17) reports that ethinyl estradiol may increase VTE risk. The review also suggests a two- to fourfold increased risk of cardiovascular mortality in trans women (17). Kozato et al. (20) observed that hormone therapy during the perioperative period did not alter postoperative VTE risk in transfeminine people (see **Table 2**).

HORMONE TREATMENT FOR TRANSGENDER MEN/TRANSMASCULINE PEOPLE

For transmasculine people, the commonly recommended hormone therapy seeks to bring testosterone levels into the typical physiological range for cisgender men (300–1,000 ng/dL) (3). Testosterone regimens consist of gels, patches, injectable esters, and testosterone undecanoate (long-acting testosterone) (3, 9, 21). Injectable esters are most commonly administered subcutaneously for patient comfort. Testosterone undecanoate raises concerns of pulmonary oil microembolism and anaphylaxis and can be subject to a risk evaluation and mitigation strategy (21).

GAHT in trans men is often expected to produce virilization (9, 22–24). Testosterone therapy can lower voice pitch, change body composition (greater lean muscle mass, muscle CSA, and grip strength), and increase libido (9, 11, 21, 22). Previous studies that have documented changes in trans men following GAHT report that they gain muscle volume and strength (9, 11). Wiik et al. (11) reported that quadriceps CSA and thigh muscle volume increased by 15% and radiological density increased by 6%. The same study reported that trans men gained muscle strength, evidenced by their improved performance on knee extensions and knee flexion. Another study (24)

compared pre- and post-GAHT fitness tests of 46 trans women and 29 trans men versus the average performance of all men and women under age 30. The study reported that trans men after 1 year of hormone treatment were able to equal or outperform cis men in numbers of pushups and situps, as well as run times (see **Table 1**).

Trans men undergoing gender-affirming treatment should be aware of the risk to bone heath, associated with hypogonadism (3), risk to fertility and pregnancy (9, 22, 23), and risk of erythrocytosis (3, 9, 25). To reduce risks associated with erythrocytosis, clinicians involved with the care of trans men can advise smoking cessation, weight loss (if BMI is high), and switching to a transdermal route of administration (25) (see **Table 2**).

T'Sjoen et al. (9) report that testosterone may increase blood pressure, hematocrit, triglycerides, and low-density lipoprotein cholesterol levels, while decreasing high-density lipoproteins. The systematic review (9) reported four studies that described the effects of testosterone, and despite the number of negative risk factors, little to no impact on cardiovascular outcomes was reported. In fact, Slack & Safer's (17) literature review found that the data are contradictory, with no significant difference in cardiovascular mortality outcomes when studies are viewed together, relative to the general population.

Research focused on oncological outcomes in trans men is also very limited (9). Based on available data, the review by T'Sjoen et al. (9) finds no significant mortality differences between trans men and the general population. There is concern regarding a link between cancer development and long-term hormonal therapy; however, there are no available data to actually suggest such a link (9, 23). Breast cancer and cervical cancer screenings are recommended for trans men on GAHT who are not electing gender-affirming surgery (GAS) (9).

Many trans men report a desire to have their own children (9, 22, 26). Previous studies have reported that reproduction can be safe and successful after GAHT, although data are limited. For example, trans men have used their own oocytes and assisted reproduction to achieve pregnancy. For this, it has been commonly advised to discontinue hormone treatment in trans men, a possible cause of distress (26). However, Greenwald et al. (26) reported successful retrieval of a stimulated oocyte from a trans man on testosterone for implantation with donor sperm in the man's cis female partner followed by a subsequent healthy live birth. T'Sjoen et al.'s review (9) reports that trans men would elect to bank their oocytes as a fertility preservation option, if such treatment were available. In this review, a study reported that >1 year of androgen treatment did not reduce primordial follicles in the ovarian cortex and cortical follicles in the ovaries of 40 trans men (9).

MENTAL HEALTH IN TRANSGENDER PEOPLE

TGD people are more likely to experience discrimination, lack of access to health care, and lack of provider comfort/knowledge (3, 27). TGD people have worse mental health outcomes than their cisgender counterparts, with increased rates of anxiety, depression, suicide attempts, and suicide. The predictors of poor mental health outcomes in TGD people are multifactorial. Risk factors include low self-esteem, lack of provider knowledge and experience, lack of access to hormone treatment, lack of interpersonal support, and hostile experiences (3, 5, 9, 27–28).

Hormonal therapy can be associated with improved mental health for trans people (4–5, 9, 27–28). In one review, three studies reported a decrease in depression and anxiety levels following hormone treatment (9). In another systematic review, seven studies were identified that reported improvement in quality of life in trans men after 1 year of GAHT. The same review included a study that showed a decrease in depression after 1 year of hormone treatment in trans women and men. The review found no evidence of hormonal therapy having adverse mental health outcomes (28) (**Table 3**).

Table 3 Selected studies on the benefits of gender-affirming hormone treatment and surgery

Title (reference)	Design, measurement	Findings
Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review (28)	Design: systematic review Measurement: changes to QOL following GAHT	Seven studies reported an increase of 5.5 points on a 10-point scale for a measure of QOL after 1 year of GAHT in trans men One study showed that trans women experienced a 16% improvement in QOL scores after 1 year of treatment Twelve studies reported a 20% decrease in depression in trans men and women after 1 year No evidence indicating GAHT had adverse effects on QOL
Penile Inversion Vaginoplasty Outcomes: Complications and Satisfaction (29)	Design: review Measurement: penile inversion vaginoplasty	Penile inversion vaginoplasty improves QOL and decreases gender dysphoria Trans women reported having increased satisfaction with sexual experiences Trans women experienced significant improvements in body satisfaction and positivity
Regret after Gender-Affirmation Surgery: A Systematic Review and Meta-Analysis of Prevalence (32)	Design: systematic review Measurement: TGD people who had GAS	TGD patients experienced very little regret (1%) following GAS When patient regret was experienced, it was attributed to poor surgical outcomes, poor social support, and poor sexual functioning

Abbreviations: GAHT, gender-affirming hormone treatment; GAS, gender-affirming surgery; QOL, quality of life; TGD, transgender and gender-diverse.

Like hormonal therapy, gender-affirming surgery (GAS) is a means for TGD people to align their bodies with their gender identities. A 2021 study describes patients reporting improved quality of life following GAS (29). The recovery period can be stressful for some; as such, postoperative psychological support (i.e., someone to speak to) can be important. For example, one study (30) that examined the provision of spiritual care following GAS in 98 patients at the Mount Sinai Center for Transgender Medicine and Surgery reported that 61% of patients were grateful for the chaplain visit, and 58% of patients requested a follow-up phone call, indicating that offering spiritual care following GAS can add a layer of support during their recovery process.

The Affirming Surgery Form and Function Individual Reporting Measure (AFFIRM) is a validated survey instrument that was recently published (31) to measure patient reported outcomes/perceptions of their GAS and to provide further data regarding GAS impact. The AFFIRM questionnaire was developed from interviews with 102 post-GAS trans women, with a face validation from a multidisciplinary clinical group. The overall Cronbach's α for AFFIRM is 0.79, with a test-retest score demonstrating reliability; z values indicate reliability in domain and total score stability (z values -1.862 to -0.005, $p < 0.05$), and intraclass coefficients of 0.54 to 0.88 indicate moderate to good absolute correlation (31).

To date, there is little evidence of significant numbers of TGD people suffering regret after GAHT and surgeries (9, 29, 32). T'Sjoen et al. (9) report that 2% of trans women and 1% of trans men regretted their choice to undergo gender-affirming treatment. Of note, dissatisfaction with surgical results along with loss of family, social, and occupational support were the lead causes of regret (9, 29, 32). In a systematic review of 27 studies, Bustos et al. (32) reported similar findings: There was little evidence (1%) of significant regret following GAS, and in studies that reported patient regret, the regret was due to the negative social factors following surgery such as poor family support, mistreatment at work, suboptimal cosmetic outcome, and poor sexual function (32).

CONCLUSION

The literature and research in this review might inform a future revision to the 2017 Endocrine Society treatment guidelines. Overall, it appears that trans women may have an increased risk of VTE and trans men may have a risk of erythrocytosis while on GAHT. Routine visits to a medical provider should monitor these risks. GAS has been shown to be helpful for many trans people; however, additional research is needed on surgical practice and support structures for postoperative patients.

Although there have been advances in research and medical practice for TGD individuals, rigorous investigation remains limited. The compilation of research thus far is primarily centered around cross-sectional studies. Longitudinal studies investigating the impact of medical interventions on the mental health and well-being of TGD individuals are paramount. Additional research should examine the impact of GAHT on athleticism, across all sports areas. Future research is also needed on examining oncological outcomes in trans men and breast development in trans women. Future longitudinal research is needed on fertility outcomes for both trans men and trans women. Much investigation has been done in higher-income countries, in which individuals have at least some access to gender-affirming care. Future research is needed to examine gender-affirming care in other regions of the world with less healthcare access.

TGD people often face barriers to health care as a result of lack of knowledgeable healthcare professionals and providers. Formal provider training should be integrated in medical/nursing education at all levels.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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