Review Article

Hormone therapy for transgender patients

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Abstract: Many transgender men and women seek hormone therapy as part of the transition process. Exogenous testosterone is used in transgender men to induce virilization and suppress feminizing characteristics. In transgender women, exogenous estrogen is used to help feminize patients, and anti-androgens are used as adjuncts to help suppress masculinizing features. Guidelines exist to help providers choose appropriate candidates for hormone therapy, and act as a framework for choosing treatment regimens and managing surveillance in these patients. Cross-sex hormone therapy has been shown to have positive physical and psychological effects on the transitioning individual and is considered a mainstay treatment for many patients. Bone and cardiovascular health are important considerations in transgender patients on long-term hormones, and care should be taken to monitor certain metabolic indices while patients are on cross-sex hormone therapy.

Keywords: Hormone therapy; transgender; gender dysphoria; cross-sex hormones

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Introduction

Transgender individuals experience discord between their self-identified gender and biological sex. Transgender men are individuals who were assigned female at birth but identify as men, and transgender women are individuals who were assigned male at birth but identify as women. While research in this area is sparse, the current evidence points toward a biologic etiology for transgenderism. These data come from studies examining children with congenital genitourinary anomalies who were assigned gender at birth (1,2), as well as postmortem cadaveric studies (3). Estimation of prevalence of transgenderism has historically been challenging. The most recent estimates in the United States have been reported from survey studies, and range from 0.3–0.5% (4,5).

The number of transgender individuals seeking cross-sex hormone therapy has risen over the years (6). The administration of exogenous virilizing hormones is considered medically necessary for many transgender individuals (7). Many transgender men seek therapy for virilization and the mainstay treatment is exogenous testosterone. Transgender women desire suppression of androgenic effects and often use anti-androgen therapy with feminizing exogenous estrogens.

The purpose of this review is to present updates on the current hormonal regimens used by transgender patients, to discuss the safety and efficacy of these treatments, and to provide a summary of the current data that exist on both their short- and long-term effects.

Guidelines

Both the World Professional Association for Transgender Health (WPATH) and the Endocrine Society have created transgender-specific guidelines to help serve as a framework for providers caring for gender minority patients. These guidelines are mostly based on clinical experience from experts in the field. Guidelines for hormone therapy in transgender men are mostly extrapolations from recommendations that currently exist for the treatment of hypogonadal natal men and estrogen therapy for

Table 1 Testosterone options for transgender men

Route	Formulation	Dosing
Oral (not available in United States)	Testosterone undecanoate	160–240 mg/day
Parental (subcutaneous, intramuscular)	Testosterone enanthate, cypionate	50–200 mg/week
		100–200 mg/10–14 days
Implant (subcutaneous)	Testopel®	75 mg/pellet
Transdermal	Testosterone gel (1%)	2.5–10 g/day
	Testosterone patch	2.5–7.5 mg/day

transgender women is loosely based on treatments used for postmenopausal women.

In the past, the guidelines for hormone therapy initiation recommended that all patients undergo a "real life test" prior to starting medical therapy. This test required patients to live full-time as their self-affirmed gender for a predetermined period of time (usually 12 months) before starting cross-sex hormones. The recommendation was intended to help patients transition socially. However, both above-mentioned societies have recognized that this step is unreasonable for many patients as social transition can be very challenging if there is incongruence between an individual's self-affirmed gender and their physical appearance. As a result, the updated guidelines do not require this step, and instead, the societies recommend that patients transition socially and with medical therapy at the same time (7,8).

WPATH recommends that hormone therapy should be initiated once psychosocial assessment has been completed, the patient has been determined to be an appropriate candidate for therapy, and informed consent reviewing the risks and benefits of starting therapy has been obtained. Per WPATH, a referral is required by a qualified mental health professional, unless the prescribing provider is qualified in this type of assessment. The criteria for therapy include: (I) persistent well-documented gender dysphoria (a condition of feeling one's emotional and psychological identity as male or female to be opposite to one's biological sex) diagnosed by a mental health professional well versed in the field; (II) capacity to make a fully informed decision and to consent for treatment; (III) age of majority; and (IV) good control of significant medical and/or mental comorbid conditions.

This fourth criterion can sometimes be the most challenging to interpret. Many patients may have concurrent mood disorders related to their gender dysphoria, and experienced providers may have success alleviating the severity of these symptoms by allowing the patient to begin the medical transition process. Later in this review I discuss the effects hormones have on quality of life and perception of personal well-being. This is a key concept and should be considered when patients are being evaluated for hormone therapy initiation. Patients with comorbid psychiatric conditions should be closely monitored and mental health support remains paramount for these patients.

Testosterone

Testosterone therapy is used to suppress female secondary sex characteristics and masculinize transgender men. The therapy used resembles hormone replacement regimens used to treat natal men with hypogonadism and most of the preparations are testosterone esters.

Current formulations for testosterone are presented in *Table 1*. Oral formulations such as testosterone undecanoate (Andriol®) are used in Europe but continue to not be available in the United States due to concerns about first-pass metabolic effects from the drug. The most commonly used formulations in the United States are those that are administered via the intramuscular or subcutaneous route, and include testosterone enanthate (Delatestryl®) and cypionate (Depo®-Testosterone). These are usually administered weekly, but if higher doses are needed to reach adequate physiologic levels, the dosing interval can be extended to every 10 to 14 days. Testosterone undecanoate (Aveed®) is a long-acting testosterone that can be administered every 12 weeks and was approved by the FDA in 2014 for treatment of male hypogonadism, and it can be used off-label to treat gender dysphoria in transgender men. Transdermal options (Androgel®, Androderm®) are also good alternatives for some patients.

Before a patient is started on testosterone, a baseline hematocrit and lipid profile should be obtained, as these

Table 2 Estrogen and anti-androgen options for transgender women

Route	Formulation	Dosing
Oral	Estradiol	2–4 mg daily
Parental (subcutaneous, intramuscular)	Estradiol valerate	5–30 mg every 2 weeks
Transdermal	Estradiol	0.1–0.4 mg twice weekly
Anti-androgens	Progesterone	20–60 mg PO daily
	Medroxyprogesterone acetate	150 mg IM every 3 months
	GnRH agonist (leuprolide)	3.75–7.5 mg IM monthly
	Histrelin implant	50 mg implanted every 12 months
	Spironolactone	100–200 mg PO daily
	Finasteride	1 mg PO daily

indices will change over time. In addition, if a patient is at significant risk for osteoporosis, a baseline bone mineral density should be obtained (9). Most providers start testosterone therapy with half the anticipated dose needed to reach maximum virilization in a patient. Goal testosterone levels (male physiologic range) are 300–1,000 ng/dL, and testosterone dosages can be quickly titrated to reach adequate levels. Studies exist looking at dose-response with regard to virilization once testosterone is initiated. Nakamura *et al.* (10) showed that early onset of treatment effects of testosterone therapy is dose-dependent, but within six months of initiating therapy, higher doses are no more effective than lower doses. Therefore, while higher doses may achieve desirable effects sooner, the risks associated with fast titration need to be assessed, and patients should be aware that testosterone effects eventually become the same over the intermediate-term.

Testopel® are FDA-approved testosterone pellets that are implanted subcutaneously. Once implanted, the pellets slowly release testosterone for a long-acting androgenic effect. They are approved for the treatment of primary hypogonadism and hypogonadotropic hypogonadism. Our group recommends that patients first be started on an alternative form of testosterone until maximum virilization is achieved and maintenance dosing is then necessary. Patients may then be transitioned to the implanted pellets. The number of pellets to be implanted depends upon the minimal daily requirements of testosterone needed to reach physiologic levels. Each pellet is cylindrical in shape and contains 75 mg of testosterone and six pellets may be implanted with each pass of the insertion device that is provided with the kits. Two pellets should be inserted for every 25 mg of parenteral testosterone needed weekly. The pellets are placed in a fatty area under the skin. Most commonly, the upper gluteal region or hip is used as a site for implantation. Approximately 1/3 of the pellets become absorbed in the first month, 1/4 in the second month and 1/6 in the third month. The effects of the pellets may last up to 6 months, but most patients require re-implantation every 3 to 4 months.

Estrogen

Hormone therapy for transgender women is intended to feminize patients by changing fat distribution, inducing breast formation, and reducing male pattern hair growth (11). Estrogens are the mainstay therapy for trans female patients. Through a negative feedback loop, exogenous therapy suppresses gonadotropin secretion from the pituitary gland, leading to a reduction in androgen production (12). Estrogen alone is often not enough to achieve desirable androgen suppression, and adjunctive anti-androgenic therapy is also usually necessary.

Ethinyl estradiol used to be the mainstay of most estrogen-directed therapies. This is no longer the case, as clinical evidence has showed a strong relationship between ethinyl estradiol and the incidence of deep venous thrombosis (13). As a result, there are strong recommendations against the use of ethinyl estradiol in transgender patients (8). Oral (Estrace®, Gynodiol®) and transdermal (Alora®, Climera®, Esclim®, Estraderm®, Vivelle®) estradiol and parenteral estradiol valerate (Delestrogen®) are currently the preferred formulations of estrogen. See *Table 2* for dosing recommendations. No studies have examined the efficacy of

the different formulations specific to transgender hormone management. After the age of 40, transdermal formulations are recommended as they bypass first pass metabolism and seem to be associated with better metabolic profiles (14).

There are no unanimous recommendations for the use of anti-androgens. Options are also listed in *Table 2*. Spironolactone is one of the most common medications used to suppress endogenous testosterone in trans female patients. The biggest risk associated with spironolactone is hyperkalemia, and this should be closely monitored. Other options include 5α-reductase inhibitors such as finasteride, but these can be associated with liver toxicity and may not be as effective as spironolactone (8). GnRH agonists can be very expensive, and are not always a good option for patients. Progestins are used by some providers, but should be used with caution as there is a theoretical risk of breast cancer associated with long-term exogenous progesterone use (15).

Effects of testosterone and estrogen

Many trans men seek maximum virilization, while others desire suppression of their natal secondary sex characteristics only. As a result, hormone therapy can be tailored to a patient's transition goals, but must also take into account their medical comorbidities and the risks associated with hormone use.

Within three months of initiating testosterone therapy, the following can be expected: cessation of menses (amenorrhea), increased facial and body hair, skin changes and increased acne, changes in fat distribution and increases in muscle mass, and increased libido (11,16). Later effects include deepening of the voice, atrophy of the vaginal epithelium, and increased clitoral size. Male pattern hair loss also can occur over time as a result of androgenic interaction with pilosebaceous units in the skin (17). Some patients find this favorable as it may be considered masculinizing. For those who do not find it favorable, 5α-reductase inhibitors can be used as adjuncts to combat alopecia. However, patients should be made aware of the potential side effects on sexual functioning that can be associated with these medications, and they should be counseled that no data exist on the use of these medications in transgender men (18). In most female-to-male patients (unless testosterone is administered during the peri-pubertal period), there is some degree of feminization that has taken place that cannot be reversed with exogenous testosterone. As a result, many transgender men are shorter, have some degree of feminine subcutaneous fat distribution, and often have broader hips than biologic males (19).

The following changes are expected after estrogen is initiated: breast growth, increased body fat, slowed growth of body and facial hair, decreased testicular size and erectile function. The extent of these changes and the time interval for maximum change varies across patients and may take up to 18 to 24 months to occur. Use of anti-androgenic therapy as an adjunct helps to achieve maximum change.

Hormone therapy improves transgender patients' quality of life (20). Longitudinal studies also show positive effects on sexual function and mood (16,18). There is biologic evidence that may explain this. Kranz *et al.* (21) have looked at the acute and chronic effects of estrogen and testosterone on serotonin reuptake transporter (SERT) binding in trans men and women. SERT expression has been shown to be reduced in individuals with major depression (22). Kranz *et al.* found that androgen treatment in transmen increased SERT binding in several places in the brain and anti-androgen and estrogen therapy led to decreases in regional SERT binding in trans women. These types of data are preliminary, but do point to the important role of hormone therapy in patients who suffer from gender dysphoria.

Hormone therapy may even have a positive effect on physiologic stress as well. Colizzi *et al.* (23) looked at 70 transgender patients on hormone therapy and measured their cortisol levels as well as their perceived stress before and 12 months after starting hormone therapy. They found that after starting cross-sex hormones, both perceived stress and cortisol were significantly reduced. This finding also has important implications for treatment.

Surveillance

Surveillance recommendations for cross-sex hormone therapy are listed in *Tables 3* and *4*. Patients on testosterone should be monitored every 3 months for one year and then every 6 to 12 months thereafter. *Tables 3* and *4* display surveillance recommendations for trans men and women. Hormones should be carefully monitored to avoid a prolonged hypogonadal state if dosing is too low, which can lead to significant losses in bone mineral density; and to avoid exposures to supraphysiologic levels, which could have significant physiologic and metabolic effects (24).

Sex steroids—testosterone and estradiol—are necessary to maintain bone health in men and women, respectively. They are responsible for bone growth and turnover, and hypogonadal states in both males and females can result in clinically significant bone loss. Testosterone has a

Table 3 Surveillance recommendations for transgender men on testosterone

Monitor for virilizing and adverse effects every 3 months for the first year, then every 6–12 months
Obtain baseline hematocrit and lipid profile and monitor at follow-up visits
Obtain baseline bone mineral density if a patient is at risk for osteoporosis; routine screening after age 60, or earlier if sex hormone levels consistently low
Monitor serum estradiol during the first 6 months and thereafter until uterine bleeding has ceased
Monitor serum testosterone at follow-up visits; target 300–1,000 ng/dL
Peak levels for parenteral testosterone measured 24–48 hrs after injection
Trough levels for parenteral testosterone measured before injection

Table 4 Surveillance recommendations for transgender women on estrogen

Monitor for feminizing and adverse effects every 3 months for the first year, then every 6–12 months
Obtain baseline hematocrit and lipid profile and monitor at follow-up visits
Obtain baseline bone mineral density if a patient is at risk for osteoporosis; routine screening after age 60, or earlier if sex hormone levels consistently low
Obtain prolactin at baseline, at 12 months after initiation of treatment, biennially thereafter
Monitor serum testosterone during the first 6 months until levels are <55 ng/dL
Monitor serum estradiol at follow-up visits; target 100–200 pg/mL

direct role in bone health maintenance, but the steroid is also aromatized peripherally to estradiol, which has a very important role as well (25). Testosterone also has an important role in increasing muscle mass, which further helps with bone health preservation. Studies have looked at bone health in transgender men on long-term testosterone therapy. Exogenous testosterone appears to have an anabolic effect on cortical bone and when dosed at physiologic levels, is adequate enough to avoid issues with bone demineralization in transgender patients (26). Transgender women may be at higher risk for bone loss despite estrogen use (27). This is likely a result of anti-androgen use, and therefore, providers should consider stopping anti-androgen therapy if and when patients undergo orchiectomy with or without genital confirmation surgery. Screening for bone loss should be performed per the guidelines for the general population, unless a patient has baseline low bone mineral density, or is at risk for osteoporosis (tobacco use, alcohol abuse, previous fractures, eating disorder, family history of osteoporosis). Patients at risk should be screened sooner and more regularly.

It is not clear whether use of exogenous testosterone increases the risk of cardiovascular disease in transgender men. Some studies have shown that testosterone has a negative effect on indices that may increase the risk of cardiovascular events. For instance, Gooren and Giltay (28) showed that long-term testosterone use reduced high-density lipoprotein cholesterol and increased triglycerides as well as inflammatory markers. Other studies have found similar changes. Wierckx *et al.* (16) looked at 50 patients on testosterone for a mean time of 10 years and found that many patients had elevated cholesterol and serum triglycerides while several had elevated blood pressure. Despite these metabolic changes, and negative impact on potential risk factors for cardiovascular disease, no studies have found an increase in the occurrence of cardiovascular events such as myocardial infarction, deep vein thrombosis, and cerebrovascular events (16,29,30).

Studies looking at the effects of estrogen on cardiovascular disease in transgender women are not very conclusive, but do show that there may be a trend toward an increased risk of heart disease, which should be further studied. Use of oral ethinyl estradiol appears to be strongly associated with cardiovascular events (30) and should therefore be avoided as a mainstay therapy for patients (31). In addition, diabetes is a significant risk factor for cardiovascular disease and may

have an important role in raising the risk of cardiovascular morbidity in trans women on estrogen, as this comorbidity has been found to be prevalent among the transgender population (32).

Large-scale prospective studies are lacking. Many of the studies that currently exist have small patient numbers as well as short or medium-term follow-up, and very few of the patients studied are over the age of 65. Furthermore, no head-to-head comparisons of hormone regimens have been published. It is therefore, not possible to draw definitive conclusions about the adverse effects of long-term cross-sex hormone use.

Special considerations

Routine laboratory monitoring of patients on cross-sex hormone therapy can be challenging because results are often reported using gender-specific reference intervals, which are not all appropriate for transgender patients. With the exception of cholesterol, triglycerides, hemoglobin and hematocrit, there are few published data on reference ranges for cardiovascular and metabolic measurements that may be important in the diagnosis and management of other diseases in transgender patients. Roberts *et al.* (33) looked at metabolic indices in male-to-female patients on hormone therapy in order to determine appropriate reference ranges. They found that hemoglobin, hematocrit and low-density lipoprotein resembled biologic female ranges. However, alkaline phosphatase, potassium, and creatinine levels were similar to male reference levels. And, importantly, triglyceride levels were higher than both biologic male and female reference ranges. From their study, the authors concluded that it is not possible to predict reference ranges for transgender women based only on what is already known about postmenopausal women on estrogen therapy, and that new reference ranges must be studied and validated to avoid diagnostic errors in this patient population.

Adolescents also seek hormone therapy for treatment of gender dysphoria. The purpose of this review was to cover guidelines and management for adult patients, but it is important to mention special considerations that must be taken when treating adolescent patients. Cross-sex hormones are usually recommended at the age of sixteen (7). However, in some situations when delay of therapy may lead to psychologic and cognitive trauma in a child, it may be appropriate to commence therapy earlier (34). In these cases, and most adolescent cases, it is important to have a multi-disciplinary approach to treatment and management, and parental support is imperative. In youth who have reached Tanner Stage 2 development, GnRH agonists are used to suppress endogenous hormones to avoid full pubertal development and cross-sex hormone therapy is initiated by or at age sixteen. There are many ethical issues to address in the care of the adolescent transgender patient, and the care of this patient population should be left to specialists who are well versed in this type of care.

It is not uncommon for patients to seek hormone therapy from alternative sources (35). In a recently published cross-sectional analysis, Mepham *et al.* (36) found that one in four trans women self-prescribe cross-sex hormones, most commonly through the Internet. In another study looking at 314 trans women in San Francisco, 49% were found to be taking hormones not prescribed by a clinician (37). Over the years, as more medical providers are gaining better experience prescribing hormones, patients are less likely to acquire hormones from these outside sources. It is important to screen patients for outside use, and to educate them about the risks associated with this. Patients sometimes feel that road blocks are placed in front of them when hormones are not prescribed right away, especially if they are being asked to seek further psychiatric care before initiating hormones. Some patients do require additional mental health care, but the time should be taken to explain to patients that the provider who intends to prescribe hormones to patients is not trying to "gate keep" the patient away from this type of therapy, but rather, he or she is ensuring that the patient has a positive outcome on the therapy. This again speaks to the importance of a multi-disciplinary approach to the care of these patients.

Conclusions

Many transgender individuals seek cross-sex hormone therapy for treatment of gender dysphoria. Hormone therapy plays an integral role in the transition process for patients. Guidelines exist to help providers prescribe and monitor therapy. Hormone therapy has been shown to be associated with positive outcomes for patients, but there are important metabolic implications of therapy that must be carefully considered when treating patients.

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Footnote

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