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Endocrine treatment of transgender individuals: current guidelines and strategies

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Abstract

Introduction: This review provides a summary of the medical and surgical care available to transgender individuals, as well as to offer proposals on how the medical field can progress to provide medically and culturally appropriate care.

Areas covered: Transgender individuals are defined as those whose gender identity differs from that recorded at birth (usually based on visualization of their external sexual anatomy). In order to align the body with the patient's gender identity, clinicians can provide hormone therapy (HT) either to suppress endogenous sex hormone secretion, to bring sex hormone levels to the range associated with the patient's gender identity, or both. Once at a steady-state, regular monitoring for maintenance of levels, as well as for known risks and complications, is required. The treating clinicians should have knowledge of trans assessment criteria, hormone therapy, surgical options, primary care, and mental health needs of transgender patients. A narrative literature review was conducted using Pubmed and EMBASE with articles then selected for relevance. The following search terms were used initially: androgen suppression, antiandrogen, breast development, chest reconstruction, cisgender, estrogen, fertility preservation, gender affirming surgery, gender identity, gender incongruence, genital reconstruction, hormone replacement, hyperlipidemia, orchiectomy, prolactin, prostate atrophy, spermatogenesis, spironolactone, testosterone, thrombogenesis, transgender, and virilization.

Expert opinion: Although guidelines exist and examples of high-quality training are readily available, to truly mainstream appropriate high-quality gender affirming health care there must be a move towards implementing systematic formal training.

Keywords: Hormone therapy, transgender care, gender incongruence, estrogen, testosterone, surgery, treatment guidelines

Article highlights

- Hormone therapy for transgender men includes testosterone administration to stimulate physical changes consistent with the patient's gender identity
- Hormone therapy for transgender women includes estrogen and androgen-suppressing agents to stimulate physical changes consistent with the patient's gender identity
- Associated risks with these therapies must be considered, and routine monitoring dependent on the specific therapy administered is recommended
- In addition to hormone therapy, there are several surgical options available for both transgender men and women to supplement hormone replacement therapy in optimizing these physical changes
- A multi-disciplinary team approach is required to tailor therapy to the individual in achieving their gender identity goals
- Advancement in management of transgender individuals requires an intentional effort to include training for all providers

1. Presentation

Gender identity is an individual's sense of being female, male, a combination of both, or neither (**Table 1).** Most transgender individuals present to clinicians in late adolescence or adulthood [1]. Data suggest that there is a biological foundation to an individual's gender identity [2] [3]. However, mechanisms are not known and presentation depends on self-report by the transgender person. Many children report a degree of gender incongruence, but not all seek medical intervention later in life [4]. In adolescence, children tend to be better able to vocalize their gender identity and may seek medical intervention around puberty given the

distressing nature of this period for gender incongruent adolescents. It is unknown why the majority of transgender individuals present in late adolescence or adulthood, but it could be due to delayed recognition, external pressure, or inability to articulate gender identity. Despite presenting at this stage, many transgender individuals report appreciation of their gender incongruence before puberty in retrospect [1] [5].

Historically, great emphasis was placed on ascertaining that a person was transgender and on determining if the transgender person was likely to succeed with treatment [6]. The basis for assessment include much bias and was termed "gatekeeping" by some. In reaction, an alternative approach arose which advocated for prescribing interventions to any person who was willing to accept the risk, an approach that received the label "The Informed Consent Model".

With greater integration of gender affirming medical care into conventional medical practice, there is a trend away from either of these extremes. Most transgender adults do not require a mental health professional to confirm they are transgender [7]. And informed consent should be obtained like for any medical intervention with the known risks / benefits to treatment described after ascertaining that the patient is capable of consenting. Mental health support can be reserved for those with morbidity that might compromise either assessment of being transgender or treatment plan. Treatment customization among current options can be decided with the patient and the provider sharing decision making once the provider has had the opportunity to review risks / benefits of treatment options [8].

2. Hormone regimens for transgender men

The primary goal of masculinizing HT is to stimulate physical changes consistent with the patient's gender identity. Testosterone is the sole hormone administered. The aim is to achieve levels within the physiological range for cisgender men (300-1000ng/dL). There are several routes available to administer exogenous testosterone (**Table 2**). These include subcutaneous or intramuscular injections, transdermal gel or patches, and subcutaneous implants. With regards to achieving desired physiologic levels, no data support one route of administration over another, but higher testosterone levels are more easily achieved with parenteral treatment [5].

Injectable testosterone preparations include testosterone enanthate (TE), testosterone cypionate (TC), and testosterone undecanoate (TU). TE and TC can both be given as subcutaneous injections every week to ten days, or intramuscularly every two to three weeks. Typical doses for the weekly administration are 50 to 100mg [9]. These doses can be doubled and given with greater dosing intervals to reduce frequency of injections, although this is associated with greater fluctuation in levels [10]. With a longer carbon side chain, TU has a significantly longer half-life than TE and TC [11] [12], and can therefore be administered every 12 weeks [13]. Due to the fact that transgender men tend to be smaller in size than cisgender men, it may be advisable to begin with lower dosing and titrate upwards to avoid supraphysiologic levels.

Testosterone gels are typically given at doses of 50-100 mg/d, while transdermal patches are given at 2.5-7.5 mg/d [13]. Patients are advised to keep the application site clothed for 4 hours after administering gels to avoid skin-to-skin contact with others. Patients are also advised to avoid showering for 4 hours to ensure absorption [14]. Due to high levels of pruritus reported with use of patches, gels tend to be more commonly prescribed than patches.

Implantable testosterone pellets are also available, but titration will be more straightforward with shorter acting agents, leaving pellets reserved for maintenance [13]. Pellets contain 75mg of active ingredient and up to 6 can be inserted at once. Two pellets are typically inserted for every 25mg of parenteral testosterone required weekly and most patients require repeat implantation every 3 to 4 months.

2.1 Treatment effects

Although many transgender men desire maximum virilization, others may wish more modest results. Unfortunately for the latter, the impact of even low dose hormone therapy cannot be reliably predicted for any given individual and patients should be prepared for a range of results.

Within 3 to 6 months of initiating masculinizing therapy, transgender men can expect to experience amenorrhea, increased libido, coarsening of skin and acne, fat redistribution, increased muscle mass, and facial hair growth [15] [16] [17]. Over longer periods of time,

patients can experience voice deepening and clitoromegaly [18] [19]. Male pattern hair loss can also occur due to the androgenic interaction with pilosebaceous hair follicles [20]. Some transgender men may welcome this change as it can be considered masculinizing, but some do not. Male pattern hair loss has been managed with 5alpha- reductase inhibitors, but patients should be counselled regarding reports of sexual function concerns, along with the lack of evidence for objective benefit in transgender men [21]. Height will not be affected by HT administered after puberty.

For the majority of adult transgender men who began HT after puberty, a degree of non-reversible physical feminization will have occurred. Many transgender men will therefore be shorter, have a degree of female fat distribution [22], and have broader hips than cisgender men [23]. Patients can expect some degree of breast atrophy with long-term androgen therapy with studies showing histological changes [24] in breast tissue of transgender men with reduced glandular tissue and increased fibrous connective tissue comparable to changes seen in post-menopausal women [25] [26].

2.2 Medical risks/safety

Apart from the potential physical side effects mentioned previously (Acne, male pattern baldness), there are biochemical and hematological changes associated with testosterone therapy. The primary reported concerns are a decrease in high-density lipoprotein (HDL) cholesterol and an increase in hematocrit (HCT) levels [27].

An increased HCT through testosterone stimulation of erythropoietin can unmask polycythemia for which an underlying explanation should be sought. HCT in transgender men has been found to rise by 4.9% in the first year of HT, with the most pronounced increase in the first 3 months, and a greater change in those taking TE and TC compared to TU [28]. Whether the latter finding relates to total dose given or the route of administration is not known. Despite this increase, data show that HCT levels for transgender men on testosterone therapy are within the same range as for cisgender men (39-51%) in a study population who had been taking gender affirming hormones for over 1 year [29].

Some studies have suggested that testosterone causes an increase in metabolic parameters that are associated with a higher risk of cardiovascular events such as HDL cholesterol [30],

triglyceride levels [31], and blood pressure [17]. However, no studies have found an increase in incidence of cardiovascular events in transgender men taking testosterone [17] [32].

Other concerns for patients on exogenous testosterone include sleep apnea, excessive weight gain and salt retention [33], although salt retention has not been studied in transgender men. Studies have not found liver toxicity with current testosterone therapy in contrast to older oral agents which are no longer used [34] [35].

2.3 Monitoring

The Endocrine Society Guidelines [36] recommend monitoring testosterone levels in transgender men every 3 months for the first year after initiating HT (i.e. with dose adjustments). Once a stable dose has been reached, and with testosterone levels within physiological parameters, it is suggested to monitor levels approximately every 6-12 months. During these routine appointments, evaluation of adverse reactions to therapy, as well as additional laboratory testing, should be conducted (**Table 3)**.

3. Hormone regimens for transgender women

The hormones used for feminization in transgender women are more complex than those used for masculinization. The aim is to lower testosterone levels into the typical female range while simultaneously increasing estrogen to physiologic levels for cisgender women (100-200 pg/ml). There is great heterogeneity in estradiol reference ranges and some have proposed higher target levels for transgender women [37]. Treating transgender women with estrogen alone will suppress androgen production, but the goal could require supraphysiologic estrogen doses with possible dose related risk to the patient. Physiologic dosing alone is rarely sufficient to suppress transgender women's testosterone to within the physiologic range for cisgender women (<50 ng/dL) [38], so an adjunct antiandrogen is typically used (**Table 4**).

Estrogen can be administered via oral, transdermal, and parenteral routes. Oral 17ß-estradiol (2 to 6 mg/d) and conjugated estrogens (2.5-7.5 mg/d) are easily administered, and are often used first line. However, there is some thought that the oral route is more thrombogenic due to the 'first pass effect'. As well, excess risk can be mitigated by using lower doses [39]. The

Endocrine Society does not list conjugated estrogens as a first line agent as they cannot be as accurately monitored due to the presence of multiple other estrogens not measured in routine serum testing increasing the risk of adverse effects [36]. If conjugated estrogens are used, blood testing could still be utilized as a rudimentary indicator of estradiol levels. It is currently unknown to what extent exogenous estradiol has more or less activity than endogenous estrogens, and there is currently no data to suggest that estradiol is the only, or even the most important, active estrogen.

Transdermal estradiol patches can be given at 0.025-0.2 mg/d with a new patch being placed once or twice a week. Parenteral estradiol valerate (2-10 mg weekly or 5-30 mg every two weeks) or estradiol cypionate (1-2.5mg weekly or 2-5mg every two weeks) intramuscular injections can also be administered, although intramuscular estrogen is not currently available in Europe. Data suggest an increased risk of thromboembolic events with the use of ethinyl estradiol [40] [41] [42] and the Endocrine Society specifically recommends against its use. Patients may switch among formulations if they suffer with side effects or if their response is inadequate. Patients should be cautioned to use only one route of administration at a time for better monitoring.

Most studies report the need for adjunctive therapy to lower testosterone to within the range of cisgender women [29] [31] [41] [43] [44]. There are two commonly used oral anti-androgen therapies; spironolactone, and cyproterone acetate.

Spironolactone is a potassium-sparing diuretic with antagonistic effects at the androgen receptor that is also reported to decrease testosterone levels [44] [43]. However, clinicians cannot rely on monitoring testosterone levels alone as spironolactone lacks central suppression. For its antiandrogen effect, spironolactone can be administered at a higher dose than used for hypertension, with 100-300 mg/d being typical oral doses.

Cyproterone acetate, a synthetic progestogen, acts centrally and suppresses gonadotropins, decreasing testosterone production. It is given orally at 10-50 mg/d and although widely used in Europe, is not approved by the FDA for use in the United States.

Gonadotropin-releasing hormone (GnRH) agonists also act centrally and offer an effective means of lowering testosterone levels. GnRH agonists are used as puberty blockers in

adolescents. They can be used to suppress hormones in adults too. However, they should be coupled with sex hormones to avoid long-term osteoporosis. They are administered as an injection that can be given monthly (3.75 to 7.5 mg) or as a depot every 3 months (11.25 to 22.5 mg) either intramuscularly or subcutaneously. Although effective, GnRH agonists tend to be given second line in the United States due to their high cost [5].

The use of progestins, such as medroxyprogesterone acetate and micronized progesterone, is not supported through research nor recommended by the Endocrine Society. Anecdotally, transgender women report improvement in breast and/or areolar development, libido, and mood with the use of progestins [45] [46], although this has not been investigated in clinical studies. While progestins have an anti-androgen effect through suppression of gonadotropins, there is also the risk that some can have androgen-like properties of their own. The risks of progestin use have been studied in older postmenopausal women, and a higher incidence of cardiovascular complications and breast cancer was associated with their use [47]. There are no well-designed studies regarding the role of progestins in feminizing HT.

Finasteride, a 5-alpha-reductase-2 antagonist, reduces the conversion of testosterone to the more potent dihydrotestosterone. Although not considered useful in transgender women who have testosterone levels within the female range, it can be considered an option for those patients who have higher testosterone levels who show male pattern hair loss [5].

In some patients, sufficient androgen blockade may not be achieved with the above regimens. In these instances, the clinician must insure good medication compliance. This is one indication for orchiectomy.

3.1 Treatment effects

Within the first 3 to 12 months of estrogen and antiandrogen treatment, patients may experience decreased facial and body hair, reduced oiliness of skin, breast tissue growth, decreased libido, decreased spontaneous erections, and redistribution of body fat [22] [48] [49] [44] [38] [50] [51] [52]. Some studies report maximal breast growth during the first 6 months of HT. Maximal current follow up is 2 years and further research is required to evaluate growth beyond this [19] [48] Patients will also experience prostate atrophy, as well as observe smaller testes due to the decreased spermatogenesis [19].

An important effect of HT to many transgender women is breast development. The course of breast development in transgender women has been studied [53], but there is much variation among individuals, similar to pubertal development. There is no evidence that progestins are beneficial to breast development [54].

3.2 Medical risks/safety

Apart from the aforementioned weight gain/fat redistribution and reduced libido associated with feminizing HT, there are other potential adverse reactions that must be considered.

The greatest concern for transgender women on estrogen therapy is venous thromboembolism (VTE). The association has long been recognized and several studies have looked at the use of estrogen and VTE among transgender individuals. Some data suggest that the increased risk of VTE in transgender women on estrogen therapy is based on individuals' other VTE risk factors, smoking cessation, and immobilization following surgery, along with formulation of estrogen used [32] [38] [55]. Increased risk was found with the use of ethinyl estradiol [32] [38], which is no longer used for transgender individuals. There is believed to be increased risk with oral estrogen compared to parenteral and transdermal routes due to the 'first pass effect' [56] [57] [58] although the decreased thromboses may simply result from a dose response with less product delivered dermally than orally. Although there are no data for benefit, many cease estrogen therapy 2-4 weeks prior to surgery to reduce the risk of VTE [17].

An increased risk of cerebrovascular events and myocardial infarctions has been observed relative to cisgender women, but no difference relative to cisgender men [55] or cisgender women taking estrogen as a contraceptive [59].

Overall cancer incidence in transgender women on HT compared to cisgender women is the same. There is also no increased breast cancer specific risk when compared to cisgender male breast cancer risk [55].

Concerns have been raised regarding the potential that feminizing HT might be associated with hypertriglyceridemia [60], insulin resistance [55] [38], elevated liver enzymes, and

hypertension. Reported fears of elevated prolactin levels [61] and prolactinoma [62] are substantiated with a rise in prolactin observed in transgender women using estrogens combined with cyproterone acetate [63] [64] [65] [66]. The prolactin upper limit reference ranges were found to be only marginally higher in transgender women on estrogen compared to cisgender women [37]. No clinically relevant prolactin rise is noted when the regimen consists of estrogens and spironolactone [67].

Apart from monitoring for adverse reactions associated with estrogen use, the clinician must also be aware of side effects associated with any antiandrogen therapy used. The primary concern with spironolactone, as a potassium-sparing diuretic, is hyperkalemia.

3.3 Monitoring

Similar to monitoring transgender males on HT, the Endocrine Society Guidelines recommend monitoring patients every 3 months for the first year after initiating HT (With each dose change), and then every 6 to 12 months (**Table 5**).

4. Surgical options

Around half of transgender patients treated medically also pursue transgender-specific surgical options [68] [69]. The Endocrine Society Guidelines recommend surgeries take place after a year of hormone therapy [36], but hormone therapy is not compulsory prior to undergoing surgery. Physicians involved in the treatment of transgender patients should have a basic understanding of the options available, their limitations, and what preparation is required. Most payers require 2 letters from mental health providers prior to surgery, although there are no data supporting such requirements. There is also debate as to whether transgender women should cease estrogen therapy preoperatively, with some surgeons advocating a suspension of HT 2-4 weeks before surgery [70]. By contrast, in 2019 at the national meeting of the Unites States Professional Association for Transgender Health (USPATH) in Washington, DC, a team from Mount Sinai Health System in New York City reported no observed increase in VTE events among transgender women who remained on estrogen treatment during gender affirming genital surgeries [69].

Medical and surgical therapy can affect fertility and should be discussed early in the care of

transgender patients [72]. Patients must be counselled on the potential impact of HT on their fertility potential and informed of the limitations in data on this subject in both transgender men and women [73]. These discussions should encourage patients to consider fertility preservation and the options available to them, including referrals to reproductive specialists. Transgender men are able to utilize cryopreservation of oocytes or embryos and transgender women cryopreservation of sperm [74]. They must also be informed that the majority of insurance companies do not cover assisted reproductive options. While reviewing fertility, the patient should also be counselled on how HT does not necessarily cause infertility and that contraception must be employed to avoid unplanned pregnancy [75].

For feminizing or masculinizing surgery, there are several options available which are reviewed in **Table 6**. Of these, chest reconstruction in transgender men is the most commonly sought with one report finding up to 93% of transgender men seeking chest reconstruction at one center [69]. Phalloplasty is the least common surgery performed due to its high morbidity [76].

Finding specialized surgeons for some of these surgeries can be difficult. For masculinizing and feminizing chest surgery, as well as facial feminization, similar procedures are undertaken for cisgender men and cisgender women. Therefore, there are many surgeons capable of performing the procedures. In contrast, genital reconstruction is far more specialized, and patients should be advised to find specialized centers with transgender experience [5] [77].

Components of feminizing genital surgery include orchiectomy, penectomy, and vaginoplasty. These procedures are complex, and involve utilizing natal tissue to maintain sensation and sexual function. A vaginal vault is created, usually by inverting the penile skin through the pelvic floor between the anus and the urethra. The scrotal skin is used to form labia majora, and a portion of the glans penis forms the clitoris. Transgender women who undergo vaginoplasty will require regular use of vaginal dilators to maintain the patency of the vaginal canal, especially in the early stages post-surgery. These patients will still have a prostate, and although it will undergo atrophy due to lower levels of androgens, they should still be monitored for pathology involving the prostate, including cancer [78]. This is also the case for any tissue that is not removed through surgery, with providers performing appropriate cancer surveillance based on organs present and not the gender identity of the

patient.

Post-surgical management of transgender women will involve ceasing the antiandrogen medication if a gonadectomy is performed. The estrogen dose was previously halved [79] [80], with the belief that pre-surgical transgender women require higher estrogen dosing to contribute to central suppression of testosterone production. However, there are no data to support halving estrogen dosing and the plan should be to customize therapy.

Masculinizing genital surgery is also very complex and involves either phalloplasty or metoidioplasty. Both procedures are often performed along with a hysterectomy and/or a vaginectomy. Phalloplasty involves the creation of a penis through transplanting tissue from elsewhere on the patient's body, typically the forearm or thigh, which is then rolled into a tube-like structure and attached to the inguinal region. A metoidioplasty only uses local genital tissue, utilizing the effects of testosterone on broadening and lengthening the patient's clitoris. The urethra can be extended using grafts from the mucosa of the patient's cheek or vaginal canal, and a scrotoplasty, with or without testicular implants, may also be performed using a graft. Erectile function is maintained in metoidioplasty. Following phalloplasty erectile implants may be considered after approximately 9 months of healing.

Due to a significantly increased risk of urethral stricture in transgender men who undergo either metoidioplasty or phalloplasty with urethral lengthening, post-surgical management should include patient education to seek medical attention for any sign of urethral stricture. Other complications relevant to both procedures include wound scarring, infection, pelvic hematomas, and rectal injury. With phalloplasty, there is the additional risk of flap loss (3.4%-7.8%) in the first few days after surgery [81].

5. Expert Opinion

5.1 Advancement in medical management of transgender individuals requires an intentional effort to include training for all providers

The approaches to care described in this manuscript are broadly accepted by physicians and scientists with evidence of that alignment clear from all major international medical societies with stated positions. Despite the wide acceptance of the current model underlying gender affirming care for transgender and gender non-binary people, substantial barriers to care for

transgender individuals remain. The largest of those barriers remains the lack of providers willing to provide the necessary care for transgender and gender non-binary persons [82].

Although multiple mainstream medical associations have published clinical practice guidelines and high-profile journals have published clinical reviews with detailed treatment guidance [5] [7], surveys conducted among medical communities demonstrate the clear lack of training in this subject. As an illustration, in one regional survey in the United States 80% of the endocrinologists responding described having no training in the care of transgender individuals [83]. This, despite the specialty having published their first guidelines for transgender hormone care in 2009 and its most recent revision in 2017 [36].

The problem of lack of training is visible at all stages of medical education throughout the world although most surveys are from the United States. In a survey of United States medical students, 67% reported that their training in transgender health care was inadequate, even though a guide for medical students was launched in 2014 by the Association of American Medical Colleges (AAMC) [84]. There are similar data for physician trainees in a number of specialties and at different points in training.

Payment for gender affirming medical care is covered in multiple European Countries along with most Canadian Provinces and the states that have the greatest population in the United States. In the United States, federal health policy makes care obligatory also. Thus at least in higher resourced areas of the world, the primary difficulty does not seem to be limited resources, but rather awareness of such resources and focus on utilizing them in formal training curricula.

Internationally, there is currently no systematic, mandatory, structured curriculum to educate either trainees or practicing physicians in a systematic way with regard to transgender health care. The World Professional Association for Transgender Health (WPATH) has created a training series for providers, and the Association of Program Directors in Endocrinology, Diabetes and Metabolism has focused on developing a specific curriculum in transgender management for endocrinology fellows, but neither are currently compulsory aspects of an official curriculum [83].

With 0.6% of the adult United States population identifying as transgender or gender non-

binary [85], along with an estimated 2.5% of the youth population, a greater focus on transgender medical education is required. Guidelines exist and examples of high-quality training are readily available. The next step to truly mainstream appropriate high-quality gender affirming health care is to implement systematic formal training. Published curricular interventions for medical trainees exist with the educational model easily accommodated in standard medical training [86]. The required additions are modest and achievable. However, as long as such organized effort is lacking, there will continue to be a deficiency of informed healthcare providers and resulting suboptimal care.

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Legend for Tables and Figures

Table 1. Common Terminology

Gender/sex: General terms describing the group of relevant biological features, self-identification, and stereotypical behaviors that might be considered male, female, or some variation.
Gender identity: An individual's sense of being male, female, or neither.
Transgender, transsexual, trans, gender nonbinary, gender incongruent, genderqueer: Adjectives used to represent persons whose gender identity does not align with their sex recorded at birth.
Cisgender, non-transgender: Terms used to refer to individuals whose gender identity is consistent with their sex recorded at birth.
Gender expression: How an individual communicates their gender identity through physical appearance, pronouns, name, mannerisms, and speech.
Gender-affirming hormone treatment and surgeries: Forms of medical interventions that trans persons may consider to align their appearance and their gender identity.
Gender transition, gender affirmation, gender confirmation: The process of alignment of an individual's gender expression and physical features with gender identity.
Gender dysphoria: The distress felt by individuals due to the misalignment between their gender identity and their sex recorded at birth. Not all trans persons have gender dysphoria, but it is a required diagnosis by many U.S. insurance companies for payment of gender reaffirming medical and surgical interventions.

Adapted from Annals of Internal Medicine 'Care of the Transgender Patient' [5]

Table 2. Hormone Regimens for Transgender Men

Parenteral Testosterone	
Testosterone enanthate or cypionate	- **50-100mg subcutaneous every 7-10 days, or intramuscular every 2-3 weeks** - **100-200mg subcutaneous or intramuscular every 2 weeks**
Testosterone undecanoate	- **1000mg every 12 weeks**
Transdermal Testosterone	
Testosterone gel	- **50-100mg topical per day**
Testosterone patch	- **2.5-7.5mg topical per day**

Table 3. Monitoring Transgender Men on Hormone Replacement Therapy

1. Monitor testosterone levels every 3 months for 1 year after initiating therapy, and every 6-12 months once in physiologic range. - For transdermal patches, levels should be measured at least 1 week after initiation and at least 2 hours after application. - For testosterone enanthate/cypionate injections, levels can be measured midway between injections with target levels 400-700 ng/dL, or measure peak and trough levels with physiologic male range. - For testosterone undecanoate, levels should be measured just before injection, with dosing interval adjustments for any levels below 400 ng/dL.
2. Measure baseline hematocrit and lipid panel every 3 months for 1 year after initiating therapy, and every 6-12 months thereafter.
3. Routine monitoring of weight, blood pressure, signs of virilization, and adverse reactions to therapy.
4. Measure baseline bone mineral density for those at risk and routine osteoporosis screening for those who stop testosterone therapy or have poor compliance.
5. Routine cervical cancer screening as per American College of Obstetricians and Gynecologists if tissue present.
6. If no mastectomy performed, routine breast cancer screening as per American Cancer Society. If mastectomy performed, annual breast examination.

Adapted from The Endocrine Society 'Guidelines on Gender-Dysphoric/Gender-Incongruent Persons [36] [51] [86]

Table 4. Hormone Regimens for Transgender Women

Estrogen	
Oral Estradiol	- 2-6mg per day maintenance dose
Oral Conjugated Estrogens	- 2.5-7.5mg per day maintenance dose
Transdermal Estradiol Patch	- 0.025-0.2mg per day, patch change every 3-7 days
Parenteral Estradiol Valerate	- 2-10mg per week - 5-30mg every 2 weeks
Antiandrogens	
Spironolactone	- 100-300mg per day oral tablet
GnRH Agonist (Leuprolide)	- 3.75-7.5mg subcutaneous or intramuscular monthly - 11.25-22.5mg subcutaneous or intramuscular 3 monthly
Cyproterone Acetate	- 10-50mg per day oral tablet

Table 5. Monitoring Transgender Women on Hormone Replacement Therapy

1. Monitor estradiol and testosterone levels in patient every 3 months for 1 year after initiating therapy, and every 6-12 months thereafter. - Monitor for signs of appropriate feminization and for any side effects of HT - Testosterone levels < 50ng/dL - Estradiol levels 100-200 pg/mL
2. For patients taking spironolactone, monitor renal function and electrolytes, especially potassium, every 3 months for first year and annually thereafter.
3. Routine cancer screening for any natal tissue present, as in non-transgender males.
4. Recommend obtaining Bone Mineral Density measurements when risk factors for osteoporosis exist, specifically in patients who stop HT after gonadectomy.

Adapted from The Endocrine Society 'Guidelines on Gender-Dysphoric/Gender-Incongruent Persons [36]

Table 6. Surgical Options for Transgender Patients

Category	Description	Additional Comments
Transgender Women		
Facial Feminization	Includes rhinoplasty, mandibular contouring, tracheal shave, brow lift, hairline alterations, lip lift and genioplasty	Many of these procedures are the same as those for cisgender woman, therefore creating good access to surgery. However, as they are considered cosmetic for cisgender women, not all are covered by insurance.
Breast Augmentation	Breasts implants to enhance size and shape of patients chest to a more feminine appearance	Commonly performed procedure for cisgender women, therefore creating good access to surgery. However, as it is considered comestic for cisgender women, surgery may not be covered by insurance.
Genital Reconstruction	Includes orchiectomy, penectomy, and vaginoplasty	Limited access to specialized vaginoplasty surgical centers
Transgender Men		
Chest Reconstruction	Includes bilateral mastectomy and male chest contouring	Surgical procedures used for cisgender men with gynecomastia, therefore creating good access to surgery.
Hysterectomy and Oophorectomy	Surgical removal of patient's pelvic reproductive organs	Commonly performed procedure for cisgender women, therefore creating good access to surgery.
Metoidioplasty	Clitoral ligament release to create micro-phallus	Limited access to specialized metoidioplasty surgical centers. Preserves sensation with sexual function. Risk of urethral stricture.
Phalloplasty	Utilizes tissue from elsewhere on the patient's body to create neophallus	Limited access to specialized phalloplasty surgical centers. High rate of complications including scar at donor site and urtheral stricture. Neophallus may have sensation through preserving clitoral tissue, but no erectile function.

Adapted from "Care of Transgender Persons" in New England Journal of Medicine [7]