Evaluation and Treatment of Gender Dysphoria to Prepare for Gender Confirmation Surgery

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ABSTRACT

Background: Gender dysphoria is the experience of marked distress due to incongruence between genetically determined gender and experienced gender. Treatment of gender dysphoria should be individualized and multidisciplinary, involving a combination of psychotherapy, social gender transition, cross-sex hormone therapy, gender-affirming surgery, and/or ancillary procedures and services. The goal of all treatment modalities is to alleviate distress and affirm the patient's experienced gender identity. This article is the first in a 3-part series focused on the diagnostic assessment and non-operative treatment of gender dysphoria. Parts 2 and 3 focus on operative aspects of gender dysphoria treatment.

Aim: To summarize the recommendations of the World Professional Association for Transgender Health (WPATH) and the Endocrine Society (ES), as well as review published literature regarding the non-operative treatment of gender dysphoria.

Methods: A review of relevant literature through January 2017 was performed via PubMed.

Outcomes: WPATH guidelines regarding diagnosis and non-surgical treatment of gender dysphoria, specifically regimens and risks of cross-sex hormone therapy were reviewed.

Results: Few physicians have experience with the diagnosis or treatment of gender dysphoria, although the number of patients seeking treatment has risen substantially in recent years. As a result, clinicians have turned to published recommendations from WPATH and ES, both of which promote high-quality, evidence-based care for patients with gender dysphoria. Successful treatment requires an individualized multidisciplinary approach. Non-operative treatment is both safe and effective for the majority of patients with gender dysphoria.

Conclusions: Guidelines from WPATH and ES, along with published literature pertaining to the diagnosis and non-operative treatment of gender dysphoria, were reviewed and summarized. **Hadj-Moussa M, Ohl DA, Kuzon WM. Evaluation and Treatment of Gender Dysphoria to Prepare for Gender Confirmation Surgery. Sex Med Rev 2018;6:607–617.**

Key Words: Gender Dysphoria; Transgender; Cross-Sex Hormone Therapy; Real-Life Experience

INTRODUCTION

Individuals with gender dysphoria experience marked distress due to an incongruence between their experienced gender identity and their biologically determined anatomy.[1] Epidemiological studies report 0.3–0.5% of adults experience gender dysphoria; experts,[2,3] and a recent review by Winter et al,[4] agree these values likely underestimate the true prevalence due to the significant social stigma associated with gender non conformity.

The number of people seeking medical attention for treatment of gender dysphoria has risen dramatically in recent years.[5,6] Unfortunately, medical schools are varied in their dedication to teaching about the diagnosis, treatment, or general health care needs of patients with gender dysphoria. Medical professionals worldwide have therefore turned to published recommendations from the World Professional Association for Transgender Health (WPATH) and the Endocrine Society (ES), both of which promote high-quality, evidence-based care for transgender patients.[2,7] Few differences exist between the 2 guidelines, although some requirements in the most recent WPATH 7th edition recommendations have been liberalized compared to those in the ES guidelines in an effort to reduce barriers to care for patients in communities lacking clinicians who have experience treating gender dysphoria. The goal of all treatment for gender dysphoria is to alleviate distress and affirm the patient's

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Table 1. Terminology and definitions[2,5,7,14,22]

Term	Definition
Sex	Biological characteristics that define male and female gender, based on external genitalia, without regard to one's gender identity.
Gender identity	A category of social identity that describes an individual's identification as male, female, or an alternative gender.
Gender non-conformity	The extent to which a person's gender identity differs from cultural norms ascribed to a particular biological sex.
Transgender	Adjective that describes a person whose expression, beliefs, or ideas do not conform with their biologically defined gender.
Gender dysphoria	Discomfort or distress caused by a discrepancy between a person's gender identity and their biologic sex (a formal diagnosis by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*).
Gender confirmation surgery	Surgery to change primary and/or secondary sex characteristics to affirm a person's gender identity.
Transition	Period of time when individuals change from the gender role associated with their biological sex to a different gender role.
Female-to-male	Adjective describing female individuals who are changing or who have changed their body and/or gender role to a more masculine body or role.
Male-to-female	Adjective describing male individuals who are changing or who have changed their body and/or gender role to a more feminine body or role.

experienced gender identity. Both WPATH and ES agree that treatment should be individualized based on each patient's specific needs and goals for gender expression, since the degree of distress patients experience related to their gender dysphoria is highly variable.[2,7] Interventions that may prove beneficial for transgender patients include psychotherapy, social gender transition, hormone therapy, gender-affirming surgery, and/or other accompanying services such as vocal coaching, permanent hair removal, and comportment counseling.[2,8] Informed consent is of paramount importance due to the considerable consequences of the hormonal therapy and surgical interventions used to treat gender dysphoria.[2,7] Thus, prior to initiating hormone therapy, any surgical intervention, or especially when deviating from published standards of care, the patient's informed consent must be obtained and documented in their medical record.

This review is the first in a 3-part series focused on the multidisciplinary treatment of gender dysphoria. The diagnosis and treatment of children and adolescents with gender dysphoria is unique and beyond the scope of this series. Part 1 includes diagnostic assessment, preventative health and screening guidelines, and non-operative treatment of gender dysphoria including psychotherapy, social gender transition, and hormone therapy. Parts 2 and 3 will review surgical treatments, including intraoperative techniques for male-to-female (MtF) and female-to-male (FtM) gender confirmation surgery (GCS), as well as ancillary procedures and services for the comprehensive treatment of gender dysphoria.[9]

DIAGNOSTIC ASSESSMENT

Establishing an accurate diagnosis is the first step in treatment for gender dysphoria.[5] This requires a good understanding of relevant medical terminology by health care providers, although the vocabulary surrounding gender issues is evolving and varies by culture and context (Table 1).

Both WPATH and ES recommend that a qualified mental health professional (MHP) make the diagnosis of gender dysphoria.[2,7] Qualified MHPs must have specific training and experience in the care of transgender and gender-non conforming patients.[2] To minimize barriers to care in communities where qualified MHPs are scarce, WPATH also endorses an "informed consent model" whereby other medical professionals with training in gender and mental health issues may also diagnose gender dysphoria.[2,5] A thorough diagnostic evaluation determines whether the patient meets *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria for gender dysphoria; examines their psychosocial functioning; and identifies their personal, professional, and economic support systems (Table 2).[1]

The Role of MHPs

In addition to accurately diagnosing gender dysphoria, involvement of a qualified MHP is helpful for a variety of other reasons.[2] These practitioners:

- Diagnose and discuss treatment options for concomitant mental health disorders, which are found in higher rates in gender dysphoric patients and if not optimized, can hinder successful treatment.
- Educate patients about options for gender identity and expression and available treatment options, helping them gain comfort with their gender expression.
- Provide appropriate referrals for medical hormone therapy following an assessment that determines the patient meets WPATH readiness and eligibility criteria, and prepare the patient for what to expect from hormone therapy.

Table 2. Gender dysphoria diagnostic criteria[10]

A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 mo duration, as manifested by at least 2 of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (in young adolescents, the anticipated secondary sex characteristics).
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).
The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

- Review gender-affirming surgical procedures with the patient, assess whether they meet WPATH eligibility and readiness criteria for surgery, and provide referrals to the appropriate surgeons.
- Provide ongoing support to patients and their families throughout treatment and transition.
- Educate and advocate on behalf of their clients, assist with changing relevant legal documents.
- Provide information and referral for peer support.

PSYCHOTHERAPY AND COUNSELING

The goal of psychotherapy and counseling in the treatment of gender dysphoria is to help patients maximize their overall psychological state and quality of life, not alter their gender identity. Experts and professional societies, including WPATH and ES, highly recommend psychotherapy for patients being treated for gender dysphoria, although it is not an absolute requirement.[2,7] Ongoing psychotherapy or counseling provides numerous benefits to patients as they transition to their desired gender identity. Through psychotherapy, some individuals are able to successfully integrate their gender identity into their lives without the need for hormone therapy or gender-affirming surgery.[2]

MHPs can help patients define their individual needs and goals for gender expression, assess their social support systems, and diagnose the presence of other mental health issues.[8,10] Therapy can help patients answer questions about their gender identity and sexual orientation; come out to their families, friends, and colleagues; enjoy an improved body image; and overcome internalized transphobia.[2] Based on their assessment, involved MHPs can help patients develop a gender-affirming treatment plan that meets their unique needs. For people who require hormonal therapy and/or gender affirming surgery, MHPs advocate on their behalf by providing necessary referrals, guiding them through updating legal documents, etc. Finally, ongoing support from a MHP throughout the transition process is helpful for patients as they navigate new territory within their families, friendships, intimate relationships, and communities. Therapy can be individual, include family members, or be undertaken in a group setting. In communities without peer support groups, the Internet can be a powerful tool to connect people with gender dysphoria.[8]

SOCIAL TRANSITION (REAL-LIFE EXPERIENCE)

Social transition, commonly termed "real-life experience" (RLE), refers to the social gender role transition period where individuals live full-time as their preferred gender identity in all aspects of their lives.[2,7] Both WPATH and ES consider social transition an important component of gender dysphoria treatment for a variety of reasons, most importantly, because transitioning gender expression can be extraordinarily difficult. Social transition conveys to the patient what to expect in their personal lives, within their families, at work, and in their communities before they undergo potentially irreversible treatment. Social transition also confirms patients' readiness for surgical intervention. MHPs can gain valuable insight into their patients during the social transition by observing how they confront challenges that arise, determining to what degree they are supported by family, friends, and colleagues, etc. Absent or inadequate experience living in a gender-congruent identity has been associated with regret following GCS.[11] Other circumstances correlated with regret, for example, poor family and social support, can also be assessed by MHPs during the patient's RLE.[12] Patients often initiate their social transition before ever seeking medical attention.

It is important for practitioners to document several aspects of a patient's social gender transition, including when it began, their degree of commitment, and how they are coping. Based on these observations, a MHP may determine that additional psychotherapy and counseling, or strengthening of support systems, are in the patient's best interest before a referral for hormonal therapy or surgery can be made.

GCS uses a combination of genital and non-genital procedures to emphasize physical characteristics congruent with a patient's gender identity.[13] An overview of GCS procedures is highlighted in Table 3 and discussed in detail in the second and third parts of

Table 3. Gender confirmation surgery

	Masculinizing surgery	Feminizing surgery
Face	• Lipofilling • Liposuction • Facial masculinization (rare) • Voice modification surgery (rare)	• Facial feminization • Thyroid chondroplasty • Hair re construction • Voice modification surgery
Body	• Subcutaneous mastectomy • Male chest contouring • Pectoral implants	• Augmentation mammoplasty • Lipofilling • Gluteal augmentation • Waist lipoplasty
Genital	• Hysterectomy • Salpingo-oophorectomy • Vaginectomy • Metoidioplasty ± urethral lengthening • Phalloplasty ± urethral lengthening • Scrotoplasty • Testicular prosthesis placement • Penile prosthesis placement	• Orchiectomy • Penectomy • Vaginoplasty + clitoro-labiaplasty • Vulvoplasty + clitoro-labiaplasty

this series.[9] Both WPATH and ES strongly recommend all patients undergoing GCS complete a social gender transition. ES guidelines require at least 3 months of RLE (or a similar duration of psychotherapy) prior to initiating hormone therapy, and at least 12 months before any gender-affirming surgery.[7] WPATH requirements are less stringent and do not require RLE before hormone therapy or some genital surgery, including hysterectomy, salpingo-oophorectomy, or orchiectomy.[2] Per WPATH guidelines, a 12-month continuous social transition is mandatory for patients undergoing re-constructive genital GCS, including metoidioplasty, phalloplasty, or vaginoplasty.[2]

HORMONE THERAPY

Cross-sex hormone therapy, which induces the secondary sex characteristics associated with the patient's desired gender while minimizing those of their biological gender, is medically necessary and effective to treat gender dysphoria for many patients.[14,15] Numerous benefits of cross-sex hormone therapy have been reported, including relief from gender dysphoria, greater quality of life, and improved sexual function.[15,16] Heylens et al[17] showed that initiation of hormone therapy was associated with the greatest reduction of psychopathology in patients with gender dysphoria. Hormone therapy has also been shown to ease patients' social transition.[7] A record of consistent and compliant hormone use is required before some gender-affirming surgeries. WPATH strongly encourages ongoing psychotherapy for patients treated with cross-sex hormones.[2] ES goes a step further, requiring some patients starting hormone therapy to complete psychotherapy, usually for a minimum of 3 months, at the discretion of their MHP as an alternative to RLE.[2,7]

The goals of medical hormone therapy are 2-fold.[12] The first is to minimize the secondary sexual characteristics of biological gender via endogenous sex hormone suppression; this leads to a more androgynous appearance. The second goal is to maximize the secondary sex characteristics of the desired gender through supplementation of cross-sex hormones. The physical effects of hormone therapy develop gradually over months to years, and are variable from patient to patient.[2,7] Hormone therapy regimens should be individualized, based on each patient's goals for treatment, medical co-morbidities, economic resources, etc.

Numerous hormone regimens have been successfully used to treat gender dysphoria; however, no large prospective studies have been conducted to establish the ideal hormone regimen for treatment of gender dysphoria.[2] In addition, availability and access to medications is highly variable. As a result, WPATH does not endorse a specific hormone regimen, but does encourage clinicians to follow ES guidelines for hormone therapy.

Hormone Therapy Eligibility Criteria

WPATH recommends hormone therapy should only be offered to patients who satisfy the following eligibility criteria[2]:

- Patient's gender dysphoria is persistent and well documented;
- Patient has the capacity to make a fully informed decision and consent to treatment;
- Patient is the age of majority in a given country (WPATH and ES both provide specific guidelines for management of pediatric hormone therapy);
- Patient's medical or mental health co-morbidities are reasonably well-controlled.

Patients considering hormone therapy should ideally undergo a psychologic assessment with a qualified MHP; however, WPATH does not strictly require approval from a mental health provider before hormone therapy is initiated.

Once necessary eligibility criteria have been satisfied, a MHP can provide the patient with a letter of referral recommending hormone therapy for treatment of their gender dysphoria. WPATH recommends that referral letters for hormone therapy or surgery include[2]:

- Patient's general identifying characteristics;
- Results of the patient's psychologic assessment, including any relevant mental health disorders;

Table 4. Baseline evaluation for hormone therapy[2,5,7,13,20,22]

Evaluate medical history, family history, psychosocial history (including tobacco use, substance abuse, mental health disorders), and reproductive goals (offer gamete preservation if relevant).
Physical examination including weight, BMI, and blood pressure should be performed.
Obtain CBC, electrolytes, renal function, glucose metabolism, lipid panel, liver function, FSH, LH, total testosterone, estradiol, and prolactin. Consider STI testing.
Obtain an EKG if patient has risk factors for CV disease.
Measure bone mineral density using a DEXA scan for patients at risk for osteoporotic fractures (personal or family history, chronic glucocorticoid use, chronic hypo gonadism).
Cancer screening for breast, cervical, and prostate cancer should be performed when recommended by national screening guidelines.
Consider thrombophilia testing in patients at risk for VTE, including protein C, protein S, ATIII, factor V, prothrombin G, and MTHFR mutations.

ATIII = anti-thrombin III; BMI = body mass index; CBC = complete blood cell count; CV = cardiovascular; DEXA = dual-energy X-ray absorptiometry; EKG = electrocardiogram; FSH = follicle stimulating hormone; LH = luteinizing hormone; MTHFR = methylene tetrahydrofolate reductase; STI = sexually transmitted infection; VTE = venous thromboembolism.

- Length of relationship between the patient and the referring MHP, including the type of evaluation completed and any psychotherapy or counseling the patient has already completed;
- A statement confirming that eligibility criteria for either hormone therapy or surgery have been met, as well as statement supporting the patient's request for medical or surgical treatment;
- Declaration that the patient has provided fully informed consent;
- A statement that the referring provider is available for consultation and coordination of care.

Patients with medical contra indications to hormone therapy should work with their MHP to craft a non-hormonal treatment plan.

Hormone Therapy Providers

WPATH guidelines authorize a variety of appropriately trained health care professionals, including primary care physicians and nurse practitioners, to prescribe and manage hormone therapy for gender dysphoria.[2,18] Redundancy in hormone prescribers is helpful because it reduces barriers to care in areas without dedicated transgender health programs. Involvement by experienced primary care physicians is especially beneficial, as they are qualified to provide comprehensive care to patients including routine health maintenance exams and cancer screenings. Patients with complex medical issues related to hormone therapy warrant referral to and should be managed by an endocrinologist.

WPATH specifically discusses the responsibilities of providers prescribing hormones for gender dysphoria.[2] Prescribers must confirm the patient has satisfied WPATH eligibility criteria, including that they agree with the diagnosis and the ability of the patient to provide informed consent. Initial evaluations should include a discussion of the patient's goals of treatment, medical history, physical examination, risk assessment for relevant co-morbidities or contra indications to hormone therapy, and obtaining necessary bloodwork. Relevant medical co-morbidities should be managed and modifiable risk factors addressed and minimized prior to starting hormones. If there are no contra-indications to hormone therapy, the provider should have a thorough discussion about realistic expectations for expected physical changes, including a general timeline, potential risks, and adverse events. Patients' questions should be answered and their informed consent documented. Because hormone therapy can lead to temporary or permanent infertility, reproductive goals should be discussed and gamete storage offered, when applicable. Once hormone therapy has begun, prescribers should perform regular physical examinations and recommended laboratory studies to monitor treatment efficacy and screen for adverse events. Finally, some patients may need documentation from clinicians that they are being treated with cross-sex hormones.

Hormone Therapy Monitoring and Safety

Follow-up is required for all patients receiving hormone therapy, both to assess clinical efficacy and to monitor for the development of potentially dangerous adverse events. The risk of adverse events associated with hormone therapy depends on patient-specific co morbidities as well as the medication preparation, route of administration, dosage, and serum level. Supraphysiologic hormone levels are associated with an increased risk of adverse events; thus both WPATH and ES recommend close monitoring of serum hormone levels to maintain them within the therapeutic physiologic range.[2,7,19] The increased risk of adverse events due to cross-sex hormone therapy is controversial.[2,20] There is a paucity of high-quality empiric data evaluating the risk of cross-sex hormone therapy, similar to many aspects of transgender medical care.

While the true risk of adverse events related to cross-sex hormone therapy has not been completely elucidated, a common theme has emerged from several studies showing increased risk of adverse events in patients with modifiable risk factors. In particular, patients with a personal or family history of cardiovascular (CV) disease should be identified and treated prior

Table 5. Monitoring for patients on hormone therapy[2,5,7,13,20,22]

Evaluate patient every 3 mo during first year and then every 6–12 mo thereafter.
Check weight, BMI, blood pressure.
Check CBC, renal function, liver function, glucose metabolism, lipid panel, and glucose metabolism.
Bone mineral density screening with DEXA scan every 1–2 y if at high risk for osteoporotic fractures. Follow general recommended osteoporosis screening guidelines if low risk.
Masculinizing hormone therapy
Measure testosterone every 3 mo until level is within physiologic range (350–1,000 ng/dL), increase or decrease testosterone dose accordingly.
Testosterone enanthate/cypionate injections, measure at mid-point between injections.
Testosterone undecanoate injections, measure shortly before the next injection.
Transdermal testosterone, measure any time after 1 wk of therapy.
Oral testosterone undecanoate, measure 3–5 h after taking medication.
Measure serum estradiol levels during the first 6 mo of testosterone therapy or until there has been no uterine bleeding for 6 mo. Estradiol levels should be <50 pg/mL to minimize feminine features and maximize virilization.
Routine cancer screenings per recommended guidelines.
Mammogram if breast tissue is present; chest and axillary examination following mastectomy.
Pap smear if cervical tissue is present.
Feminizing hormone therapy
Check serum electrolytes, especially potassium, for patients taking spironolactone.
Measure serum estradiol every 3 mo until level is within physiologic range (100–200 pg/dL), increase or decrease estrogen dose accordingly.
Estradiol valerate/cypionate injections, measure at mid-point between injections.
Transdermal estradiol, measure any time after 1 wk of therapy.
Oral estradiol, measure any time after 1 wk of therapy.
Measure serum testosterone every 3 mo until level is within physiologic range (<55 ng/dL).
Measure prolactin levels at baseline, after 12 mo, and then every 1–2 y.
Routine cancer screenings per recommended guidelines.
Prostate exam and PSA if prostate tissue is present.
Chest and axillary examination, consider mammogram.

BMI = body mass index; CBC = complete blood cell count; DEXA = dual-energy X-ray absorptiometry; PSA = prostate specific antigen.

to the initiation of cross-sex hormones. Smoking is associated with higher rates of polycythemia and stroke in patients taking testosterone, and increases the risk of venous thromboembolism (VTE) in patients taking estrogen.[5,18,19] Smokers should be counseled to quit before starting hormone therapy. There is no conclusive evidence that either feminizing or masculinizing hormone therapy leads to an increased risk of any malignancy.[2,12,21]

Baseline Evaluations

Before initiating hormone therapy a complete history and physical examination, including family history, psychosocial history, discussion of family planning goals, and relevant additional testing should be performed for all patients (Table 4).[2,7,12,20] In particular, risk of CV disease including personal or family history should be noted. Co-existing medical conditions should be optimized. Bone mineral density should be assessed in patients at risk for pathologic fractures.[5] Consider baseline thrombophilia screening in patients with a family history of VTE.[20,22] Cancer screening should be completed based on patient risk and national screening guidelines.[2]

Follow-Up Evaluations

Patients receiving hormone therapy should be re-evaluated every 3 months during the first year of therapy and every 6–12 months thereafter to monitor for expected physical changes and the development of adverse events (Table 5).[7] ES recommends all patients treated with cross-sex hormone therapy be screened regularly for CV disease.[7] Estrogen and testosterone both protect bone density, therefore patients who are hypo-gonadal as a result of gonadectomy or interruption of hormone therapy are at high risk for osteoporosis and should be screened every 1–2 years.[7,12]

Preventative Health and Cancer Screening

In addition to the follow-up required for monitoring hormone therapy, patients with gender dysphoria should receive routine health maintenance examinations, vaccinations, and cancer screenings at intervals that follow national recommendations for non-transgendered individuals.[2,19]

Masculinizing Hormone Therapy

The goal of masculinizing hormone therapy is to supplement and maintain testosterone levels within the normal physiologic

Table 6. Phenotypic effects of hormone therapy[2,5,7,20,24]

Onset	Testosterone effects	Estrogen effects
0–3 mo	Increased facial acne Body fat redistribution	Decreased libido Decreased spontaneous erections
3–6 mo	Cessation of menses Clitoral enlargement Vaginal atrophy	Body fat redistribution Loss of muscle mass and strength Facial skin softening, decreased acne Breast growth Testicular atrophy
>6 mo	Increased facial and body hair Scalp hair loss Increased muscle mass and strength Deepening voice	Decreased facial and body hair Decreased sperm production

range for an adult man (320–1,000 ng/dL) using the lowest possible dose of exogenous testosterone.[2,7] Testosterone therapy can be successfully administered via several regimens.[7,23] Masculinizing hormone therapy may require suppression of endogenous estrogen with gonadotropin-releasing hormone (GnRH) agonists or progestins for complete cessation of menses. Overall, testosterone therapy appears to be associated with fewer risks than feminizing hormone therapy.

Physical examination is the best way to assess the efficacy of masculinizing hormone therapy. Effects of masculinizing hormones develop over months to years and include: increased acne, growth of facial and body hair, male pattern baldness, increased muscle mass, body fat redistribution, interruption of menses, clitoral enlargement, vaginal atrophy, deepened voice, and increased libido (Table 6).[7,20,24]

Contra-Indications and Adverse Events

The use of testosterone is contra-indicated in individuals who are pregnant or have severe coronary artery disease, breast or endometrial cancer, active substance abuse, or untreated polycythemia (hematocrit ≥55%).[5,7,20] If there are questions about the severity of coronary artery disease, consultation from the patient's cardiologist for cardiac clearance is appropriate. Obtain a medical oncology consultation for patients with a history of estrogen-dependent cancers, since the aromatization of testosterone to estrogen can theoretically increase oncologic risk in these patients.[2]

Physicians should monitor patients receiving testosterone therapy for side effects, although testosterone therapy for transgender men appears to be quite safe.[14] Polycythemia is the most common adverse event, and is most common with injectable preparations.[25] Other reported side effects include weight gain, androgenetic alopecia, acne, sleep apnea, and transient elevation of liver enzymes.[2,21] Wierckx et al[14] showed a higher rate of type 2 diabetes in transgender men being treated with testosterone therapy than either transgender women or cross-gender matched controls. Testosterone may be associated with an atherogenic lipid profile; however, the risk of CV disease in transgender men does not appear to be increased compared to the general population.[2,7,14,20,26,27]

There does not appear to be a higher rate of cancer for transgender men treated with testosterone.[20,28,29] There has been concern that testosterone supplementation could stimulate development of breast cancer via aromatization to estrogen, however, few cases have been reported.[29,30] FtM patients who have undergone mastectomy may have residual breast tissue so should have annual chest and axillary examinations and be educated about the small but theoretical risk of developing breast cancer.[19] 2 Cases of ovarian cancer and no cases of endometrial cancer have been reported in FtM patients.[20] FtM patients who have not undergone mastectomy, total hysterectomy, or salpingo-oophorectomy should have routine cancer screenings based on nationally published guidelines for biological women.[2,7] Undergoing mastectomy, hysterectomy, and salpingo-oophorectomy may change the need for ongoing gynecologic cancer screening for FtM patients, but formal screening guidelines have yet to be established.

Hormone Regimens

Testosterone. Testosterone administration routes include oral, transdermal, intramuscular, buccal, and implantable formulations (Table 7). Each is associated with advantages and drawbacks. Low cost is the primary advantage of testosterone injections, which are the most commonly reported preparation of testosterone used for cross-sex hormone therapy.[24] Injections are associated with the highest risk of polycythemia, as well as considerable variability in serum testosterone levels, which can cause cyclic mood swings from elevated mood or aggression with supra-therapeutic levels following an injection to fatigue and depression associated with nadir levels before the next injection.[20,25] This effect can be mitigated by reducing the interval of time between injections. Testosterone undecanoate injections, which are not available in the United States, maintain stable serum testosterone levels over a 12-week period.[31] Oral testosterone is also not available in the United States due to the risk of hepatotoxicity.[24] Transdermal patches and gels produce testosterone levels that mimic physiologic variations since they peak 4 hours after placement and then taper until the next dose is given.[20] Gels can be transferred via skin contact and is very dangerous

Table 7. Hormone therapy regimens[2,7,13,20,22]

Masculinizing hormones	
Testosterone undecanoate 160–240 mg PO daily	Liver toxicity, expensive, not available in United States, dietary fat reduces bioavailability, less effective virilization
Testosterone undecanoate 1,000 mg IM every 12 wk	Stable serum levels, not available in United States
Testosterone enanthate or cypionate 100–200 mg IM every 2 wk or 50% dose weekly	Inexpensive, highest polycythemia risk, mood swings due to fluctuating serum levels
Testosterone gel 1% 2.5–10 g TD daily or 1.62% 40.5–81 mg TD daily	Stable serum levels, risk of transfer to others, expensive, less effective virilization, incomplete amenorrhea
Testosterone patch 2.5–7.5 mg TD daily	Stable serum levels, musky odor, expensive, skin irritation, less effective virilization, incomplete amenorrhea
Testosterone 30 mg buccal BID	Pulsatile levels mimic endogenous testosterone secretion, gum irritation, bitter taste
Testosterone implant 150–450 mg SQ every 3–6 mo	Effective for several months, requires incision for placement, risk of extrusion (rare)
Feminizing hormones	
Estradiol 2–6 mg PO daily	Inexpensive, highest VTE risk
Estradiol patch 0.1–0.4 mg TD twice weekly	Lowest VTE risk, skin irritation, slow onset
Estradiol valerate or cypionate 5–30 mg IM every 2 wk or 50% dose weekly	Highest levels of circulating estrogen, risk of abuse or overdose, slow onset
Anti-androgen medications	
Cyproterone acetate 50–100 mg PO daily	Widely available (except in United States), liver toxicity (rare), depression
Spironolactone 100–400 mg PO daily	Hypo-kalemia, hypo-tension, gynecomastia
Finasteride 2.5–5 mg PO daily	Reduced androgenic alopecia, limited evidence of efficacy
Flutamide 125–250 mg PO daily	Treats excessive seborrhea, liver toxicity
Goserelin 3.6 mg SQ every 4 wk	Few side effects, gynecomastia, expensive
Leuprorelin 3.75 mg IM every 4 wk	Expensive
Medroxyprogesterone 150 mg IM every 3 mo	Causes cessation of menses, endometrial hyperplasia

BID = twice a day; IM = intramuscular; PO = oral; SQ = subcutaneous; TD = transdermal; VTE = venous thromboembolism.

especially to pregnant women and children. They carry a black-box warning from the Food and Drug Administration due to the risk of secondary exposure to children, where cases of precocious puberty and aggression have been reported.[24,32] Buccal testosterone preparations achieve physiologic levels rapidly and are well tolerated by patients.[20] Testosterone pellets can be placed subcutaneously and are effective for up to 6-month intervals.[20]

Progestin. Some FtM patients who have not undergone hysterectomy may benefit from the use of progestins, GnRH agonists, or endometrial ablation for cessation of menses despite testosterone therapy.[2,22] A 3- to 6-month course of medroxyprogesterone is the most commonly prescribed, as GnRH agonists tend to be cost-prohibitive.[24]

Feminizing Hormone Therapy

The goal of feminizing hormone therapy is to supplement and maintain serum estrogen at the level of an adult woman (<200 pg/mL).[7] This requires concurrent administration of anti-androgen medications to suppress endogenous testosterone to biologic female levels (<55 ng/dL).[7] Feminizing hormone therapy is more complex and associated with more adverse events than testosterone therapy.[7,14,20]

Physical examination is the best way to assess the efficacy of feminizing hormone therapy. Effects of feminizing hormones occur gradually over several months to years and include: increased proportion of body fat, loss of muscle mass, facial skin softening, decreased libido, reduced erectile function, breast tissue growth, testicular atrophy and impaired spermatogenesis, loss of facial and body hair, and male pattern baldness (Table 6).[7,20,24]

Contra-Indications and Adverse Events

The use of estrogen is contra-indicated in patients with a history of VTE, hyper-coagulable disorders, estrogen-sensitive malignancies, severe hepatic dysfunction, or active substance abuse.[2,20]

VTE is the most feared adverse associated with estrogen use. Contemporary studies have shown estrogen therapy is associated with a 1−6.2% increased risk of VTE, especially for patients who are more than 40 years of age, immobilized, smokers, or with thrombophilic disorders.[14] The risk of VTE has decreased significantly due to the introduction of peri-operative thrombotic prophylaxis, cessation of estrogen peri-operatively, and the elimination of synthetic ethinyl estradiol from hormone regimens, since it alone increased the risk of VTE by 20-fold.[14,33] The risk of mortality due to CV and cerebrovascular disease may be modestly elevated for feminizing cross-sex hormone therapy, especially for smokers, although not conclusively.[14,20] Consider consultation from the patient's cardiologist if there is concern about the risk of CV disease. Feminizing hormone therapy may be associated with gallstones, transient liver enzyme elevation (rarely severe hepatic dysfunction), weight gain, migraine headaches, emotional liability, and hyperlipidemia.[7,20,21,24] Although the actual prevalence is likely much lower, early studies reported up that to 20% of patients receiving feminizing hormones developed reversible enlargement of the pituitary gland and elevated prolactin levels.[20]

There does not appear to be an increased risk of malignancy for patients receiving feminizing hormone therapy.[2] ES recommends MtF individuals treated with estrogen follow breast cancer screening guidelines for biologic women, despite the low reported risk.[5,7,28,29] Anti-androgen medications are likely protective against prostate cancer; however, ES does recommend prostate cancer screening per national guidelines.[7] This recommendation is of particular importance for MtF patients who began androgen deprivation in middle age since they have not benefited from the potential protective effect of androgen deprivation on prostate cancer risk. 2 Cases of prostate cancer have been reported in MtF patients.[34] Benign prostatic hyperplasia requiring intervention has been reported in a small number of MtF patients, despite several decades of estrogen therapy.[35]

Hormone Regimens

Estrogens. Estrogen supplementation induces feminine characteristics in transgender women. Estradiol is the only compound whose serum level can be monitored; therefore, ES recommends against the use of conjugated, bioavailable, or synthetic estrogens in patients receiving feminizing hormone therapy.[7]

Estradiol can be administered through oral, transdermal, or intramuscular routes (Table 7).[7,20,24] Transdermal preparations are often favored because they produce therapeutic effects at lower doses, have stable serum levels, reduced VTE risk, and require less frequent administration thereby improving patient compliance.[2,20,22]

Anti-androgens. Anti-androgen medications reduce masculine characteristics by decreasing levels of circulating androgens or by blocking their effects. The goal of anti-androgens is to reduce serum testosterone to a level compatible with a biologic woman (<55 ng/dL).[7] A secondary advantage of anti-androgens is that by reducing the effect of circulating androgens, a lower dose of exogenous estrogen can be used to induce feminization, which reduces the risk of adverse events associated with estrogen use. Estrogen's protective effect on bone density may be overshadowed by the androgen deprivation induced by anti-androgens, and increase the risk of osteoporosis, although this has not been confirmed.[36]

Several types of medications can be used for their anti-androgen properties (Table 7). Cyproterone acetate is a progestational compound and the most commonly used anti-androgen worldwide, except in the United States, where it is not available and spironolactone is more commonly utilized.[22,24] GnRH agonists are gaining popularity because they powerfully lower testosterone levels, are widely available, and have long half-lives and minimal side effects.[36] Unfortunately, GnRH agonists are often cost-prohibitive. Anti-androgens should be discontinued following orchiectomy, which eliminates the majority of endogenous androgens.[12,33]

WPATH does not recommend routine use of progestins, aside from cyproterone, for feminizing hormone therapy since they have no role in feminization and increase the risk of adverse events.[2]

CONCLUSION

The number of patients presenting for treatment of gender dysphoria has risen dramatically in recent years. Most medical school curriculums provide little information about the health care needs of this unique patient population. Guidelines issued by the WPATH and ES support high-quality evidence-based treatment for gender dysphoria. By following these guidelines, practitioners can safely and successfully treat gender dysphoria using a combination of psychotherapy, social gender transition, hormone therapy, and ultimately GCS. In this article, the first in

a 3-part series, we have summarized the non-operative evaluation and management of gender dysphoria. The next 2 articles will focus on surgical aspects including pre-operative evaluation and eligibility, an overview of relevant surgical procedures, detailed operative techniques for GCS, as well as ancillary procedures and services used for the treatment of gender dysphoria.

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REFERENCES

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
2. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. **Int J Transgend 2012;13:165-232.**
3. Scheim AI, Bauer GR. Sex and gender diversity among transgender persons in Ontario, Canada: results from a respondent-driven sampling survey. **J Sex Res 2015;52:1-14.**
4. Winter S, Diamond M, Green J, et al. Transgender people: health at the margins of society. **Lancet 2016;388:390-400.**
5. Wilczynski C, Emanuele MA. Treating a transgender patient: overview of the guidelines. **Postgrad Med 2014;126:121-128.**
6. Reed B, Rhodes S, Schofield P, et al. "Gender variance in the UK: prevalence, incidence, growth, and geographic distribution." Web. 12 December 2016. http://xa.yimg.com/kq/groups/17851560/542410794/name/GenderVarianceUK-report.pdf. Accessed May 30, 2018.
7. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. **J Clin Endocrinol Metab 2009;94:3132-3154.**
8. Wylie K, Knudson G, Khan SI, et al. Serving transgender people: clinical care considerations and service delivery models in transgender health. **Lancet 2016;388:401-411.**
9. Hadj-Moussa M, Ohl DA, Kuzon WM. Feminizing genital gender-confirmation surgery. **Sex Med Rev 2018 Feb 14. pii: S2050-0521(17)30144-0. doi: 10.1016/j.sxmr.2017.11.005. [Epub ahead of print].**
10. Bockting WO. Psychotherapy and the real-life experience: from gender dichotomy to gender diversity. **Sexologies 2008;17:211-224.**
11. Djordjevic ML, Bizic MR, Duisin D, et al. Reversal surgery in regretful male-to-female transsexuals after sex reassignment surgery. **J Sex Med 2016;13:1000-1007.**
12. Gooren LJ. Care of transsexual persons. **N Engl J Med 2011;364:2559-2560.**
13. Colebunders B, Brondeel S, D'Arpa S, et al. An update on the surgical treatment for transgender patients. **Sex Med Rev 2017;5:103-109.**
14. Wierckx K, Elaut E, Declercq E, et al. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. **Eur J Endocrinol 2013;169:471-478.**
15. Newfield E, Hart S, Dibble S, et al. Female-to-male transgender quality of life. **Qual Life Res 2006;15:1447-1457.**
16. Murad MH, Elamin MB, Garcia MZ, et al. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. **Clin Endocrinol (Oxf) 2010;72:214-231.**
17. Heylens G, Verroken C, De Cock S, et al. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. **J Sex Med 2014;11:119-126.**
18. Dahl M, Feldman JL, Goldberg JM, et al. Physical aspects of transgender endocrine therapy. **Int J Transgend 2006;9:111-134.**
19. Eyler AE, Evan A, Feldman J. The transsexual male. In: Heidelbaugh J, ed. Clinical Men's Health: Evidence in Practice. 1st ed. Philadelphia: Elsevier; 2008. p. 561-584.
20. Fabris B, Bernardi S, Trombetta C. Cross-sex hormone therapy for gender dysphoria. **J Endocrinol Invest 2015;38:269-282.**
21. Wierckx K, Van Caenegem E, Schreiner T, et al. Cross-sex hormone therapy in trans persons is safe and effective at short-time follow-up: results from the European network for the investigation of gender incongruence. **J Sex Med 2014;11:1999-2011.**
22. Unger CA. Care of the transgender patient: the role of the gynecologist. **Am J Obstet Gynecol 2014;210:16-26.**
23. Gooren LJG, Giltay EJ. Review of studies of androgen treatment of female-to-male transsexuals: effects and risks of administration of androgens to females. **J Sex Med 2008;5:765-776.**

24. Knezevich EL, Viereck LK, Drincic AT. Medical management of adult transsexual persons. **Pharmacotherapy 2012;32:54-66.**

25. Jones SD, Dukovac T, Sangkum P, et al. Erythrocytosis and polycythemia secondary to testosterone replacement therapy in the aging male. **Sex Med Rev 2015;3:101-112.**

26. Meriggiola MC, Berra M. Safety of hormonal treatment in transgenders. **Curr Opin Endocrinol Diabetes Obes 2013; 20:565-569.**

27. Elamin MB, Garcia MZ, Murad MH, et al. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. **Clin Endocrinol (Oxf) 2010;72:1-10.**

28. Gooren LJ, van Trotsenburg MAA, Giltay EJ, et al. Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. **J Sex Med 2013;10:3129-3134.**

29. Brown GR, Jones KT. Incidence of breast cancer in a cohort of 5,135 transgender veterans. **Breast Cancer Res Treat 2015; 149:191-198.**

30. Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. **Clin Breast Cancer 2011;11:417-419.**

31. Mueller A, Kiesewetter F, Binder H, et al. Long-term administration of testosterone undecanoate every 3 months for testosterone supplementation in female-to-male transsexuals. **J Clin Endocrinol Metab 2007;92:3470-3475.**

32. Food and Drug Administration. Testosterone gel safety concerns prompt FDA to require label changes, medication guide. News release. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm149580.htm. Accessed October 1, 2017.

33. Asscheman H, T'Sjoen G, Lemaire A, et al. Venous thromboembolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. **Andrologia 2014;46:791-795.**

34. Turo R, Jallad S, Prescott S, et al. Metastatic prostate cancer in transsexual diagnosed after three decades of estrogen therapy. **Can Urol Assoc J 2013;7:e544-e546.**

35. Brown JA, Wilson TM. Benign prostatic hyperplasia requiring transurethral resection of the prostate in a 60-year-old male-to-female transsexual. **BJU Int 1997;80:956-957.**

36. Mueller A, Zollver H, Kronawitter D, et al. Body composition and bone mineral density in male-to-female transsexuals during cross-sex hormone therapy using gonadotrophin-releasing hormone agonist. **Exp Clin Endocrinol Diabetes 2011;119:95-100.**