

Medical Management of Adult Transsexual Persons

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Disclosures

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Abstract and Introduction

Abstract

Gender identity disorder (GID), or transsexualism, is an increasingly recognized medical condition with an expanding body of medical literature to support the use of established therapeutic guidelines. Transsexualism can be effectively managed through exogenous cross-sex hormone administration used to induce development of desired sex characteristics, as well as use of other agents, such as aldosterone antagonists, aimed at decreasing physical characteristics of the undesired sex. Many complications can arise with the use of the available therapies, and these must be considered before determining the appropriate course of action. This review describes methods, including both pharmacotherapy and surgical interventions, for effective medical management of both male and female adults with GID. In addition, specific goals of therapy as well as safety aspects with long-term use of pharmacotherapeutic agents are discussed. This review also discusses some special considerations for treating patients with significant, yet common, comorbid diseases such as human immunodeficiency virus infection, acquired immunodeficiency syndrome, and viral hepatitis, as these conditions may complicate the clinical course and preclude some patients from using certain therapies. Pharmacist involvement in the management of transsexualism can be extremely beneficial to patients and other health care providers.

Pharmacists can help determine the appropriate therapy, optimize dosages, monitor for adverse effects, and educate patients on what to expect during their therapy. Pharmacists should become knowledgeable about guidelines and current literature on transsexualism, understand the monitoring parameters for safe and effective therapy, and establish themselves as partners in the collaborative management of this disorder.

Introduction

Transsexualism, also known as transgenderism, gender dysphoria, or gender identity disorder (GID), is a term coined by Magnus Hirschfeld in 1923, describing the condition in which one wishes to live as, and associates with characteristics of, the opposite sex.[1] In addition, the individual experiences ongoing discomfort in his or her genetic gender role.[2] The most widely accepted estimates on prevalence come from The Netherlands, reporting 1 in 11,900 males and 1 in 30,400 females.[3] Estimates of prevalence in the United States are considered to be similar.[4] Increasing recognition of transsexualism, as well as increased provider experience with cross-sex hormone use, has resulted in a substantial amount of literature describing optimal treatment strategies and potential adverse effects of the agents.

Despite this increasing body of evidence, many practitioners, including pharmacists, have limited experience and knowledge of current treatment strategies. The first treatment recommendations for patients with GID were published in 1979 and updated in 2001 by the World Professional Association for Transgender Health; the recommendations provide standards of care for use of psychiatric and medical management of this population.[4] In 2009, the Endocrine Society published the first U.S. clinical practice guidelines for transsexualism incorporating more recent research and clinical experience.[1]

The pharmacist's role in the treatment of patients with GID has not been published. Thus, the objective of this review is to enhance pharmacist understanding of GID guidelines and current literature, identify monitoring parameters for safe and effective therapy, and establish the pharmacist's role in assisting these individuals.

Diagnosis and Psychiatric Management

In accordance with current guidelines, diagnosis of GID should be established by a mental health provider trained in treating patients with this disorder.^[1] Diagnosis should follow the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* to classify this condition as GID. [Table 1](#) highlights criteria according to the DSM-IV-TR and *International Classification of Diseases, Tenth Revision*.^[1,2,5] Although the term GID may be considered judgmental by

some, this term is commonly used in the published literature, including the Endocrine Society guidelines and DSM-IV-TR criteria.^[1,2] This review uses the term GID when making statements that are consistent with these guidelines.

Gender identification usually occurs in early childhood. The contributing factors to gender identity are still not fully understood,^[1] and no biologic or psychologic evidence exists to identify a direct cause for development of GID.^[6] When an individual is diagnosed with GID and desires treatment, a "real-life experience" is encouraged during which the individual lives as the gender of choice, to demonstrate full commitment to and understanding of a gender role change.^[1,7] When the real-life experience is completed or adequate psychotherapy has been started, the patient's mental health is stable, and it has been determined that the patient will adhere appropriately to drug therapy, cross-sex hormone therapy may be started.^[1]

Before starting therapy, patients should be educated on the risks and adverse effects of therapy as well as on anticipated temporary and permanent changes. They should receive a timeline showing when to expect the development of sex characteristics. They also should be counseled about fertility issues. Both the patient and clinician should sign an informed consent form as outlined in the standards of care before any treatment is started.^[8]

Drug Management for Male-to-Female Transition

Pharmacotherapy

The endocrine treatment of male-to-female (MtF) patients is complex, with many options, and should be individualized based on patient desires and expected outcomes. The cornerstone agent in the feminization of MtF patients is estrogen. Antiandrogens inhibit the actions of androgen and are often used with estrogens to further reduce endogenous testosterone levels, thereby boosting the feminizing effects of estrogen. Many patients believe that progestins have a role in transition to female habitus by increasing breast tissue development; however, evidence regarding the role of progestins is limited, and studies show no benefit in feminization, with possible harmful metabolic effects.^[3,8] Current guidelines do not address the preferential order in which therapies should be chosen. Patient characteristics and clinical response should guide drug selection decisions.

Prescribers should be aware that no drugs are approved by the United States Food and Drug Administration for treatment of transsexualism and that any pharmacotherapy used is prescribed off-label.

The goals of treatment revolve around reducing the secondary sex characteristics of the assigned birth gender and inducing those of the patient's gender identity. In MtF patients, this is achieved by maintaining serum estradiol levels within the normal range for healthy premenopausal women (<200 pg/ml) and suppressing testosterone levels to those normally found in women (<55 ng/dl). Both estradiol and testosterone levels should be monitored regularly in order to avoid supraphysiologic levels and to minimize the risk of adverse effects. In addition, the physical signs of feminization should be closely monitored to help guide the treatment of MtF persons. Physical changes expected to occur include decreased body and facial hair, decreased oiliness of the skin, induction of breast growth, decreased muscle mass and strength, and a redistribution of body fat to more closely resemble the female habitus.^[1] [Table 2](#) provides a timeline of these expected changes.

Estrogen Therapy Many commercially available estrogen formulations are available ([Table 3](#)). Oral, transdermal, and intramuscular estradiol or its esters can be monitored by serum estradiol levels. Conjugated and synthetic estrogens cannot be monitored through blood tests and therefore are of limited use in patients being treated for GID.^[1] Oral ethinyl estradiol has been shown to carry a higher risk for venous [thromboembolism](#) in the MtF population, and due to the high doses necessary to treat these individuals, it is not recommended for use.^[9] Therefore, 17 β -estradiol as an oral, transdermal, or injectable preparation is the recommended treatment of choice for MtF individuals.^[1,10] Evidence suggests that the lowest thromboembolic risk is with transdermal preparations. This method of administration should be favored, especially for those at greatest risk for thromboembolic events, including individuals older than 40 years, those who smoke, and those who have diabetes mellitus or liver disease.^[1]

The dose of estrogen needed for the treatment of MtF patients is about 2–3 times the recommended doses for hormone replacement therapy in postmenopausal women.^[11] The recommended dose for oral 17 β -estradiol is 2–6 mg/day. The recommended dosage for transdermal 17 β -estradiol is 0.1–0.4 mg topically twice/week, and the recommended dosage of injectable estradiol is 5–20 mg intramuscularly every 2 weeks. Doses

should be titrated individually based on serum estradiol and testosterone levels, as well as the physical degree of feminization.^[1] If intramuscular forms are used, it is recommended to measure levels midway between injections to avoid measuring peaks or troughs of drug concentrations seen immediately after and before injections, respectively. If using transdermal or oral formulations, serum levels may be sampled at any time during the course of therapy due to the steady-state concentration being achieved within 1 week after initiation of therapy. The time of day at which levels are sampled does not significantly impact hormone concentrations.^[1]

To our knowledge, no studies exist comparing the use of injectable estradiol with either transdermal or oral preparations in MtF individuals. Some patients do not achieve hormonal goals despite use of the maximum recommended dose of either oral or transdermal estrogen preparations. Many MtF patients prefer injectable estrogen therapy as this may provide higher levels of circulating estrogens; however, this formulation may take longer to reach steady state, as it is injected in a depot form intramuscularly and has a higher potential for abuse or overdose.^[10,11] If minimal breast development is seen after the first 2 years of estrogen therapy, some clinicians advocate a temporary switch to injectable estrogen in an attempt to boost breast development, but the effectiveness of this approach has not been determined.^[11] Injectable estradiol may also be considered if hormonal goals cannot be achieved on maximum doses of transdermal or oral preparations.

Antiandrogen Therapy Antiandrogens have been shown to be effective in reducing testosterone levels and decreasing male pattern hair growth.^[1] In Europe, the most widely used agent is cyproterone acetate, which is used in many studies involving MtF patients; however, this agent is not available in the United States because of concerns for liver toxicity. Often started in conjunction with estradiol, spironolactone inhibits testosterone secretion and androgen binding to receptors and may exhibit some estrogenic activity. Typical spironolactone doses are 100–400 mg/day.^[1,8] If clinical goals are not achieved with this combination, finasteride may be used to slow male pattern balding by blocking the conversion of testosterone to dihydrotestosterone. Finasteride is usually dosed at 2.5–5 mg/day, and evidence of efficacy is limited.^[8]

Less frequently used, flutamide inhibits androgen binding but has not been shown to lower serum testosterone levels, is associated with liver toxicity,

and has not demonstrated efficacy in MtF patients.^[11] Gonadotropin-releasing hormone agonists given with estrogen also are infrequently used for the treatment of MtF transition. One report of 60 MtF transsexual patients treated with subcutaneous injections of goserelin acetate 3.8 mg every 4 weeks along with oral 17 β -estradiol for 24 months found this regimen to be effective in reducing testosterone levels, with a low rate of adverse events.^[12] The physical change of breast development was also assessed; however, 70% of study subjects were dissatisfied with the degree of development and sought breast augmentation. As with estrogen therapy, doses of goserelin are titrated based on laboratory response and markers of feminization.

Progestin Therapy Progestins are sometimes used in the treatment of MtF patients, citing enhanced breast growth. In contrast, the combination of progestin with estrogen has not shown benefit in small studies of MtF populations. The Women's Health Initiative demonstrated an increased risk of coronary heart disease, stroke, thromboembolic events, and [breast cancer](#) when treating postmenopausal women with combined estrogen and progestin.^[10,11,13] These data have not been replicated in the MtF population; however, it is possible that this increased risk would be paralleled in MtF individuals. There is also concern with adverse effects, such as increased risk of depression, and metabolic consequences, such as weight gain and lipid changes.^[8] Because of these risks and lack of data on effectiveness, the use of progestins is not recommended in current guidelines and should not be advocated.^[1,10,11]

Effectiveness of Therapy

Breast formation begins within the first 3–6 months of cross-sex hormone therapy.^[8] Maximal growth is usually achieved after 2 years of hormone administration. However, 50–60% of MtF transsexual patients will find breast growth insufficient with hormone therapy alone. This may be due to the disproportion between breast size and height and male dimensions of the chest in MtF individuals. At this point, breast augmentation is often considered.^[14]

Sexual hair growth becomes thinner and lighter as hormone treatment continues and may eventually diminish.^[15] However, even with combined estrogens and antiandrogens, the elimination of male facial hair is difficult to achieve. Additional measures such as electrolysis or laser treatment are commonly necessary to eliminate this masculine trait.

Neither estrogens nor antiandrogens have any effect on the properties of voice in MtF transsexual patients.^[16] Voice training with a speech or language therapist is the most effective means for developing a healthy voice within the frequency ranges for a biologic female. Laryngeal surgery may also be used to alter the frequency of the voice, but effectiveness, patient satisfaction, and quality-of-life measures with this option have not yet been determined.

Monitoring and Safety

Serious adverse effects seen with long-term cross-sex hormone treatment in MtF transsexual patients may include weight gain, emotional lability, migraines, infertility, hepatic dysfunction, hyperprolactinemia, cholelithiasis, thromboembolic events, and rarely suicide. One should also consider the risk of cardiovascular disease and hormone-related tumors.^[17,18,19,20,21] Monitoring schedules have been recommended by the Endocrine Society in an attempt to avoid any potential adverse effects from occurring in those receiving cross-sex hormone therapy. Clinical and laboratory monitoring should be conducted every 3 months during the first year of endocrine treatment and then once or twice/year thereafter. At these visits, serum testosterone and estradiol levels should be measured with the goal of obtaining normal physiologic values for women (<55 ng/dl and <200 pg/ml respectively).^[11] Other recommendations for routine monitoring are outlined in Table.4

There have been conflicting reports on the cardiovascular effects of estrogens in MtF patients. A prospective study of MtF patients found favorable changes in lipid profiles with increased high-density lipoprotein cholesterol (HDL) and decreased low-density lipoprotein cholesterol (LDL) levels.^[22] However, these changes are accompanied by increased weight, body mass index, total body fat, blood pressure (both systolic and diastolic), triglyceride levels, and markers of [insulin resistance](#).^[10,17,22,23] The decrease in LDL levels may have also been associated with transition to smaller, more dense LDL particle size.^[22] Oral estrogen therapy has been shown to increase levels of the inflammatory and hemostatic markers interleukin-6, C-reactive protein, and factor IX, all of which may be predictive of future cardiovascular disease. These effects were not seen in groups treated with transdermal estrogen, further advocating for the use of this preparation.^[24,25] A large cohort of MtF individuals treated with either oral or transdermal estrogen, followed for 10 years showed no increase in

cardiovascular mortality despite a 32% prevalence of tobacco use.^[17] Thus, the conflicting data make it difficult to determine if estrogen is protective or detrimental in terms of cardiovascular health in MtF persons. Patients should have a baseline evaluation of traditional cardiovascular risk factors, as highlighted in [Table 4](#), before beginning any cross-sex hormone treatment.

In one study, the occurrence of venous thromboembolism increased 20-fold in MtF patients treated with estrogens and antiandrogens.^[17] Most thromboembolic events occurred within the first year of therapy. Again, the rate was higher in those treated with oral estrogen than in those treated with transdermal preparations.^[9,17,26] The rate of thromboembolic events in MtF patients has also been shown to be higher in those aged older than 40 years, similar to patterns seen in biologic women treated with estrogens.^[9,26,27] Health care professionals should obtain a very thorough personal and family history, including thromboembolic events, in patients beginning cross-sex hormone treatment.^[17] Screening for inherited thrombophilia is not routinely recommended but may be considered, especially in those with a family history positive for thromboembolic events.

Alterations in mood and memory have been associated with estrogen therapy in women. A recent study found no association between memory or a change in cognitive abilities that show sex differences with the use of estrogen in MtF patients.^[28] Studies have found increased mortality of transsexual patients receiving treatment compared with the published rate for the general population, primarily due to an increased risk of suicide in MtF persons aged 25–39 years.^[17,29] Special attention to emotional health should be taken during the treatment of MtF individuals, with referral to mental health providers as appropriate.

Because of the presence of estrogen receptors on pituitary lactotroph cells, up to 20% of MtF patients treated with estrogen may see an increase in prolactin levels. In most cases, prolactin levels return to the normal range after estrogen doses are decreased or the drug is discontinued.^[1,30] In one case report, a dopamine agonist was effectively used when levels did not return to normal after stopping estrogen.^[20] The risk of prolactinomas is thought to be very low; however, it is important to monitor prolactin levels, which should be obtained at baseline, at 6 and 12 months, and annually thereafter. Concomitant use of psychotropic drugs may also increase the risk of elevated prolactin levels.^[1,30]

Hormone-dependent cancers are a concern in MtF patients treated with long-term estrogen therapy. A few cases of breast cancer in MtF persons being treated with estrogen for 5–11 years have been published.^[1.10.31.32] The risk in MtF patients is thought to be low, but firm conclusions have not been determined.^[31] In addition to an annual medical examination, self-examination of the breast should be done regularly as is recommended for biologic women.^[1.31] The prostate is not removed in sex reassignment surgery as it is a cumbersome procedure. Therefore, the risks for [benign prostatic hyperplasia](#) and [prostate cancer](#) still exist. Prostate cancer is rare, especially in those starting androgen deprivation therapy before age 40 years, but cases of prostate cancer and benign prostatic hyperplasia have been reported in MtF individuals.^[31] It is uncertain whether the condition was present before the initiation of cross-sex hormone therapy. Prostate-specific antigen levels should be monitored and routine prostate examinations performed, as recommended for biologic men.^[1.14.31] Based on a recent U.S. Food and Drug Administration warning, a risk for high-grade tumors exists with the use of finasteride.^[33] Thus, appropriate screening for prostate cancer before initiation of finasteride is essential. The prevalence of hormone-dependent tumors appears to be low, but it is very possible that cases are underreported.^[31]

Effects of estrogen use on bone mineral density (BMD) and osteoporosis risk in MtF patients show mixed results. It is generally accepted that the use of estrogen provides protective effects on BMD. A few studies have actually shown a decrease in BMD in the MtF population, thereby concluding that these patients are at a higher risk for developing osteoporosis and related fractures.^[34.35] Other studies have shown an increase in BMD after cross-sex hormone treatment, supporting the hypothesis that estrogen is beneficial for bone health.^[10.12] Bone health should be a condition of interest and appropriately monitored in the long-term follow-up of MtF persons. Because of the lack of experience with MtF patients of advanced age, the Endocrine Society suggests testing BMD at baseline if risk factors for osteoporosis exist. If risk factors are not present, the guidelines state that testing should begin at age 60 years or in those not compliant with hormone therapy.^[1]

Drug Management for Female-to-Male Transition

Pharmacotherapy

The agent primarily used for endocrine treatment of female-to-male (FtM) patients is testosterone. The goals of medical management of the FtM transition are to maintain testosterone levels in a range considered physiologically normal for men (320–1000 ng/dl) as well as to avoid potential adverse effects that can occur with testosterone therapy. Because of the wide range of testosterone levels accepted as normal, other physical attributes of men, such as increased virilization, deepening of voice pitch, male-pattern hair growth, and male body contour, as well as cessation of menses are desired and often guide decisions for therapeutic management.^[1,11,14]

Numerous preparations of testosterone are available commercially. In the United States, oral testosterone is not available due to its risk of hepatic toxicity; thus, FtM patients in the United States can use either transdermal and injectable testosterone.^[11] [Table 5](#) lists commercially available testosterone supplements in the United States, the standard dosages used for FtM transition, and adverse effects commonly associated with their use.^[36]

When determining the appropriate method of testosterone delivery, many considerations should be taken into account. Transdermal testosterone is available in either patch or topical gel formulation and has been shown to provide less variation in serum testosterone levels compared with injectable preparations. In addition, testosterone administered transdermally more closely mimics physiologic testosterone levels.^[11] Barriers to transdermal testosterone include site irritability seen in up to 66% of patients using transdermal patches.^[37] Transdermal patches also have been found to achieve low-normal ranges of testosterone levels in hypogonadal men, which may translate to a lessened change in physical appearance and virilization in the FtM patient.^[38] Transdermal testosterone administered by topical gel achieves levels of testosterone in the mid-moderate range of normal; however, some limitations exist with this formulation as well.^[38] Although it is less frequent than with patches, gel formulations can result in skin irritation (~5–6%), and application can result in a musky odor.^[37] A more significant concern of topical gel testosterone formulations is the risk of interpersonal transfer after administration to shoulders and upper arms. Although skin contact after the gel has dried is generally accepted as safe, these products do contain a black-box warning stemming from reports of secondary exposure to children, resulting in inappropriate sexual development.^[37,39] All transdermal formulations of

testosterone can be quite costly for patients who can not apply prescription insurance benefits for this elective therapy.

The most well-described formulation of testosterone therapy used to treat FtM patients is intramuscular injection of testosterone esters (cypionate or enanthate). These injections are given every 1–2 weeks based on patient response and adverse effects. Dosing may be administered at 1-week intervals if patients sense peaks and troughs in their testosterone levels, translating to cyclic variations in mood or virilism.^[8,37] Injection site reactions can be common with intramuscular testosterone, with up to 33% of hypogonadal men who received the injections having local reactions.^[37] Because of the viscous nature of the injectable formulation and the need to inject into muscle to obtain an extended duration, a 1.5-inch, 22-gauge needle is often used. This can be a deterrent to some people despite the infrequent dosing. In addition, if the patient is unable to self-administer, although injectable testosterone is less expensive than transdermal, the cost of office visit charges to administer the drug can be a financial burden to the patient.^[37]

Other supplemental agents have been used with testosterone if menses does not cease. In fact, supplemental therapy is very frequently needed to stop menses.^[14] Depot medroxyprogesterone has shown efficacy in stopping menses and reducing estrogen levels to concentrations found biologically in men. Intramuscular medroxyprogesterone 150 mg every 3 months can be given when starting testosterone and is usually discontinued after the patient has had 3–6 months of testosterone therapy. Exposure of medroxyprogesterone should be limited in an attempt to reduce the risk of endometrial hyperplasia.

Effectiveness of Therapy

Evaluation of FtM patients using testosterone therapy has provided an accepted timeline of when physical sex characteristics of men should present. [Table 2](#) demonstrates this timeline of expected changes.^[1]

The testosterone preparations vary in their effectiveness, with injectable formulations typically associated with the most substantial increases in testosterone levels and more rapid physical changes in the FtM patient. Although no substantial, published data currently demonstrate the effectiveness of injectable formulations compared with other formulations, patient and provider reports consistently demonstrate this trend.

Monitoring and Safety

Commonly described effects noted in FtM patients using testosterone include development or worsening of acne, increased musculature, increased hair growth, enlargement of the clitoris, vaginal tissue atrophy, and possible psychiatric changes (aggressive behavior).^[38,40] Although rare, cases of [ovarian cancer](#) in FtM patients treated with androgens have been reported. If a patient desires to undergo surgical sex reassignment, the ovaries typically would be removed 18–24 months after the start of testosterone administration.^[10] If ovarian removal does not occur, patients should be followed and screened for ovarian cancer by a gynecologist experienced in the management of transsexual persons. Monitoring schedules have been recommended by the Endocrine Society in an attempt to avoid any adverse effects from occurring in those receiving testosterone therapy. A recommended timeline for monitoring is shown in [Table 6](#). Patients should be monitored every 2–3 months in the first year of therapy to assess therapy effectiveness and monitor for potential adverse reactions. As stated previously, at these visits, serum testosterone levels should be measured with the goal of obtaining a concentration within a target range of 350 – 700 ng/dl.^[1]

One must consider pharmacokinetic properties of the hormone delivery system when obtaining serum testosterone levels. Deciding when to measure levels follows the same principles as outlined in the MtF section describing estrogen therapy. In addition, estradiol levels should be measured after initiation of testosterone to ensure that decreases occur. This should be continued for the first 6 months of therapy or until uterine bleeding has stopped for 6 months. Estradiol levels should be less than 50 pg/ml for maximal effectiveness of therapy and inhibition of female sex characteristics to occur.^[1]

Other patient monitoring is performed to avoid adverse effects that may occur with hormone replacement therapy. Baseline BMD testing should be done if other fracture risks exist. One must also remember that patients who have cervical tissue and have not undergone mastectomy must still undergo women's health screenings such as Pap smears and mammograms as recommended by the American College of Obstetricians and Gynecologists and the American Cancer Society.^[1] Although liver dysfunction has been reported with the use of oral testosterone, it is not thought to be an issue with injectable and transdermal forms of the

hormone. However, up to 15% of FtM patients see an increase in liver enzyme levels, so periodic monitoring is suggested.^[1,17]

Testosterone use may increase cardiovascular risk due to increased atherogenicity of lipid parameters and potential for worsening insulin sensitivity.^[22,27] Testosterone administration may also increase cardiovascular risk due to its erythropoietic effects and potential for lowering total homocysteine levels.^[41] In addition, increased circulating androgen frequently results in weight gain, which can, in turn, increase blood pressure and further complicate [insulin resistance](#) and sleep apnea.^[27] A recent meta-analysis reported no significant effect of hormones on cardiovascular outcomes during the treatment of GID using cross-sex hormones.^[23] This analysis evaluated 16 studies that included 651 FtM patients. Lipid profiles in the FtM patients demonstrated statistically significant decreases in HDL levels and increases in triglyceride levels, as well as a slight increase in systolic blood pressure (1.74 mm Hg). However, the authors were unable to find a direct link to more important cardiovascular outcomes such as death, stroke, myocardial infarction, or venous [thromboembolism](#). The authors concluded that the evidence reported in the trials was inconclusive and stated that additional study is warranted.

Special Populations

Transsexual patients commonly present with significant comorbidities that complicate their therapeutic plan. Human immunodeficiency virus (HIV) infection, acquired immunodeficiency syndrome (AIDS), and hepatitis C have been seen in this population, although the data describing cross-sex hormone use in these populations are lacking.

Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

A 2007 systematic review evaluating U.S. HIV behavioral prevention literature reported an increased frequency of HIV in the transsexual population.^[42] This was attributed to mental health disorders, physical abuse, social and economic problems, risky sexual behavior, and untreated transsexualism. A discrepancy found between serotesting and patient self-reporting of HIV infection suggested that many of these individuals were unaware of their serostatus. The FtM patients were not associated with HIV as consistently as were MtF patients; however,

preventive strategies should be discussed with all transsexual patients. Education and HIV testing for these individuals should be of high importance.

The treatment of HIV in MtF persons can prove particularly difficult. Little has been reported about the treatment of HIV in this population; however, studies have examined the use of antiretroviral therapy in combination with oral contraceptives in biologic female patients.^[40] Significant and unpredictable changes in estradiol levels were seen when oral contraceptives were used in combination with nonnucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors. Some NNRTIs decreased levels of estrogens by up to 29%, whereas others increased levels by up to 37%. Similarly, some protease inhibitors decreased estrogen levels by up to 47% and others increased levels by up to 48%.^[40,43] The dose of estrogen in oral contraceptives is much lower than the amount needed for the treatment of MtF persons, so extrapolating these results to MtF patients is unreliable. Clinicians should be aware that the possibility for interaction exists. Patients must fully understand the risks of estrogen therapy and the increased risk of adverse events before combining estrogen and antiretroviral therapy. Adjusting and closely monitoring the dosage of estrogen must be considered when treating MtF patients who are also taking antiretroviral therapy.^[40]

Hypogonadal men with immunodeficiency due to HIV or AIDS were found to have an increased level of sex hormone-binding globulin (SHBG).^[44] This, in turn, can falsely elevate levels of free and total testosterone. Thus, in transsexual patients with HIV or AIDS, clinicians should use a calculated free testosterone level that accounts for elevated SHBG levels and albumin concentrations. Again, this has not been validated in the transsexual patient population, however, clinicians should be aware of the laboratory abnormalities that may exist in this patient population.

Viral Hepatitis

Cases of estrogen or testosterone use in transsexual patients with viral hepatitis have not been published to our knowledge. Caution is advised when using estrogen preparations in patients with hepatic dysfunction. A few studies found it safe for biologic women with hepatitis B or C to use transdermal estradiol.^[45,46] Again, the doses used in these women would be

much lower than the doses used to treat MtF individuals, and the results should be extrapolated with caution.

Oral testosterone use should be avoided due to the potential for hepatic toxicity. One published case reported hepatic adenoma that developed in a transsexual individual after 3 years of oral testosterone therapy.^[47] No studies have evaluated the use of testosterone replacement in the FtM patient with hepatic impairment.^[48]

Surgical Intervention and Postoperative Hormone Therapy

Sex Reassignment Surgery

Sex reassignment surgery is the ultimate goal for most transsexual patients. Criteria must be met to undergo surgery and have been outlined by the Endocrine Society.^[1] They include being of legal age and using cross-sex hormone therapy for at least 1 year while participating in real-life experience as the desired gender. The patients must have participated in psychotherapy and have knowledge of costs, complications, and long-term expectations of the surgery. It is preferred that patients being treated with hormone therapy for GID have demonstrated the ability to maintain stable mental health and relationships with others as well as achieved a feeling of comfort in their gender identity. Available surgeries for transsexual patients can be extensive and quite costly. Because the procedures are not typically recognized as medically essential by insurance companies, many patients are required to pay for procedures entirely by their own means.

Male-to-Female Surgery Sex reassignment surgeries for MtF patients include breast augmentation, gonadectomy, penectomy, and vaginoplasty.^[1] In neovagina creation, the skin of the penis is inverted to create the vaginal wall with the scrotum serving as the labia majora. Tampon dilators must be worn to maintain depth and width of the vagina until it is being used frequently for intercourse. Cosmetic surgery can create labia minora and a clitoris with neurovascular supply from the previous tip of the penis.

Breast augmentation procedures should be delayed until at least 2 years of cross-sex hormone therapy has been completed since breasts will continue to grow during this time.^[1] Breast augmentation is often sought, as 50–60% of MtF individuals deem breast development to be insufficient with cross-sex hormone therapy alone.^[1,14] Patients may also consider

electrolysis or laser treatments to remove facial and body hair, or surgery to lessen the width of the jaw to a more feminine appearance.

Since estrogen therapy may cause an increased risk of venous thrombosis, therapy is often interrupted for surgery. It has been recommended to discontinue cross-sex hormone administration for 3–4 weeks before elective surgical intervention and for 1 week after or until complete mobilization is regained, whichever is longer.^[1,14] After sex reassignment surgery, antiandrogen therapy may be discontinued, but some patients continue to use it to reduce sexual hair growth.

Female-to-Male Surgery Many FtM patients undergo mastectomy as hormone therapy only marginally decreases breast size.^[1] In genital reconstruction, the scrotum is created from the labia majora. Surgically, penile and testicular prostheses are implanted; however, to achieve an erection, a mechanical device must be inserted. To ablate functioning female sex organs, oophorectomy, vaginectomy, or a complete hysterectomy may be performed.

Hormone Therapy

Many patients choose to continue cross-sex hormone therapy for fear that they will lose the physical characteristics of the identified sex without the continuation. In MtF patients, the dose of cross-sex hormones should be significantly reduced after surgery; some sources recommend a decrease to half the preoperative dose and further dose titration based on serum hormone levels, whereas FtM patients often continue testosterone therapy at doses they used preoperatively.^[1,3,10,11] Continuation of cross-sex hormones may also be beneficial after surgery in maintaining BMD.^[10]

Pharmacist Involvement

The medical management of transsexual patients provides ample opportunity for pharmacist-physician collaboration in ensuring that patients reach and maintain the goals of therapy. Pharmacists should be involved initially in the discussion of potential therapies and their risks for patients transitioning. In addition, pharmacists should assess the use of herbal or complementary agents commonly used in this patient population and determine how their use will impact the patient's clinical course. Many drug-drug interactions exist with the use of cross-sex hormone therapy, and pharmacists must be able to identify these potential interactions to

avoid complications of therapy. Because the drugs used in the transition of transsexual individuals commonly impose adverse effects on patients, a pharmacist may be able to suggest ways to avoid or ameliorate the reactions. For example, to limit skin reactions that occur from a transdermal patch, sites may be rotated or the use of an alternative dosage form may be recommended. In addition, because the use of oral estradiol in patients who smoke is not recommended due to the increased risk for thromboembolic events, a pharmacist could offer smoking cessation counseling and management of pharmacotherapy aimed at helping divert the patient from tobacco use.

It is well known that hormone therapies can be quite expensive and often are not covered by a patient's insurance plan. A pharmacist can help identify the most cost-effective therapy and facilitate patient enrollment into a drug assistance program if the patient qualifies.

Pharmacists should evaluate the risk:benefit ratio of each formulation of therapy based on each patient's individual risk factors. Commonly prescribed drugs among providers who may not be familiar with current guidelines include conjugated estrogens or oral contraceptives. A pharmacist knowledgeable of cardiovascular risks and poor monitoring capabilities of these formulations should intervene to recommend a product containing 17β -estradiol. In addition, after therapy is selected, pharmacists can optimize patient administration. For example, if injectable agents are used, pharmacists should evaluate the suspension vehicle, keeping in mind patient allergies, to avoid hypersensitivity. Common vehicles for injectable estradiol and testosterone include cottonseed oil, castor oil, and sesame oil. In addition, when self-injection is chosen, pharmacists are well equipped to educate patients on appropriate injection technique. Pharmacists should also be aware of potential errors in dosing related to the confusion that may occur with the availability of multiple concentrations of injectable hormones and be able to counsel patients on measuring and administering the appropriate dose. Conversely, if topical gels or transdermal patches are used, pharmacists should educate patients on proper use and pitfalls to avoid.

Finally, pharmacist involvement could occur in laboratory monitoring after initiation of therapy as well as in titration of hormone therapy based on results of that monitoring and the patient's description of physical changes or adverse drug reactions. Protocols can be established with providers to

guide the decision-making process with regard to drug titration based on laboratory values and clinical presentation.

Conclusion

With the increasing recognition of GID, pharmacists will likely encounter patients using hormone therapy to achieve sex characteristics of their identified gender. It is pertinent for pharmacists to be familiar with the standards of care that have been developed to optimize patient safety and outcomes. There are many therapeutic options for the treatment of GID, but they do not come without risks. The risks and benefits of therapy should be appropriately weighed and extensively discussed with each patient desiring cross-sex hormone therapy.

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