Hormonal Therapy and Preventive Care of Transgender Patients

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Hormonal Therapy and Preventive Care of Transgender Patients

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Abstract
Transgenderism occurs when an individual's gender identity conflicts with the individual's biological sex. A variety of methods may be used in order to reconcile this disparity in transgender individuals including psychological counseling, cross-sex hormone therapy and sex reassignment surgery. The most important role for pharmacists in the treatment of transgender patients is in dispensing hormonal medications for cross-sex treatment. Hormone therapy may be used to suppress characteristics of the patient's biological sex as well as to induce development of characteristics that correlate with the patient's gender identity. In male-to-female (MtF) transgender patients, the most commonly used medications include agents which suppress testosterone such as mineralocorticoid receptor antagonists and gonadotropin-releasing hormone (GnRH) agonists. This is in addition to estrogen therapy, which causes feminization. By far the most commonly used medication for female-to-male (FtM) transgender patients is testosterone to induce masculinization. Medroxyprogesterone or GnRH agonists may also be used in FtM patients to suppress female characteristics. Pharmacists should be aware of the risks associated with cross-sex hormone therapy in transgender patients as well as the side effects and monitoring required for these therapies. Pharmacists may also play a role in being able to recognize signs of appropriate feminization or masculinization in MtF and FtM patients.

Key Terms
Transgender Persons, Transsexualism, Testosterone, Estrogens, Gonadotropin-releasing Hormone, Pharmacists

Introduction
In today's changing world, the patient population continues to increase in its diversity. A recently emerging population is the transgender population. A transgender individual can be defined as a person whose gender identity and birth sex are in conflict with one another. This means a biological female identifies one's gender as being male, or a biological male identifies one's gender as being female. When it comes to transgendered individuals, a majority may experience gender dysphoria, defined as discomfort or distress caused by a discrepancy between the individual's sex and perceived gender role.1 This differs from gender nonconformity in which the individual expresses one's gender that differs from the culture and social norm.

Gender dysphoria can be associated with transgender individuals. A set Diagnostic and Statistical Manual of Mental Disorder (DSM) criteria does exist for gender dysphoria. It should be noted that there is controversy with the DSM-5 criteria for gender dysphoria. Health care providers should use the criteria to identify if an individual who claims to be transgender meets the criteria of gender dysphoria, not necessarily transgenderism itself. If the individual meets the DSM-5 criteria, only then should therapy be initiated. Currently, the DSM-4 and V should not be considered mutually exclusive. The two criteria build on one another, providing a better case for an individual who identifies as transgender. The DSM-4 criteria are established on diagnosing gender dysphoria rather than transgenderism. The DSM-5 criteria are an established set of behaviors observed in individuals with gender dysphoria in which the more criteria that are met, the stronger the indication for gender dysphoria.2 The DSM-4 criteria for gender dysphoria in adolescents and adults follows (adapted from Belluardo-Crosby and Lillis3):

- A resilient and adamant identification with the opposite gender (not merely a desire for any perceived cultural advantages of being the other sex). In children, the disturbance is manifested by four (or more) of the following:
  - Repeatedly stated to be, or insistence that he or she be addressed as the other gender (pronouns of the other gender);
  - In boys, preference for cross-dressing or appearing in female attire; in girls, insistence on wearing only stereotypical masculine clothing (presentation of the other gender);
  - Strong and persistent preferences for roles in make-believe play or persistent fantasies of being the other sex (assuming the role of the other gender);
  - Intense desire to participate in the stereotypical games and pastimes of the other sex (further assumption of the role of the other gender);
- Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex.
- The disturbance is not concurrent with a physical intersex condition (not a biological issue).
- The disturbance causes clinically significant distress or impairment in social, occupational or other important areas of functioning.

What DSM-5 aimed to accomplish compared to DSM-4 included the use of "incongruence" in place of "disorder" and other patient-friendly language to diminish the stigma that is often associated with transgenderism and gender dysphoria being considered mental illness that should be remedied. Likewise, it humanizes the patients being subjected to the criteria. Lastly, the language is shifted to note the incongru-
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The DSM-5 criteria for gender dysphoria in adolescents and adults follows (adapted from Belluardo-Crosby and Lillis2):

- A separation between one's expressed gender and assigned sex of at least six months' duration, as marked by at least two of the following:
  - Incongruence between one's expressed/experienced gender and primary/secondary sex characteristics (or, in prepubescent adolescents, the foreseen secondary sex characteristics);
  - Strong desire to be rid of one's current sex characteristics because of a marked dissociation with one's expressed gender (or, in prepubescent adolescents, a desire to prevent the development of the expected secondary sex characteristics following puberty);
  - Strong desire for the primary and/or secondary sex characteristics of the other biological sex;
  - Strong desire to be or present as the other gender (or some alternative gender different from one's assigned gender);
  - Strong desire to adapt or change the other gender and its societal role (or some alternative gender different from one's assigned gender);
  - Strong principle 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 misery or dysfunction in activities of daily living or with a significantly increased risk of suffering such as distress or disability.

The following discusses treatment options, monitoring parameters and risk prevention strategies related to transitioning the patient between male-to-female (MtF) and female-to-male (FtM), and the role a pharmacist has in this transition.

Male-to-Female (MtF)
Testosterone Suppression

Male-to-female hormone therapy begins with an antiandrogen agent to reduce the amount of natural testosterone produced. This is achieved with spironolactone (oral, 100-200 mg/d), a mineralocorticoid receptor antagonist that produces decreased testosterone production.3 Spironolactone is contraindicated in patients with renal failure; therefore, monitoring for hypotension, hyponatremia, hyperkalemia and renal function should be done throughout the first week, every month for three months, and then every three months.4 Gonadotropin-releasing hormone (GnRH) agonists can also be used to suppress testosterone production, in that they result in receptor down-regulation, ultimately resulting in reduced testosterone levels. These GnRH agonists also reduce testosterone levels through a complex negative feedback mechanism whereby excess testosterone production results in suppression of the hypothalamic-pituitary-gonadal axis, thus ultimately resulting in reduced testosterone levels (Figure 1).5 The only agent studied and reportedly displaying clinical efficacy is goserelin, given 3.6 mg subcutaneously every 28

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Figure 1. Negative Feedback Mechanism with GnRH Stimulation.5

Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus to the anterior pituitary gland to stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Luteinizing hormone acts on Leydig cells in the testes to produce testosterone which contributes to spermatogenesis. Follicle stimulating hormone acts on Sertoli cells in the testes to contribute to spermatogenesis. Gonadotropin-releasing hormone agonists, such as goserelin, result in receptor down-regulation, ultimately resulting in reduced testosterone levels. Gonadotropin-releasing hormone agonists also lead to increased levels of FSH, LH and testosterone resulting in negative feedback to ultimately decrease endogenous GnRH, FSH and LH release and their downstream effects.
days. Adverse effects in men are minimal compared to women, but hypercalcemia and hyperglycemia should be monitored. In either therapy, testosterone levels should be assessed every three months until in the normal female range (15-70 ng/dL).

**Estrogen**

Estrogen therapy can be initiated simultaneously with testosterone suppression, but is most effective when ideal testosterone levels have been achieved. Estrogen forms vary but are equally effective and can be chosen based on patient preference. Common dosage forms and doses are as follows: oral estradiol (2-6 mg/d), transdermal estradiol (0.1-0.4 mg twice weekly), intramuscular estradiol valerate (5-20 mg every two weeks) or intramuscular estradiol cypionate (2-10 mg weekly). Estradiol levels should be monitored every three months with testosterone and kept within normal female range, ideally <200 pg/ml. Antiandrogen and estrogen therapies will have noticeable feminizing effects on patients within three to six months of initiation. These include a decrease in hair growth, libido, spermatogenesis, erection, testicle size and muscle mass, and an increase in breast growth, nipple size and fat distribution.

**Clinical and Lab Monitoring**

Regular monitoring of serum electrolytes (specifically sodium, calcium and potassium), liver function, renal function, lipids, complete blood cell count, blood pressure, weight and a physical exam should occur pretherapy and every three months in the first year of therapy and then at least once annually.

**Surgical Options**

If the patient is considering sexual reassignment surgery, the patient should be adherent to hormone therapy for at least one year prior to surgery to ensure drug therapy adherence thereafter for life. The patient should also have a committed surgeon and physician who will prescribe and monitor established hormone therapy. Surgical options for MtF patients include breast augmentation, facial reconstruction, orchiectomy (removal of the testes) or penile disassembly (repositioning the skin, nerves and blood supply of the penis to form female parts) followed by vaginoplasty, clitoroplasty and cessation of menses. In the Endocrine Society guidelines, parenteral dosage forms may be used, and the regimens followed should be continued.

**Risks and Prevention**

In women, unopposed estrogen has been known to increase the risk of breast cancer, hypertension, cerebrovascular disease and cardiovascular disease, including cardiovascular events such as venous thromboembolism and myocardial infarction. In transgender patients, an increased risk of the same cardiovascular events has been documented in multiple studies due to estrogen therapy. Lifestyle factors such as smoking and sedentary lifestyle further exacerbat these risks. However, in patients also taking spironolactone for its antiandrogen properties, hypertension may not be an issue because spironolactone is a mineralocorticoid receptor antagonist that results in increased sodium, chloride and water excretion and thus decreased blood pressure. Routine monitoring of vital signs (specifically blood pressure) and a physical assessment should be done at each office visit to reduce the risk of cardiovascular events.

No long-term study on transgender patients has been conducted to adequately describe if MtF patients are at an increased risk of breast cancer. The Endocrine Society guidelines recommend that all MtF patients still follow routine breast, prostate and colon cancer screenings to minimize their risk. An increase in prolactin levels has been documented with estrogen stimulating the pituitary gland to produce more lactotrophs (cells in the pituitary gland that secrete prolactin) leading to an enlarged gland. Excess prolactin levels have the additional effect of decreasing GnRH release to suppress testosterone production which is desired in these patients. Despite these desired effects, prolactin levels should still be monitored at baseline prior to estrogen therapy, in one year and biannually thereafter for development of prolactinoma. Transient liver enzyme elevations of three times the upper limit of normal and cholecystitis (inflammation of the gallbladder from bile buildup) can be increased; hence, liver function tests should be performed at least annually.

The MtF patients do not present an increased or decreased risk for hypercholesterolemia, diabetes, osteoporosis or other chronic disease states uncommon to their existing risk factors or sex. Therefore, health care professionals should monitor, treat and educate on these conditions based on the individual patient's health profile following standard guidelines.

**Female-to-Male (FtM) Testosterone**

The main cross-sex hormone therapy used for FtM transgender individuals is testosterone. Transdermal or parenteral dosage forms may be used, and the regimen follows the principles used to treat hypogonadism in men. Testosterone is an endogenous androgen which acts to promote growth of male sex organs and maintain secondary sex characteristics. Some effects of testosterone therapy in FtM transgender patients are the same as the effects that occur in hypogonadal men including increased muscle tissue, decreased fat tissue, increased body and facial hair, increased acne, male pattern baldness and increased libido. Effects of testosterone therapy that occur specifically in FtM patients include clitoromegaly, decreased fertility, deepening of voice, and cessation of menses. In the Endocrine Society guidelines, specific testosterone formulations listed include intramuscular testosterone enanthate and testosterone cypionate, transdermal testosterone 1 percent gel, and testosterone patch. In addition, although listed in the guidelines as unavailable in the United States, an intramuscular testosterone formulation (Aveed®), was approved by the U.S. Food and Drug Administration (FDA) in March 2014.
This formulation is indicated to treat hypogonadism in males. Perhaps it may soon be used for the treatment of FtM transgender patients as well since testosterone treatment in FtM patients follows the guidelines used for male hypogonadism. Although new to the United States, testosterone undecanoate has been used safely for FtM treatment in Europe for several years.\textsuperscript{18-20} Suggested doses of different testosterone formulations for FtM transgender patients are listed in Table 1.\textsuperscript{21}

**Monitoring of Testosterone Therapy**

Maintaining testosterone levels within the normal male range (320-1000 ng/dL) is important as levels in the supraphysiological range increase the risk of serious adverse events which include erythrocytosis, excessive acne and fluctuation in mood. Rarely, coughing episodes may occur following intramuscular injection.\textsuperscript{21} The Endocrine Society suggests that physicians measure serum testosterone levels every two to three months until levels are within the normal male range.\textsuperscript{3} For testosterone enanthate and testosterone cypionate, injections levels should be measured midway between injections, and the dose should be adjusted accordingly if the serum testosterone level is more than 700 ng/dL or less than 300 ng/dL. For testosterone undecanoate injection, testosterone levels should be measured just before administration of the next injection. For transdermal testosterone preparations, testosterone levels may be measured any time after one week of therapy.

**Other Drug Agents**

In cases in which testosterone therapy fails to cause cessation of menses, a progestin-like agent such as medroxyprogesterone acetate may be added to the patient’s therapy or endometrial ablation may be performed.\textsuperscript{3} Medroxyprogesterone induces amenorrhea by transforming a proliferative endometrium into a secretory endometrium.\textsuperscript{22} Additionally, depot medroxyprogesterone or GnRH agonists may be administered to FtM patients before beginning testosterone therapy to decrease the levels of estrogen to the level found in biological males.\textsuperscript{3} The Endocrine Society does not delineate dosing or monitoring parameters for medroxyprogesterone or GnRH therapy in FtM transgender patients.

Gonadotropin-releasing hormone agonists are generally used in adolescents to suppress development of unwanted sex characteristics.\textsuperscript{3} Drug therapy to suppress puberty may begin after the patient begins exhibiting the physical changes of puberty, which in girls is when breast development begins. The GnRH agonists are advantageous for pubertal suppression because their effects are reversible with cessation of therapy. In girls, GnRH agonists will cause cessation of menses as well as atrophy of breasts. However, physical sex characteristics that are not completely reversible with GnRH agonists include large breasts as well as short stature. Normal pubertal development resumes immediately upon termination of GnRH agonist therapy. Treatment with cross-sex hormone therapy may be initiated at 16 years of age.

**Surgical Options**

Sex reassignment surgery may be recommended for patients following at least one year of compliant cross-sex hormone therapy.\textsuperscript{3} Surgical sex reassignment options for FtM transgender patients include subcutaneous mastectomy, hysterectomy/salpingo-oophorectomy, reconstruction of the urethra which may be combined with phalloplasty, vaginectomy, scrotoplasty and implantation of erection and/or testicular prostheses.\textsuperscript{1} Additional aesthetic procedures may also be performed such as liposuction, lipofilling, pectoral implants and voice surgery. Patients who undergo gonadectomy will need hormone replacement therapy in addition to postsurgery monitoring in order to prevent adverse events due to chronic hormone deficiency. Patients who do not continue hormone therapy after gonadectomy will be at an increased risk for bone loss due to a decline in estrogen and testosterone levels.

**Preventive Care-Disease Risk Factors**

The use of cross-sex hormone therapy has raised concerns

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**Table 1. Testosterone Doses in Female-to-Male Transgender Patients.\textsuperscript{21}**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone enanthate (generic only) or testosterone cypionate (Depo\textsuperscript{-}-Testosterone) IM (intramuscular) injection</td>
<td>150-200 mg IM every 2 weeks or 75-100 mg/week</td>
</tr>
<tr>
<td>Testosterone undecanoate IM injection (Aveed\textsuperscript{®})</td>
<td>750 mg (3 mL) IM initially, 750 mg IM after 4 weeks, then 750 mg IM every 10 weeks thereafter</td>
</tr>
<tr>
<td>Testosterone 1% gel (AndroGel\textsuperscript{®}, Testim\textsuperscript{®}, Vogelxo\textsuperscript{™})</td>
<td>5-10 g/day</td>
</tr>
<tr>
<td>Testosterone patch (Androderm\textsuperscript{®})</td>
<td>Apply 1 or 2 patches daily to deliver 5-10 mg over 24 hours</td>
</tr>
</tbody>
</table>
about whether administration of hormonal agents may alter an individual's risk factors for certain diseases. Conditions of particular concern in FtM patients include cardiovascular health, bone density and cancer risk.

**Cardiovascular Health:** Testosterone therapy in FtM transgender patients has been found to cause a decrease in high-density lipoprotein levels and an increase in triglyceride levels resulting in a lipid profile that is more atherogenic, but data is conflicting regarding whether the change in lipid profile has a negative influence on cardiovascular health. For example, Van Kesteren et al. found no difference in cardiovascular outcomes in FtM patients compared to the general population, whereas a systematic review and meta-analysis of 10 studies that included FtM groups found that data were insufficient to evaluate cardiovascular outcomes. More research is needed to evaluate the effect that cross-sex hormone treatment has on cardiovascular disease risk. Therefore, since optimum management of cardiovascular risk factors in FtM transgender patients is currently unknown, clinicians should follow currently established guidelines for cardiovascular management, such as the National Cholesterol Education Program's Adult Treatment Panel III or the practice guidelines from the American College of Cardiology/American Heart Association. These publications offer guidance on how to assess an individual's risk of atherosclerotic cardiovascular disease and how to treat dyslipidemias. However, the clinical guidelines for transgender treatment do not suggest whether physicians should use the patient's biological sex or gender identity when assessing cardiovascular risk.

**Bone Density:** Bone mineral density (BMD) should be measured at baseline before cross-sex hormone administration for FtM transgender patients who also have risk factors for fractures due to osteoporosis. Risk factors include previous fracture, family history of osteoporosis, use of glucocorticoids and prolonged hypogonadism. Appropriate dosing of testosterone is important for maintaining BMD in FtM patients. In a study examining BMD and bone metabolism in transgender patients, BMD measurements were reported the same after one year of testosterone administration compared to baseline, but BMD declined after long-term examination at 28 to 63 months. Due to the decline in estrogen levels, FtM transgender patients may experience decreased BMD over time, so testosterone dosing needs to be sufficient to maintain bone mass. Serum luteinizing hormone (LH) levels may be a useful biological marker for assessing whether testosterone dose is adequate to maintain BMD, as LH levels were found to be inversely related to BMD.

**Cancer Risk:** Cross-sex testosterone therapy may increase the risk of endometrial and ovarian cancer. A proposed mechanism for the elevation of endometrial cancer risk is the conversion of testosterone to estrogen which in turn causes endometrial hyperplasia and may progress to endometrial carcinoma. However, no cases of endometrial cancer have been reported in FtM patients. The increased risk of ovarian cancer may be due to the increased expression of androgen receptors in the ovaries after long-term testosterone administration, but this cause and effect relationship is not yet fully established. Estrogen receptors may also play a role in increasing ovarian cancer risk because of the excess estrogen that exists after the conversion of testosterone to estrogen. Three cases of ovarian cancer development in FtM transgender patients have been reported: two cases occurred in the Netherlands and the third occurred in Rhode Island, USA. In all three cases, the medical practitioners were unable to determine whether the ovarian cancer was caused by testosterone therapy. These risks of endometrial and ovarian cancer may be eliminated if the patient chooses to undergo total hysterectomy and oophorectomy.

**Clinical and Laboratory Monitoring**

The Endocrine Society's clinical practice guidelines recommend that FtM transgender patients on cross-sex hormone therapy should be monitored by a physician every two to three months for the first year of therapy and then once or twice per year during subsequent years. Physical exams during these visits should include measurement of weight, blood pressure and complete blood count as well as monitoring of renal function, hepatic function, lipid levels and glucose levels. In addition, FtM transgender patients should be monitored for signs of appropriate virilization as well as adverse reactions from testosterone therapy. Estradiol levels should be measured until there has been no menstruation for six months. For FtM patients, estradiol levels should be below 50 pg/mL. Bone mineral density should be measured starting at 60 years of age as well as in patients who are not adherent to hormone therapy. Additionally, patients should receive an annual pap smear if cervical tissue is still present. Guidelines also recommend that if a FtM patient has not had a mastectomy, the patient should receive mammograms according to the current recommendations from the American Cancer Society. It is important to realize that these screenings may be emotionally as well as physically painful to FtM patients since they directly conflict with the patient's gender identity. Health care providers should be aware of the distress FtM transgender patients may feel about receiving a pap smear or mammogram, but providers still need to reaffirm the necessity of such screenings for protecting the patient's health.

**Role of the Pharmacist**

With the expanding role of the pharmacist, pharmacists may have the opportunity to assist with transition of their transgender patients. Transition can be defined in two ways: first, it can refer to the time period during which the individual undergoes change in his or her physical, legal and social characteristics of the gender opposite to one's biological sex in order to align with one's gender identity; and second, it can refer to the consistent process of physical and psychological adaptation. Pharmacists who are involved should know a general timeline of characteristics that may manifest themselves in transgender individuals transitioning from MtF or FtM. Figure 2 contains estimates for when certain feminizing (Figure 2A) or masculinizing (Figure 2B) effects appear in transgender individuals.
Figure 2. Timeline of Feminizing Effects Observed in MtF Patients on Hormonal Therapy (2A) and Timeline of Masculinizing Effects Observed in FtM Patients on Hormonal Therapy (2B). 24, 32-33

Figure 2A.

1-3 Months after start of transition
• Reduced libido
• Reduced incidence of non-sexual induced erections

3-6 months
• Fat Redistribution to buttocks, thighs, and hips
• Change in muscle mass and strength
• Change in skin composition
• Reduced testicle size

6-12 months
• Reduced body hair, excluding scalp*

Figure 2B.

1-6 months
• Increased acne and skin oiliness
• Redistribution of body fat
• Cessation of menses
• Enlargement of the clitoris
• Vaginal Atrophy

6-12 months
• Gain of muscle mass and strength
• Deepened voice/tone
• Loss of Scalp Hair
• Increased facial or body hair

Please note: These timelines are only a reference, and individuals undergoing transitional therapy may experience these characteristics earlier or later than what has been described. Individuals should consult their prescriber if they believe their therapy is ineffective.

*Further actions such as laser treatment may be needed to remove all male sexual hair.
Being able to recognize these characteristics is important as they give pharmacists and clinicians markers in the timeline of a patient’s transition. Additionally, lab values including hormone levels pertaining to cross-hormonal therapy or transitional therapy also play an important role in a patient’s transition especially in the first year.3

All MtF patients should be evaluated in general every two to three months within the first year to ensure a stable and safe transition.24 Similarly, FtM patients should be evaluated along the same general timeline as MtF patients with one every two to three months for the first year and annual or biannual follow ups after the first year. As with MtF patients, serum testosterone should be measured about every two to three months until at a normal physiological range equal to a biological male.35 The transgender population remains an underserved population in the medical field. By educating health care professionals on the therapies and issues surrounding an individual undergoing transition, the stigma surrounding transgender individuals can be eliminated.36 Questions should be asked in regard to issues surrounding transgenderism but to a point that they are addressed in a sensitive and professional manner. Keep in mind, not all individuals who are transgender struggle with issues pertaining to gender.28 Pharmacists are usually the first health care professional an individual may approach for help, thus being able to triage a situation with a transgender patient may be very important for that individual. In cases where pharmacists are beyond their resources to help a transgender patient, the patient should be referred to their physician or a mental health professional experienced in gender identity issues.

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