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Clinical pearls of gender-affirming hormone therapy in transgender patients

Amanda Irving, PharmD, BCPP[1]
William B. Lehault, PharmD, BCPP[2]

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Abstract

Despite the growing visibility of transgender individuals in the mainstream media, this population still encounters discrimination as well as many barriers to receiving appropriate care. Of note, not all medical providers are familiar with gender-affirming hormone treatment for transgender patients. Gender-affirming hormone treatment is used in transgender patients to reduce characteristics of their natal sex and induce those of their desired sex. Pharmacists have a potential role to make a positive impact by providing information regarding gender-affirming hormone treatment. This article aims to give an overview of the medications used in gender-affirming hormone treatment, the desired effects caused by these medications, the expected timeline to achieving these effects, and to provide information as to where these treatment guidelines can be found.

Keywords: transgender, gender-affirming hormone therapy, estrogen, testosterone, female-to-male, male-to-female, transcare

[1] (Corresponding author) Commander, US Public Health Services, Federal Bureau of Prisons, Central Processing Pharmacy Services, Petersburg, Virginia, airving@bop.gov, a_irving06@yahoo.com, ORCID: http://orcid.org/0000-0003-0455-5954; [2] Lieutenant Commander, Chief Pharmacist, US Public Health Services, Federal Bureau of Prisons, Federal Correction Institute Otisville, Otisville, New York, ORCID: http://orcid.org/0000-0001-8376-3393

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Background

Despite the growing visibility of transgender individuals in the mainstream media, this population still encounters extremely high rates of stigma and discrimination. According to the National Transgender Discrimination Survey,[1] 90% of those surveyed reported experiencing harassment, mistreatment, or discrimination on the job and 26% reported that they had lost a job due to being transgender or gender nonconforming. In addition to employment discrimination, transgender individuals also experience housing, health care, and public accommodation discrimination (ie, hotels, restaurants, airports, and stores).[1]

It was reported that 50% of transgender individuals have to teach their medical providers about transgender care.[1] A survey of 176 allopathic and osteopathic medical schools in Canada and the United States from 2009 to 2010 reported that the median time dedicated to teaching lesbian, gay, bisexual, and transgender (LGBT)-related content in the whole of the curriculum was approximately 5 hours.[2] Although no such study has been conducted in relation to pharmacy school curricula, it reasons that LGBT topics are still not covered to an adequate degree.[3] Inability to access appropriate health care may lead transgender individuals to purchase hormones from unlicensed sources and transition without being followed by a medical provider.

Mental Health Statistics

There are many factors that may adversely affect a transgender individual's mental health compared to

cisgender individuals. Factors such as increase in discrimination, harassment, and violence may contribute to negative mental health outcomes. According to the National Transgender Discrimination Survey the prevalence of suicide attempts was 41% among transgender individuals. The overall US population has a lifetime suicide attempt rate of 4.6%.[4] The results from a retrospective cohort study[5] done in a Boston-based community health center of 180 transgender participants aged 12 to 29 showed that transgender youth have an elevated probability of having a *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition transgender diagnosis of depression (50.6% vs 20.6%) and anxiety (26.7% vs 10.0%) when compared to cisgender youth. Suicidal ideation, suicide attempt, self-harm without lethal intent, and both inpatient and outpatient mental health treatment were also disproportionately represented in transgender youth. The results of this study[5] showed that training programs and continuing education programs for primary care and mental health providers should include gender identity education and that there is a need for providers to familiarize themselves with community resources for transgender youth.

Pharmacist Role in Transgender Care

Pharmacists have the potential to make a positive impact in the lives of transgender patients. Many transgender individuals are on hormone therapy, which allows for frequent interaction with pharmacists. Pharmacists can use these interactions to counsel patients on side effects associated with hormone use.[3] Pharmacists may also use this opportunity to provide information regarding hormone treatment and the associated expectations as the medication package inserts do not contain information specific to transgender-related health concerns.[3]

Hormone Therapy

Hormone treatment is designed to induce characteristics of the desired sex while reducing characteristics of the natal sex and allowing individuals to project their gender identity. Treatment is individualized and may require education, counseling, real-life experience, medical evaluation, hormone treatment, and in some cases sex reassignment surgery. Evidence from a literature review[6] suggests that hormone treatment for transgender individuals is safe and without a large risk of adverse events when under the supervision of a medical provider. Per the Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People, feminizing and masculinizing hormone therapy may have effects on mood (ie, mood swings) and potentially contribute to mood disorders (eg, premenstrual dysphoric disorder or postpartum depression); however, there is no clear evidence that testosterone or estrogen therapy is directly associated with the worsening of mental health conditions.[8] However, there may be negative outcomes associated with not treating the patient or abruptly stopping treatment. Vin Tangpricha[7] mentions in the article, "Safety of transgender hormone therapy," that withholding hormone therapy or not providing the proper referrals for care may increase the suicide risk in the transgender population.

Male-to-Female

Feminizing treatment for male-to-female individuals consists of using an estrogen or antiandrogen alone or a combination of the two with a potential progestin adjunct. Individuals should be treated with the lowest effective hormone doses, and the focus of treatment should be based on the individual's response and not just hormone levels. To minimize side effects and added risks, it is recommended to maintain estrogen levels in the physiologic range for menstruating nontransgender women.[8] Goal levels of treatment are serum estradiol $<$200 pg/mL and testosterone $<$55 ng/dL.[9]

Antiandrogens

Antiandrogens, such as spironolactone and finasteride, reduce testosterone levels, allowing estrogen therapy to be used at lower doses. Spironolactone is a potassium-sparing diuretic that can decrease testosterone levels by directly inhibiting testosterone secretion and androgen binding to the androgen receptor. Spironolactone can cause suppression of facial and body hair growth, male pattern baldness, libido, and sexually stimulated erections and can also lead to modest breast growth. Finasteride and dutasteride are antiandrogens that inhibit the enzyme responsible for converting testosterone to its more potent form, 5-alpha-dihydrotestosterone. These antiandrogens can be given as an adjunct to spironolactone or can be used alone in individuals intolerant to spironolactone. Antiandrogens have been shown to decrease the loss of scalp hair, reduce body hair growth, and improve skin consistency.[10]

Estrogen

Estrogens are 1 of the 2 main sex hormones in females that are responsible for feminization in the form of physical appearance and sexual characteristics. Some of the physical changes estrogen contributes to include development of breasts and redistribution of body fat. Softening of the skin and testicular atrophy may also occur while on estrogens. The different formulations of estrogen available include parenteral, transdermal, and oral tablets. Conjugated estrogens (Premarin®, Pfizer, Philadelphia, PA) have been used in the past; however, their use is no longer recommended due to being unable to measure estradiol blood levels with this formulation. Use of estrogen should be individualized, and doses should start low and be titrated as needed based on hormone levels and individual tolerance.

Female-to-Male

Masculinizing treatment consists mainly of testosterone supplementation. Not all patients will desire the same degree of transition, and the dose of testosterone should reflect the goals of the patient. Goal levels of treatment should be within the male physiological range. Lab reference ranges for total testosterone range from 350 to 1100 ng/dL.[8] For patients on injections, testosterone levels are measured midway between doses and have a target range of 350 to 700 ng/dL.[9]

Testosterone

Testosterone is used to induce male sex characteristics. Several formulations are available, including intramuscular injections, transdermal patches, and gels. Oral testosterone formulations are available; however, due to extensive liver metabolism and the potential for liver damage, they are not used.

Drug Effects Timeline

The onset of effects from hormone treatment may take months to occur with the maximum effect taking years to achieve. In male-to-female hormone treatment, one can expect a decrease in muscle mass and strength, softening of the skin, redistribution of body fat, breast growth, and decreased testicular volume to occur 3 to 6 months after starting hormone therapy; maximum effect may take 2 to 3 years. Other effects, such as decreased libido and decreased spontaneous erections, may be noted sooner in 1 to 3 months with a maximum effect noted in 3 to 6 years.[9]

In female-to-male hormone treatment, it may take anywhere from 1 to 6 months to notice fat redistribution and 2 to 6 months to notice a cessation of menses and clitoral enlargement. Maximum effect of the aforementioned takes more than 1 year to occur. Increased body hair growth, scalp hair loss, and an increase in muscle mass and strength may take anywhere from 6 to 12 months to occur.[9] Increasing doses too rapidly is unlikely to expedite the transition but may cause added side effects. Therefore, it is important to discuss the timelines and expectations of the hormone effects with patients.

Monitoring Treatment

Monitoring is important as gender-affirming hormone therapy has the same risks associated with hormone replacement therapy in biological males and females. Medical conditions can be exacerbated by hormone therapy. Estrogen is associated with thromboembolic disease, macroprolactinoma, breast cancer, coronary artery disease, cerebrovascular disease, severe migraine headaches, and potentially, irreversible infertility.[9] Other adverse effects associated with male-to-female therapy include weight gain, dyslipidemia, and insulin resistance. Testosterone use in female-to-male therapy carries the risk of breast or uterine cancer, erythrocytosis, and severe liver dysfunction.[9] Other adverse effects associated with testosterone therapy include increase in weight, oily skin, acne, male pattern baldness, vaginal atrophy, dyslipidemia, mood changes, and potentially, irreversible infertility.

Monitoring parameters should include weight, serum estradiol, and serum testosterone levels at baseline, every 3 months during the first year of treatment, and then every 6 to 12 months after the first year of treatment for individuals taking estrogen.[8] Complete blood counts, liver function, lipid and glucose metabolism, and prolactin levels should be monitored at the provider's discretion. If spironolactone is being used, potassium levels, serum creatinine, and blood urea nitrogen should be monitored at 3 months, 6 months, and then every 6 to 12 months.[8] Monitoring of masculinizing hormone therapy should include total testosterone levels every 3 months for the first year of therapy and then as needed after the first year.[8] Hemoglobin and hematocrit should be monitored at baseline, every 3 months for the first year, and then yearly. Estradiol levels should be monitored as needed while on masculinizing hormone therapy.[8] Risk factors and medication side effects should also be monitored.

Resources for Guidance

Several organizations have published guidelines and recommendations for hormone therapy for transgender or gender nonconforming individuals. The World Professional Association on Transgender Health created *The Standards of Care* to provide clinical guidance to health professionals when treating transgender individuals.[10] Another valuable resource regarding treatment guidelines is the Endocrine Society's "Endocrine treatment of transsexual persons."[9] The University of California, San Francisco, Center of Excellence for Transgender Health[8] has created an extensive guideline for both primary and gender-affirming care of transgender and gender nonbinary people.

Conclusion

Knowledge of hormone therapy for treatment of transgender individuals is crucial for appropriate patient care; however, many providers receive minimal education in this domain during their curricula.[2] Improved knowledge and cultural competency by providers will improve patient care and outcomes. Fortunately, national guidelines can act as a valuable resource for providers new to the field.

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