NCPD 2.0 Contact Hours

Pharmacotherapy of Transgender Children and Adolescents

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Abstract: This article will review the pharmacology used for patients with gender dysphoria who wish to use puberty blockers or cross-sex hormonal support. Dosages, proper usage, adverse effects, and monitoring parameters for each treatment period are described.

KEY WORDS: transgender, pharmacology, pubertal blockade, transgender men, transgender women

INTRODUCTION

Gender dysphoria has been reported to affect an estimated 0.39% of adults in the United States and approximately 0.69% of adolescents. The American Psychiatric Association has removed the word "disorder" from the definition for gender dysphoria, and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* has changed the term "gender identity disorder" to "gender dysphoria." The clinician providing care for the transgender patient should be familiar with the common terminology used in transgender medicine. They are summarized in Table 1 found in the Supplemental Material, available at http://links.lww.com/JPSN/A15.

When a clinician wishes to prescribe gender-affirming medication, the first step is to evaluate if the patient meets the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria for gender dysphoria (see Table 2, available at http://links.lww.com/JPSN/A16, and Table 3, available at http://links.lww.com/JPSN/A17, in the Supplemental Materials). If the adolescent chooses to start gender-affirming medical treatments, short- and long-term risks of medical treatments need to be reviewed at each medical visit because the patient's views and understanding of the information will change over time as they mature. This article provides an overview to medications, proper usage, monitoring, and side effects.

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PUBERTAL BLOCKADE

For patients who present with gender dysphoria in early puberty (Tanner Stage 1 or 2), suppression of puberty will allow them more time to explore their gender identity with their mental health professional and family without continued progression into biological puberty. For girls, Tanner Stage 2 includes breast development and elevated papilla plus increased areolar diameter. For boys, Tanner Stage 2 includes genital development including penile enlargement and testicular volume of 4 ml. Initiation of puberty-suppressing medical treatment at this stage will allow for reversal of the early changes. In addition, suppression of pubertal hormones at Tanner Stage 2 allows for better cosmetic outcomes for those youth who proceed with gender-affirming hormone treatment (Hembree et al., 2017; Wiepjes et al., 2018).

Puberty begins with the activation of gonadotropin-releasing hormone (GnRH) within the hypothalamus. The pulsatile release of GnRH, in turn, causes the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) within the anterior pituitary gland. These hormones effect both female development of breasts and male development of gonads. GnRH analogs (GnRHa) are the preferred agents for the suppression of puberty (Wiepjes et al., 2018). They are Food and Drug Administration approved for the treatment of central precocious puberty, and their mechanism of action is to suppress luteinizing hormone and follicle-stimulating hormone release from the anterior pituitary gland. They

are considered safe and reversible medications. Agents in this class include leuprolide acetate, histrelin acetate, and triptorelin pamoate. They can be dosed monthly; every 3, 4, or 6 months; or annually (see Table 4 in the Supplemental Material, available at http://links.lww.com/JPSN/A18). The depot options (leuprolide and triptorelin) are sustained-release formulations and administered in various doses and intervals. The subcutaneous histrelin implant requires a minor surgical procedure for insertion and removal and is replaced annually. The starting dose of monthly depot leuprolide acetate ranges from 7.5 to 15 mg; and that for the 12-week preparation, either 11.25 or 30 mg. Doses are increased as needed to achieve adequate suppression (Bangalore Krishna et al., 2019). There is no evidence that one agent or dosing regimen is superior to another. Clinicians should discuss all the available dosing options with patients and supporting adults, including the expected duration of therapy, the frequency of administration and short- and long-term side effects, and out-of-pocket costs. For those with insurance, which may or may not cover these medications, prior insurance approval may be necessary.

Adverse Effects of GnRHa Treatment

The peak time for bone formation is during puberty and is supported by optimal nutrition, calcium intake, and Vitamin D status plus weight-bearing exercise. However, the rise in sex steroids during puberty is an important and contributing factor. Therefore, the primary risk of pubertal suppression in gender dysphoria may include adverse effects on bone mineralization. This may be reversed with sex hormone treatment (Vlot et al., 2017), and calcium supplementation may be beneficial in optimizing bone health in GnRHa-treated individuals (Antoniazzi et al., 2003). Hot flashes are occasionally seen in the initial phases of GnRHa treatment in female patients because of declining estrogen concentrations. This, however, resolves quickly. Finally, there are unknown effects on brain development.

Once transgender adolescents are started on pubertal suppression, regular monitoring at 3-month intervals is recommended (Hembree et al., 2017). This should include a physical examination, laboratory testing, and bone density testing using dual-energy x-ray absorptiometry (DXA). Recommended test and frequency are summarized in Table 5 in the Supplemental Material (available at http://links.lww.com/JPSN/A19). Although measurement of gonadotropin and sex steroid levels is recommended, there is no precise level that is currently recommended. Efficacy is based on clinical efficacy and the mental well-being of the adolescent.

HORMONE THERAPY FOR TRANSGENDER INDIVIDUALS

For Transgender Adolescents

The overall goal of treatment should be discussed with the patient with the treating mental health professional, medical practitioner, patient, family, and/or supportive adults before initiating gender affirming hormone (GAH) treatment. Some patients may wish to achieve full masculinization or feminization possible from hormone intervention, whereas others may only want sufficient hormones to achieve an androgenous appearance or to relieve symptoms of gender dysphoria. In addition, some patients will be happy with hormone treatment only and do not care to progress to surgery for a complete transition, whereas others would like to complete the process for full transition. The goals of the patient should be established before initiating any GAH therapy. Finally, the risk of adverse effects associated with treatment should be discussed with the patient. Adverse effects of feminizing and masculinizing therapies are outlined in Table 6 in the Supplemental Material (available at http://links.lww.com/JPSN/A20).

Once the decision is made to proceed with GAH, it is recommended that all transgender persons be counseled on the effects of transition on their fertility preservation. In addition, GAH treatment is not a reliable for of contraception, and testotosterone is a teratogen that is contraindicated in pregnancy, therefore all transgender people who have gonads and engage in sexual activity that could result in pregnancy should be counseled on the need for contraception.

The key principle for GAH therapy is to replicate as closely as possible the hormone environment of the patient's gender identity. The Endocrine Society suggests that transgender children can make their own medical decisions at the age of 16 (Hembree et al, 2017). It should be noted that the age of consent to medical treatments without parental consent varies and clinicians should be familiar with the regulations in the area in which they practice. In addition, some specialty clinics now initiate GAH treatment at a younger age based on the patient's state of development (transcare.ucsf.edu). Hormone doses are initiated at a low dose and slowly increased to mimic the changes that occur with puberty.

TRANSGENDER WOMEN

Optimal medical treatment includes an estrogen in combination with an androgen blocker to reduce exogenous testosterone levels. The most common estrogen formulation used is 17-β estradiol, which may be

administered by oral, transdermal, or parenteral routes (Hembree et al., 2017). Oral estradiol is typically the least expensive formulation. Historically, other estrogen formulations (ethinyl estradiol, conjugated estrogens) were used; however, their use was discontinued because of high rates of venous thromboembolism (Streed et al., 2017). For initiation of puberty, oral estradiol is initiated at 5 mcg/kg per day (max: 0.25 mg) daily, and transdermal estradiol is initiated at 6.5 mcg twice weekly. Titration occurs at 6-month intervals and is outlined in Table 7 in the Supplemental Material (available at http://links.lww.com/JPSN/A21). Intramuscular (IM) estradiol is used less commonly and is typically reserved for patients who do not achieve hormonal goals despite using the maximum recommended dose of either oral or transdermal estrogen.

The physical feminizing effects will occur gradually with dose titration. In the first 1–3 months, the patient will experience decreased libido and decreased spontaneous erections (Abramowitz & Tangoricha, 2018). Within 3–6 months, body fat will redistribute to the hips and buttocks, and the patient will experience decreased muscle strength, skin texture change (less oily), decreased testicular volume, and breast growth. At the 6- to 12-month period, hair growth will decrease, and by 2 years, most of the physical changes will occur (Hembree et al., 2017).

Treatment with estrogen alone is usually insufficient to reduce testosterone levels to the physiologic range for cis women, so transgender women will require the addition of adjunctive antiandrogen therapy for lowering testosterone to the female range. This should be initiated in adolescents once they reach their adult dose of estradiol. In the United States, spironolactone is used most commonly (Abramowitz, 2019; Abramowitz & Tangpricha, 2018). Spironolactone inhibits testosterone α secretion, blocks androgen receptor binding, and may also have estrogenic activity (Hembree et al., 2017). The typical dose range is 100–300 mg daily. Spironolactone is a diuretic that does not cause renal losses of potassium and is associated with the risk of hyperkalemia. Therefore, the dose is started low and titrated slowly. In addition, potassium levels must be monitored during treatment. Cyproterone acetate and GnRHa are the androgen blockers used most in Europe. Cyproterone acetate is not available in the United States because of concerns for liver toxicity (Meriggiola & Gava, 2015b), and GnRHa are significantly more expensive than oral spironolactone. The 5α-reductase inhibitor finasteride blocks the conversion of testosterone to dihydrotestosterone. Although it does not reduce testosterone levels, it may be used in patients with contraindications to spironolactone (Coleman, 2012). Dosing of antiandrogen agents is summarized in Table 6 in the Supplemental Material (available at http://links.lww.com/JPSN/A20).

Monitoring of Transgender Women

Routine monitoring should take place every 3 months during the first year of treatment (Hembree et al., 2017). The key to close monitoring is to avoid supratherapeutic levels of estrogen that may lead to an increased risk of adverse events. Goal hormone levels should correspond to those of cis women: testosterone levels < 50 ng/dl and serum estradiol levels that should not exceed the peak physiologic range of 100–200 picograms/ml. If there are no complications and hormone levels are stable, monitoring may be extended to every 6 months to 1 year. All aspects of monitoring visits are summarized in Table 8 in the Supplemental Material (available at http://links.lww.com/JPSN/A22).

TRANSGENDER MEN

There are several androgen preparations available for the treatment of male transgender patients (see Table 7 in the Supplemental Material, available at http://links.lww.com/JPSN/A21). Testosterone is most often administered either parenterally or transdermally. The enanthate or cypionate formulation can be administered IM or subcutaneously every 1–2 weeks, whereas the undecanoate salt may be administered IM every 10–12 weeks. Transdermal testosterone may be administered as a gel or patch. The transdermal route of administration may be associated with skin irritation and risk of testosterone gel transfer to others. Short-term studies comparing parenteral with topical administration have shown no difference with regard to body composition, metabolic parameters, safety, compliance, or satisfaction (Meriggiola & Gava, 2015a). Recommendations are to initiate treatment with a parenteral formulation, and once adult-level doses are reached, a transdermal formulation of testosterone may be considered (Abramowitz, 2019).

The physical masculinizing effects will occur gradually with dose titration. During the first 1–6 months of treatment, the following changes are expected: increased muscle mass, redistribution of fat mass, increased sexual desire, increased oiliness of the skin, increased facial and body hair, and cessation of menses. Expected changes from 6 months to 1 year include deepening of the voice, clitoromegaly, and, sometimes, male-pattern hair loss (Hembree et al., 2017; Meriggiola & Gava, 2015a). For transgender men who transition after puberty, testosterone therapy may decrease glandular activity of the breast but will not decrease breast size (Gooren, 2005). The

main undesired adverse effect of testosterone therapy is acne. Acne prevalence and severity will peak at 6 months but may resolve in transgender men who continue treatment.

Monitoring of Transgender Men

As with transgender women, transgender men should be monitored closely in the first year, every 3 months. The major goal of monitoring treatment is to achieve testosterone levels in the normal cis male range, that is, 400–700 ng/dl (normal range may vary based on assay). According to the national guidelines, for testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections and, for the undecanoate injection, it should be obtained immediately before the injection. For the long-acting undecanoate formulation, if the serum level is <400 ng/dl, the dosing interval should be adjusted. For the transdermal formulations of testosterone, the testosterone level should be measured 2 hours after application; however, the patient must receive transdermal therapy for a minimum of 1 week before obtaining a level (Hembree et al., 2017). Since testosterone normal serum levels may be assay dependent, it is essential to be familiar with the assay your laboratory uses and its normal range. If there are no complications and hormone levels are stable, monitoring may be extended to every 6 months to annually. Details of recommended monitoring are summarized in Table 9 in the Supplemental Material (available at http://links.lww.com/JPSN/A23).

RISK AND ADVERSE EVENTS

The largest concern of testosterone therapy is the possible increased risk of cardiovascular events (Streed et al, 2017). Testosterone therapy in transgender men has been associated with increased low-density lipoprotein (LDL) and triglycerides and a decreased high-density lipoprotein (HDL); therefore, close monitoring of the patient is essential. Elevations in hemoglobin and hematocrit have been reported in patients treated with testosterone; therefore, it is recommended to closely monitor hemoglobin and hematocrit. As with transgender women, there is a possibility of bone loss, so baseline studies and follow-up are critical.

GENDER-AFFIRMING SURGERY

A complete review of gender-affirming surgeries is out of the scope of this publication; however, it is important for the clinician to be familiar with recommendations concerning hormone therapy and surgery. Current guidelines recommend that transgender adolescents reach a stable adult dose and are maintained for 1 year before any gender-affirming surgeries involving the genitals or gonads. For transgender adolescent women, it is recommended that breast augmentation surgery be delayed until they have been titrated to stable maintenance therapy and then continued for a full 2 years.

There is a theoretical increased risk of thromboembolism in transgender women treated with estrogen and surgical procedures. The associated immobility of the procedure confers additional thromboembolic risk. Given the perceived increased risks, hormone therapy is frequently held perioperatively. The endocrine guidelines by Hembree et al. do not offer advice for what to do with hormone therapy surrounding surgery, and there are minimal data to guide the decision. Gooren suggests that estrogen therapy be held 2–4 weeks before gender-affirming surgery and should not be reinitiated until 3–4 weeks postoperatively or once the patient is fully mobile (Gooren, 2005). Hormones may be continued for outpatient procedures or shorter procedures (4–5 hours) where the patient is mobile after the procedure. Due to the lack of clear guidelines, the surgeon and the hormone-prescribing clinician should collaborate to decide on when to hold and when to resume hormones for surgical procedures.

CONCLUSIONS

The recognition and acknowledgment of gender dysphoria in children and adolescents is evolving. Children with gender dysphoria that persist or worsens with the initiation of puberty can be treated with pubertal suppression with GnRHa. This treatment has been shown to be safe and effective and can give the child more time to make decisions about further treatments.

Treatment with GnRHa is reversible, and adolescents may decide later to remain with the puberty of their gender assigned at birth or continue life with gender-affirming hormone therapy (GAHT). Decisions about which options to pursue should be made with collaboration with a mental health professional, the patient, their family and/or supportive adults, and the primary care provider. Decisions should include the patient's goals of therapy balanced with possible risk factors. Treatment must be individualized for each patient. It is recognized that treatment with GnRHa at the onset of puberty and GAHT are associated with significant improvements in mental health, specifically decreased depression and anxiety. Clinicians should be aware of the current dosing guidelines for initiating and maintaining patients on GAHT and the recommended monitoring to prevent adverse effects. The primary care provider should be a partner in the care of the transgender individual.

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