CONNECTICUT MEDICAL ASSISTANCE PROGRAM
DEPARTMENT OF SOCIAL SERVICES
&
KEPRO
QUARTERLY NEWSLETTER

Affirming Gender Through Clinical Pharmacology

The September 2022 Connecticut Medical Assistance Program newsletter is the second in a two-part series on medication use in the transgender population. The previous quarterly newsletter focused on historical aspects, barriers to healthcare, and guideline based pharmacological treatment with Gonadotropin Releasing Hormone analogues (GnRHa). The current newsletter will focus on guideline-based gender affirming hormone therapy in the transgender population.

The goal of gender affirming hormone therapy is suppression of endogenous sex hormones to reduce secondary sex characteristics of the gender assigned at birth while providing treatment with exogenous sex hormones at the dose and level of the affirmed gender. The timing and age of when to begin treatment should be agreed upon by the health care team and the patient seeking gender affirming care. Sex hormone therapy is not currently FDA approved to affirm gender and most safety and efficacy data is extrapolated from use in cisgender menopausal women and cisgender hypogonadal men.[1] Hormone therapy is considered partially irreversible on certain secondary sex characteristics and fertility, therefore, it is recommended that fertility counseling and preservation options be discussed prior to starting therapy.[2] Dosing with gender affirming hormone medications should be increased on a gradual taper to mimic puberty, however, patients who have already completed puberty can receive escalated dosing regimens.[3,4]

Trends show that older adolescents who present for treatment are started on a short course of GnRHa (approximately 6 months) prior to initiating gender affirming hormone therapy, whereas adult patients presenting for treatment are started on gender affirming hormone therapy without a trial of GnRHa.[5] Gender affirming hormone therapy can be initiated if the following criteria are met:[3,4]

- Patient expresses desire to begin gender affirming hormone therapy
- Patient has reached an appropriate age to provide informed consent (18 years of age or 16 years of age with parental consent)
- Patient is under the care of an interdisciplinary medical team

Pharmacological Therapy – Feminizing Hormone Therapy

Estrogen and antiandrogen medications are the cornerstones of feminizing hormone therapy in transfeminine patients. Expected permanent changes with estrogen treatment include breast growth, testicular volume loss, and infertility.[3,4,6] Reversible changes include body fat redistribution, decline in muscle mass, decline in sexual desire, and a decrease in body/facial hair growth.[3,4,6] 17β estradiol is biochemically equivalent to endogenous estradiol and is the estrogen of choice for gender affirming hormone therapy in transgender females. Ethinyl estradiol, commonly found in oral contraceptives (OCs), and conjugated equine estrogens, are not recommended due to the risk of thromboembolism. 17β estradiol

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is available as oral, sublingual, transdermal, or injectable formulations (Table 1). When considering medication choice it is important to weigh patient preference, cost, availability, formulation, and individual risk factors. During treatment, estradiol and total testosterone levels should range from 100-300 pg/mL and < 50 ng/dL, respectively. This is consistent with levels seen in premenopausal cisgender women; however, it is important to understand individual patient objectives of therapy. Patients identifying as female on the gender spectrum will likely fall in the higher range of estradiol and lower range of testosterone compared to nonbinary patients who may desire less feminization with gender affirming hormone therapy, the latter approach is often referred to as microdosing.[1,3,4]

While providing individualized treatment is key, remaining within recommended therapeutic range is important as supratherapeutic levels of estrogen can increase the risk of adverse events such as thromboembolism, hypertension, stroke, and liver dysfunction.[3,4] Common side effects associated with therapeutic levels of estrogen include mood swings, weight gain, headaches, and hot flashes.[1] Desired effects and estimated onset of physical changes are included in Table 2 and are important to discuss with patients to set expectations early in therapy.[3,4,6] Breast growth may be enhanced by using lower and slowly titrated doses of estrogen or adding medroxyprogesterone as adjunctive therapy.[1,6] It should be noted that estrogen therapy does not affect voice pitch, and guidelines recommend that patients see a speech pathologist for pitch adjustment.[1] Recommended monitoring of serum estradiol and total testosterone should occur at baseline, every 3 months for the 1st year, and subsequently once a

Table 1. Gender Affirming Hormone Therapy[1,3,4,6,7,11]

Estradiol (17β estradiol)		
Drug	**Dosing**	**Clinical Pearls**
Estradiol oral/ sublingual tablet	2-6 mg/day	Doses > 2 mg/d should be given twice daily in divided doses. Higher risk of thromboembolism compared to other formulations.
Estradiol transdermal patch	0.025-0.2 mg/day (New patch placed every 3-5 days)	Least risk of thromboembolism and recommended for patients at risk of VTE, CVD, and who are of older age. Slower onset of action compared to other formulations
Estradiol valerate (IM)	5-30 mg every 2 weeks	Increased pharmacokinetic variability. Less risk of thromboembolism compared to oral.
Estradiol cypionate (IM)	2-5 mg every 2 weeks	Increased pharmacokinetic variability. Less risk of thromboembolism compared to oral.
Anti-Androgens		
Spironolactone oral tablet	100-300 mg/day (max: 400 mg/day)	Doses > 50 mg/d should be given twice daily in divided doses. Deceases testosterone levels. May increase gynecomastia. Causes orthostatic hypotension.
Finasteride oral tablet	1 mg/day (max: 5mg/day)	Beneficial for patients who cannot tolerate spironolactone. Benefits patients with androgenic alopecia. Less feminizing compared to spironolactone, considered weaker to spironolactone.
Dutasteride oral tablet	0.5 mg/day (max: 0.5 mg/day)	Alternative to finasteride with similar caveats.
Testosterone		
Drug	**Dosing**	**Clinical Pearls**
Testosterone enanthate or cypionate (IM or SC)	50 – 100 mg IM/SC weekly or 100-200 mg IM/SC every 2 weeks	Allows provider to double the dose for every two-week dosing.
Testosterone undecanoate	1000 mg every 12 weeks	Longest acting and most used formulation once patients are stabilized on therapeutic dose. Requires Risk Evaluation and Mitigation Strategy (REMS) Program monitoring.
Testosterone transdermal patch	2.5-7.5 mg/day	Avoids cyclical patterns of testosterone. Can cut patch to adjust for lower doses.
Testosterone gel 1% and 1.6%	50-100 mg/daily in the morning	Apply to upper arms or shoulders. Avoid cutaneous transfer to other people. Do not swim or bathe for up to 6 hours after application. Avoids cyclical patterns of testosterone.
Testosterone axillary gel 2%	90-120 mg/daily in the morning	Application via pump. 1 pump = 30 mg. Multiple pump applications (>30 mg) should utilize both armpits.
Testosterone cream	50-100 mg/day	Prepared by compounding pharmacies.

year.[1,3,4] In addition to monitoring estradiol and testosterone levels, blood pressure, weight, renal, hepatic, cholesterol and glucose levels should be monitored regularly. Prolactin monitoring is not recommended but should be considered in patients receiving concurrent medications that cause hyperprolactinemia (risperidone, paliperidone, haloperidol), especially since these medications may be used to treat comorbid mental health conditions. If hyperprolactinemia occurs, reducing the dose of estrogen or changing concurrent therapy to a medication that does not affect prolactin is recommended.[3,4]

17β estradiol is co-administered with antiandrogen therapy to further suppress endogenous testosterone.[3,4] Spironolactone, an antiandrogen and potassium sparing diuretic, directly blocks androgens when administered at high doses and may permit a lower dose of estrogen to be used due to its potentially weak estrogenic activity.[1] The recommended dose of spironolactone for feminization is 50-200 mg twice a day. Adverse effects can include orthostatic hypotension, hyperkalemia, hyponatremia, polyuria, and polydipsia.[3,4] Recommended monitoring includes serum creatinine, potassium, and blood urea nitrogen at baseline, every 3 months for the 1st year, and subsequently once a year.[1,3,4] Alternate antiandrogens include: 5α reductase inhibitors (finasteride, dutasteride), progestogens (oral micronized progesterone, medroxyprogesterone) which lack safety and efficacy data and may increase risk of cardiovascular disease, and GnRHa which are costly compared to other options.[1]

Table 2. Onset of effects of gender affirming hormone therapy[3,4,6]

Feminizing effects of estrogen therapy	Expected onset	Maximum onset	Reversible once hormones are stopped
Body fat redistribution	3-6 months	2-3 years	Yes
Breast growth	3-6 months	2-3 years	No
Decreased testicular volume	3-6 months	2-3 years	No
Decreased sperm production	Variable	Variable - > 3 years	Possibly permanent
Decreased muscle mass	3-6 months	1-2 years	Yes
Skin softening/reduced oiliness	3-6 months	unknown	Yes
Decreased sexual desire and spontaneous erection	1-3 months	3-6 months	Yes
Decreased body and facial hair growth	6-12 months	> 3 years	Yes
Masculinizing effects of testosterone therapy	**Expected onset**	**Maximum onset**	**Reversible once hormones are stopped**
Skin oiliness/acne	1-6 months	1-2 years	Yes
Facial/body hair growth	3-6 months	3-5 years	No
Androgenic alopecia (if genetically inclined)	6-12 months	variable	No
Increased muscle mass	6-12 months	2-5 years	Yes
Decreased fat mass	3-6 months	2-5 years	Yes
Cessation of menses	2-6 months	n/a	Yes
Clitoral enlargement/ vaginal atrophy	3-6 months	1-2 years	No
Deepened voice	3-12 months	1-2 years	No

Pharmacological Therapy – Masculinizing Hormone Therapy

Bioidentical testosterone is the cornerstone of masculinizing hormone therapy in transmasculine patients. Expected irreversible changes with testosterone treatment include hair follicle virilization, voice drop, clitoromegaly, and possible male pattern baldness.[3,4,6] Reversible changes include cessation of menses, decreased body fat, increase in muscle mass and sexual desire, and an increase in body/facial hair growth.[3,4,6] Formulations include subcutaneous, intramuscular, long acting injection, transdermal patch, gel, axillary roll-on, implanted pellets, and intranasal spray (Table 1).[1]

Short acting agents are commonly used in hormone naïve patients due to frequent dosage adjustments during titration, however, patients can be switched to longer acting agents once stabilized at therapeutic doses.[8] While guidelines do not recommend one formulation of testosterone over another, injectable formulations are most commonly used.[7] In patients who are transitioning from GnRHa to testosterone, it is common practice to continue GnRHa with testosterone treatment until the target adult dose of testosterone is met.[6,9] Total testosterone levels in patients receiving gender affirming hormone therapy should range from 320 – 1000 ng/dL.[3,4] This is consistent with levels seen in

cisgender men; however, it is important to recognize individual patient goals of therapy. Nonbinary patients may want to limit masculinizing effects with a lower total testosterone level (microdosing), whereas patients identifying as masculine on the gender spectrum will likely fall in the higher range of testosterone. Supratherapeutic levels of testosterone can lead to erythrocytosis, hypertension, lipid changes, and obesity.[3,4,8] Additionally, excess testosterone can be re-aromatized back to estrogen causing the opposite effect desired in transmasculine patients. This can be used as a counseling point for patients requesting higher testosterone doses or reluctant to lower their dose.

Unwanted side effects associated with therapeutic testosterone levels include androgenic alopecia (if genetically inclined) and acne, especially on the chest, back, and upper arms, which can be exacerbated by a chest binder. Younger age at the start of testosterone therapy correlates with a higher likelihood of an acne diagnosis.[9] Testosterone induced acne can worsen quality of life and should be addressed if developed to avoid negative impacts on mental health. Amenorrhea in transgender males receiving testosterone therapy is common, but if the patient is sexually active, contraception is recommended.[9] Desired effects from testosterone therapy and estimated onset of physical changes are included in Table 2 and are important to discuss with patients to address expectations.[3,4,6] Monitoring of serum testosterone, hemoglobin, and hematocrit is recommended at baseline, every 3 months for the 1st year of treatment, and then subsequently once a year. In addition to monitoring testosterone levels, blood pressure, weight, renal, hepatic, cholesterol and glucose levels should be monitored regularly.

Monitoring does not begin and commence with laboratory values alone, assessment and treatment of the whole patient should be considered, including mental health aspects. Staying abreast of changes to terminology, barriers to care, and modifications to current guidelines such as The WPATH Standards of Care and the Endocrine Society Treatment Guideline is paramount. Engaging with a multidisciplinary team to provide affirmative, non-stigmatized care can ensure transgender patients receive equitable care to their cisgender counterparts. GnRHa and gender affirming hormone therapy improve gender dysphoria/incongruence, mental health, and increase gender affirmative physical changes.[10] While gender affirming surgery is out of the scope of this article, certain physical changes and characteristics may not be possible without surgery. Therefore, addressing patient expectations and planning for patient transition into adult care is crucial. Table 3 includes resources for transgender healthcare within the State of Connecticut and beyond.

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Table 3. Key Resources and Links for Providers and Patients:

CT Providers with LGBTQ Focused Care Programs

- Anchor Health CT
- Apex Community Care, Inc
- Community Health Center: Center for Key Populations
- Hartford Gay and Lesbian Health Collective
- LGBTQAI Responsive Services as Wheeler
- Middlesex Health Transgender Medicine
- Yale Medicine: Pediatric Gender Program

CT Community Centers and Resources

- CCSU LGBT Center
- Connecticut Coalition to End Homelessness LGBTQ Resources
- CT Gay and Lesbian Chamber: An LGBTQ + Alliance for Business Opportunities
- CT Trans Advocacy Coalition
- Film: "Becoming Myself: A Transgender Perspective on Behavioral Health"
- Kids in Crisis
- New Haven Pride Institute
- Rainbow Support Group
- Triangle Community Center
- UCONN Rainbow Center
- Yale University Office of LGBTQ Resources

CT Support Groups

- Institute of Living LGBTQ Specialty
- OutCT Youth Group
- Stamford Lighthouse
- Waterbury Youth Services, LGBT Group

Resources Beyond Connecticut

- CDC LGBT Health
- GLAD Legal Rights
- Human Rights Campaign
- National Center for Transgender Equality
- National Resource on LGBTQ Aging
- PFLAG
- Pride Institute
- Pronouns Matter
- SAMHSA LGBT National and Regional Resources
- Suicide Prevention for LGBTQ
- The Trevor Project Crisis and Suicide Hotline
- Trans Fertility Co.
- Trans Lifeline