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Endocrine treatment of transgender and gender-diverse people

Because gender self-identification can be nonbinary, the use of hormone therapy to achieve a patient's goals for physical changes must be based on individualized assessment, treatment, and follow-up monitoring.

ABSTRACT: Endocrine therapy is used to change the body's physical characteristics to reduce gender dysphoria or incongruence. Feminizing endocrine treatment involves the use of ovarian hormones or anti-androgen drugs; however, venous thromboembolism or meningioma can be associated risks. Masculinizing endocrine treatment involves testosterone supplementation, but lower high-density-lipoprotein cholesterol, increased triglycerides, and risk of polycythemia may occur. In youth, gonadotropin-releasing hormone agonist therapy can be used as a reversible means of suppressing unwanted puberty and preventing irreversible body changes. Physicians can provide treatment that achieves a patient's goals and minimizes the risk of causing harm by conducting an initial assessment, prescribing medications based on individual factors, and providing follow-up treatment monitoring. Physicians who treat youth must be trained in childhood and adolescent developmental psychopathology. They must also be able to diagnose gender dysphoria or incongruence, establish the youth's capacity to make decisions regarding their medical care and to understand the relatively irreversible changes in physical characteristics and reproductive capacity that will occur, and ensure that the youth has parental or other adult support and will be able to transition safely in their home setting. Counseling may be required for youth who suffer from anxiety, depression, or suicidality.

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Endocrine therapy is used to change the body's physical characteristics to reduce gender dysphoria or incongruence. Its use can be considered when a diagnosis of gender dysphoria or incongruence has been made, and the World Professional Association for Transgender Health criteria for treatment **[Box]** have been met.[1]

The physician's goal for endocrine therapy is to provide effective treatment that has a minimum risk of causing harm. Treatment "effectiveness" involves understanding a patient's goals for physical changes and working to achieve them through administration of endocrine medications. Because gender self-identification is a nonbinary spectrum of feminine and masculine traits, it is important to understand an individual's needs. For example, some people who identify as nonbinary in the transmasculine spectrum may not desire virilization but instead want only a small dose of testosterone to achieve a slightly less feminine and more androgynous appearance.

Initial medical assessment should include the patient's history, a physical examination, and laboratory testing of blood hormone levels together with testing of liver, kidney, cholesterol, and diabetes status in order to give the patient adequate information to provide informed consent.

Before administration of endocrine treatments, patients must be aware of the drug-specific potential adverse effects, plus the likely loss of reproductive potential (sperm production and oocyte release).

World Professional Association for Transgender Health criteria for hormone therapy in adults.[1]

1. Persistent, well-documented gender dysphoria.
2. Capacity to make a fully informed decision and consent to treatment.
3. Age of majority in a given country.
4. Significant medical or mental health concerns are reasonably well controlled.

Feminizing endocrine treatments

Ovarian hormones

Estrogen supplementation has two actions: it increases feminizing effects at target tissues and reduces masculinizing blood levels of testosterone through suppression of the hypothalamic–pituitary–testicular axis. Physical changes include breast growth, softer skin, and changes

in body composition, such as fat redistribution from the abdomen to the hips. Estradiol use is preferred to conjugated estrogens because of lower potential of venous thromboembolism.[2] Transdermal estradiol may have a better safety profile than oral estradiol in patients who are at increased risk of venous thromboembolism.[3] Risk factors include age greater than 50 years, tobacco use, body mass index greater than 27 kg/m^2, and postoperative state. Initial history should also determine if the patient or their family have a history of venous thromboembolism.

Clinical controversy has surrounded progesterone supplementation. Advocates point to the physiologic role of micronized progesterone in breast, nipple, and areolar development and suppression of testosterone secretion by reduction of pituitary secretion of gonadotropins.[4] Progesterone is used in hormone therapy of cisgendered women, particularly in the context of prevention of endometrial hyperplasia, which is not a consideration in transgendered women.

Anti-androgen drugs

Spironolactone is an antagonist that blocks the action of androgen at its receptor and reduces testosterone levels. Feminizing effects of anti-androgens include breast development and reduction of androgen-sensitive face and body hair.

Cyproterone acetate is a synthetic progestogen with strong anti-androgen and antigonadotrophic effects. A recent observational cohort study of cisgender and transgender girls and women showed a dose- and duration-of-use-dependent increase in the risk of meningioma treated by radiation or surgery. With doses of 25 or 50 mg daily, risk of meningioma increased from 4.5 to 23.8 per 1 000 000 patient years compared to the control group.[5] This has led to discussions about avoiding the use of cyproterone or limiting the dose to no more than 12.5 mg daily **[Table 1]**.[6]

Masculinizing endocrine treatment

Testosterone

Testosterone supplementation increases androgen action at target tissues and suppresses ovarian sex steroid production. Desired masculinizing effects include deeper voice, increased

TABLE 1. Basic feminizing regimen in adults. (Adapted from "Endocrine therapy for transgender adults in British Columbia: Suggested guidelines";[6] updated April 2015.)

	Estrogen		Androgen antagonists	
Agent	Micronized 17beta-estradiol		Spironolactone	Cyproterone acetate
Brand name*	Estrace	Estradot, Oesclim	Aldactone	Androcur
Administration	Oral	Transdermal	Oral	Oral
Dose range	1–8 mg daily	50–200 mcg patch twice weekly	25–300 mg daily	12.5–50.0 mg daily
Cost of generic agent at usual dose† before dispensing fee‡	4 mg daily ~$30 per month	100 mcg patch twice weekly ~$40 per month	200 mg daily ~$20 per month	50 mg daily ~$45 per month
BC PharmaCare benefit	Yes	Possible on case-by-case basis via Special Authority request for patient with venous thromboembolism risk from oral estradiol	Yes	Yes (requires Special Authority)

Progestin options		
Agent	Micronized progesterone	Medroxyprogesterone acetate
Brand name*	Prometrium	Provera
Dose range	100–300 mg daily	10–40 mg daily
Cost of usual dose† before dispensing fee‡	200 mg daily ~$115 per month	20 mg daily ~$20 per month
PharmaCare benefit	No	Yes

Note: Some patients choose intramuscular injection of estradiol valerate, which is available in BC from compounding pharmacies. The cost of 10 mg per week is ~$80–$120 per month depending on the pharmacy.
* All brand name formulations are also available as generics.
† Prices for oral medications per Pharmacy Compass. Accessed February 2020. www.pac.bluecross.ca/pharmacycompass; price for transdermal estradiol per pharmacist quote, February 2020.
‡ Dispensing fees in the range of $10–$12 per prescription.

TABLE 2. Basic masculinizing regimens in adults. (Adapted from "Endocrine therapy for transgender adults in British Columbia: Suggested guidelines";[6] updated April 2015.)

	Injection (intramuscular or subcutaneous)		Transdermal
Agent	Testosterone cypionate	Testosterone enanthate	Testosterone crystals in gel
Brand name	Depo-Testosterone	Delatestryl	AndroGel
Dose range	25–100 mg subcutaneous/intramuscular weekly or 50–200 mg intramuscular every 2 weeks. Adjust dose to achieve mid-normal male testosterone range on sample drawn halfway through injection cycle		2.5–10.0 g daily
Cost of average dose before dispensing fee	50 mg per week ~$14 per month	50 mg per week ~$16 per month	5 g daily ~$160 per month
BC PharmaCare benefit	Yes, with Special Authority stating female-to-male transgender	Yes, with Special Authority stating female-to-male transgender	Possible on case-by-case basis with Special Authority stating female-to-male transgender and contraindication to intramuscular injection

Note: Self-injection techniques for patients are provided in the *Transgender Health Injection Guide* https://fenwayhealth.org/wp-content/uploads/2015/07/COM-1880-trans-health_injection-guide_small_v2.pdf.

male pattern facial and body hair, increased muscle mass, reduced fat mass, and cessation of menstruation. Adverse effects may include acne, scalp alopecia, lower high-density-lipoprotein cholesterol, increased triglycerides, and risk of polycythemia. Testosterone is usually administered by intermittent intramuscular injection of testosterone cypionate or enanthate. Subcutaneous injection has also been shown to be effective in pharmacologic studies.[7] Daily transdermal testosterone preparations are used in patients when injections are not possible or desired. Transdermal preparations are more expensive and may result in lower testosterone serum levels than injected testosterone **[Table 2]**.[6]

Treatment of youth

Medical treatment for transgender and gender-diverse youth has been available in BC for more than 20 years.[8] Separate eligibility[1] and treatment regimens[8] exist for youth **[Table 3]**. Unlike in adults, gonadotropin-releasing hormone agonist therapy can be used as a reversible means of suppressing unwanted puberty and preventing irreversible body changes (e.g., breast or beard growth). This can be initiated once puberty has begun (Tanner 2). Depending on the youth's persistent level of dysphoria, family support, and emotional and intellectual maturity, hormones can be offered as early as 13.5 to 14.0 years. Escalating-dose hormone regimens for youth allow for more gradual, natural pubertal development to better match that of their age peers.

It is vitally important that all transgender and gender-diverse children and youth have access to providers who are trained in childhood and adolescent developmental psychopathology.[1] This involves making the diagnosis of gender dysphoria or incongruence, establishing the youth's capacity to make decisions regarding their medical care and to understand the relatively irreversible changes they will undergo in terms of body changes and reproductive capacity, and ensuring that the youth has parental or other adult support and will be able to transition safely in their home setting. While the diagnosis of gender dysphoria or incongruence may be relatively straightforward in some of youth, as a group they are burdened with high rates of anxiety, depression, and suicidality,[7] and therefore, may require intensive counseling to allow them to move forward with successful medical transition.

Endocrine treatment for gender dysphoria or gender incongruence is similar to many medical interventions. The goals of treatment are to improve the patient's quality of life while minimizing the risk of adverse effects.

Monitoring treatment

Monitoring endocrine treatment is individualized and includes assessment of the patient's degree of dysphoria and desired physical changes, as well as the presence of possible adverse effects. Levels of estradiol, testosterone, lipid, glucose or glycosylated hemoglobin, liver enzyme, and electrolyte and creatinine levels are measured at intervals determined by the clinical situation, laboratory results, and frequency of dosage adjustments. Some sample monitoring regimens have been published.[9]

TABLE 3. Puberty suppression for transgender youth.

Agent	Leuprolide acetate for depot suspension
Brand name	Lupron Depot
Administration	Intramuscular
Dose range	3.75–7.50 mg every 4 weeks 11.25–22.50 mg every 13 weeks
Cost of usual dose* before dispensing fee†	$4600–$5600/year
BC PharmaCare benefit	Yes, with Special Authority

* Prices for medications per www.drugsearch.ca. Accessed February 2020.

† Dispensing fees in the range of $10–$12 per prescription.

Summary

Endocrine treatment for gender dysphoria or gender incongruence is similar to many medical interventions. The goals of treatment are to improve the patient's quality of life while minimizing the risk of adverse effects. This is done through initial assessment, prescription of medications based on individual factors, and subsequent reassessment of patient factors and laboratory results. Like any practitioner-patient interaction, intervention works best when a cooperative dialogue with a well-informed patient or family is undertaken with knowledge of the individual psychosocial context of treatment. ■

Competing interests

None declared.

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