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An introduction to gender-affirming hormone therapy for transgender and gender-nonbinary patients

Abstract: Transgender and gender-nonbinary patients may present to primary care providers seeking gender-affirming hormone therapy. Patients who meet criteria for diagnosis of gender incongruence may start or continue hormone therapy after providing informed consent. Prescribing and monitoring of masculinizing and feminizing hormone therapy can be managed in primary care settings.

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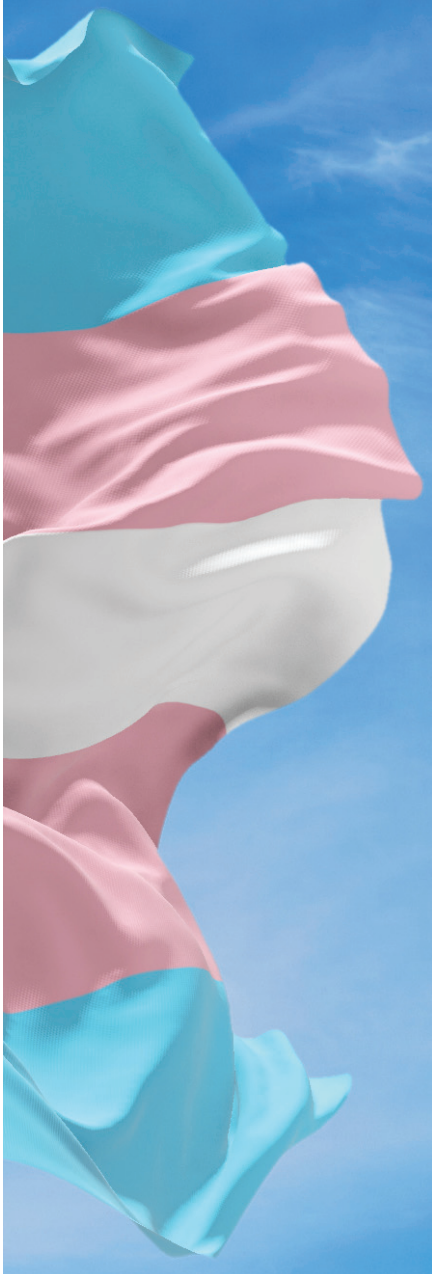

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Every healthcare provider, including NPs, will care for transgender and gender-nonbinary (TGNB) patients whether they are aware of this part of their patient's identity or not. Primary care providers (PCPs) will likely encounter TGNB patients seeking gender-affirming medical and/or surgical interventions. Provision of gender-affirming hormone therapy (GAHT) is within the scope of primary care and does not necessitate referral to a specialist.[1] Treatments for other forms of hormone replacement (testosterone for hypogonadal nontransgender men, estrogen/progesterone for nontransgender menopausal women) are regularly addressed in the primary care setting.

This article, authored by a team of TGNB-identified NPs, provides the essential information PCPs need to initiate or continue GAHT for TGNB adults. All prescribing of GAHT is considered off-label use. A full discussion regarding GAHT for youth and adolescents is beyond the scope of this article; other resources provide detailed information on this subject.[2] Caring for TGNB patients extends beyond the management of GAHT alone; providers may refer to resources cited throughout this article for further information on health maintenance, social gender affirmation, mental health, HIV treatment and prevention, and gender-affirming surgeries for patients who are TGNB. PCPs

Keywords: gender-affirming hormone therapy, gender dysphoria, gender identity disorder, gender incongruence, gender-nonbinary, hormone replacement therapy, transgender, transgender healthcare

should invite interprofessional collaboration with behavioral health, social work, case management, gender-affirming surgery care teams, insurance navigators, and legal partners as needed to provide holistic care for TGNB patients.[1] Collaboration with an endocrinologist experienced in caring for patients who are TGNB, if available, may be appropriate in medically complex cases.

Ensuring that culturally competent GAHT is available in primary care settings is an essential part of addressing the systemic health disparities affecting TGNB communities.[3] TGNB people are three times more likely to be unemployed than cisgender (nontransgender) people, and over two times more likely to be living in poverty. These disparities are further compounded for TGNB people with multiple marginalized identities; TGNB people of color experience even higher rates of unemployment and poverty.[4] According to the 2015 US Transgender Survey, 33% of TGNB respondents had not sought healthcare in the past year because of cost. When people who are TGNB do seek healthcare, they are often met with a lack of cultural competence by providers, as well as discrimination, harassment, and abuse. A third of respondents who had seen a healthcare provider in the past year reported having at least one negative experience related to their gender identity within a healthcare setting. These negative experiences included: having to teach the provider about TGNB care, being refused treatment, being verbally harassed, or being physically or sexually assaulted.[4] PCPs prepared to provide gender-affirming care can help repair trust between TGNB patients and healthcare systems. In addition, PCPs should facilitate reporting of complaints for patients who encounter mistreatment.

Straightforward interventions in the clinic environment make primary care settings more welcoming for TGNB patients. Providers and staff should include their pronouns on their badges and when introducing themselves. All patients, not just those perceived to be TGNB, should be asked for their chosen name, pronouns, sexual orientation, gender identity, and sex assigned at birth; this information should be documented in the electronic health record.[5] Providers and staff should receive ongoing education regarding gender identity and TGNB health.[2] Unnecessarily gendered language should be avoided whenever possible (for example, "pregnant people," not "pregnant women").[6] All-gender bathrooms should be offered, especially for single-occupancy restrooms. The diversity of gender identities and expressions represented in clinic's posters, brochures, and other marketing materials should be considered.[2]

Understanding the differences between gender identity, sex assigned at birth, and sexual orientation is essential to providing care to TGNB patients (see *Glossary of terms relevant to transgender and gender nonbinary identities*).[7] Language about identities is constantly evolving. Ask patients which terms they use to describe themselves and research unfamiliar vocabulary.

Gender incongruence

Diagnostic criteria for "Gender Incongruence of Adolescence and Adulthood" from the World Health Organization's International Classification of Diseases, version 11 (ICD-11)—not yet in use in the US—are used to assess adult patients seeking to initiate GAHT.[8,9] ICD-11 is the first revision of the ICD to include the diagnosis gender incongruence. Previously, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnostic criteria for gender dysphoria (or gender identity disorder, as it appears in ICD-10) were used to assess patients seeking GAHT.[10,11] The concept of *gender dysphoria* describes the distress that may arise from the incongruence between a person's gender identity and their sex assigned at birth.[10] As not all TGNB people seeking GAHT will experience gender dysphoria, the new diagnostic criteria for gender incongruence are more inclusive of a wider range of TGNB experiences. Notably, ICD-11 locates the diagnosis of gender incongruence within "Conditions related to sexual health," while gender identity disorder is located within "Mental and behavioral disorders" in ICD-10.[9,11] The inclusion of gender dysphoria and gender identity disorder as psychiatric diagnoses is controversial, as many TGNB people feel that it pathologizes their experiences.[12]

Prior to initiation of GAHT, the provider will evaluate if the patient meets the diagnostic criteria for gender incongruence: "a marked and persistent incongruence" between the patient's gender identity and sex assigned at birth, which may lead the patient to seek medical and/or surgical interventions to better align their body with their gender identity.[9] Unlike the gender dysphoria diagnosis, gender incongruence does not have a criterion for "clinically significant distress or impairment" in the patient's ability to function at work, school, or other area.[9,10] ICD-11 does not require a specific minimum

Glossary of terms relevant to transgender and gender nonbinary identities*

Cisgender	*(adjective)* A person whose gender identity is consistent in a traditional sense with their sex assigned at birth; for example, a person assigned female sex at birth whose gender identity is woman/female.
Gender affirmation	*(noun)* The process of making social, legal, and/or medical changes to recognize, accept, and express one's gender identity. Although this process is sometimes referred to as transition, the term gender affirmation is recommended.
Gender dysphoria	*(noun)* Distress experienced by some people whose gender identity does not correspond with their sex assigned at birth.
Gender expression	*(noun)* The way a person communicates their gender to the world through mannerisms, clothing, speech, behavior, etc. Gender expression varies depending on culture, context, and historical period.
Gender identity	*(noun)* A person's inner sense of being a girl/woman/female, boy/man/male, something else, or having no gender.
Gender-Nonbinary	*(adjective)* Describes a person whose gender identity falls outside of the traditional gender binary structure of girl/woman and boy/man.
Intersex	*(adjective)* Describes a group of congenital conditions in which the reproductive organs, genitals, and/or other sexual anatomy do not develop according to traditional expectations for females or males. The medical community sometimes uses the term "differences (or disorders) of sex development" to describe intersex conditions.
Sex assigned at birth	*(noun)* The sex (male or female) assigned to an infant, most often based on the infant's anatomical and other biological characteristics.
Sexual orientation	*(noun)* How a person characterizes their emotional and sexual attraction to others.
Transgender	*(adjective)* Describes a person whose gender identity and sex assigned at birth do not correspond based on traditional expectations.
Trans man/ transgender man	*(noun)* A transgender person whose gender identity is boy/man/male may use these terms to describe themselves. Some will use the term man.
Trans woman/ transgender woman	*(noun)* A transgender person whose gender identity is girl/woman/female may use these terms to describe themselves. Some will use the term woman.

*Adapted with permission from *LGBTQIA+ Glossary of Terms for Health Care Teams.*[7]

time frame in regards to "persistent incongruence" for diagnosis of gender incongruence; the authors encourage providers to trust in patients' lived experiences when assessing for adequate persistence of their experienced gender incongruence. The patient does not need to have disclosed their TGNB identity to others to establish the presence of their gender incongruence.[13] No length of time in psychotherapy is required prior to a gender incongruence diagnosis.[8]

Open-ended questions typically elicit sufficient information to make a gender incongruence diagnosis for a patient seeking to initiate GAHT. Possible questions include:

"How do you describe your gender identity?"

"How long have you identified this way?" and

"What changes from hormones do you hope for?"

See the *World Professional Association for Transgender Health Standards of Care (WPATH SOC) Version 8* for more details on establishing the gender incongruence diagnosis. Please note that the WPATH SOC version 8 was available only in draft form at the time this article went to press.[8]

While ICD-11 came into effect for World Health Organization member states on January 1, 2022, the timeline for its implementation in the US and within individual institutions' electronic health records (EHR) is unclear.[14] Limited guidance is available regarding EHR coding when diagnosing gender incongruence in this interim period. Some providers may continue to use the diagnosis of "gender dysphoria," while others may use "endocrine disorder, unspecified." Coding choices may affect insurance coverage in some circumstances. The authors encourage providers to use the more inclusive gender incongruence diagnostic criteria despite these logistical challenges.

Models of care for GAHT initiation

Two models of care exist for initiation of GAHT for adult TGNB patients: the "informed consent model" (ICM) and the "standard model" (SM).[15] Counterintuitively, the ICM is the standard of care for initiating GAHT in the US; many nationally recognized transgender health programs in the US use informed consent-based protocols.[2,16,17] The ICM affirms that TGNB patients have the autonomy to assess the risks and benefits of GAHT and make a decision based on this information. According to the ICM, seeking GAHT or having a TGNB identity in and of itself does not necessitate a referral to behavioral health or psychiatry.[15] However, a person seeking GAHT may also present with other signs or symptoms, such as anxiety or depression, which could warrant such a referral.

TGNB patients who experience relief of gender dysphoria symptoms on GAHT are often better able to address their other health needs.

The SM is no longer recommended in the *WPATH SOC Version 8*.[8] The SM strongly recommended that all TGNB patients be evaluated by a "qualified mental health professional" prior to initiation of GAHT.[18] Mental health requirements for GAHT disrupt a potentially therapeutic relationship by placing the mental health provider in a "gatekeeper" role.[15]

The ICM generally necessitates that a patient has capacity to consent for their treatment. In the ICM, a patient who has the capacity to consent for their other medical care also has the capacity to consent for GAHT. Inability to provide informed consent, however, is not an absolute contraindication to provision of GAHT. In circumstances in which a patient is unable to provide informed consent, it may be appropriate for the patient to offer assent while their guardian or other healthcare proxy provides informed consent on their behalf.[8] Resources regarding gender-affirming care for people with serious mental illness are available.[19]

TGNB people may present with coexisting medical and psychiatric concerns. Distress related to lack of access to GAHT may prevent TGNB people from being able to engage in their own medical or mental health care for these other conditions. TGNB patients who experience relief of gender dysphoria symptoms on GAHT are often better able to address their other health needs.[2] Providers should discuss risks and benefits related to possible interactions between GAHT and coexisting health conditions as a part of the informed consent conversation and exercise shared decision-making. GAHT should not be withheld due to a coexisting medical or psychiatric condition, provided that other diagnostic criteria are met and in the absence of an absolute medical contraindication.[8]

Obtaining informed consent should include comprehensive counseling regarding GAHT. Use of written patient education materials ensures that patients receive detailed and consistent information. At minimum, the informed consent discussion should include explanation of medical options, expected reversible and permanent changes, short- and long-term risks, implications for fertility and contraception, safe medication administration, relevant gaps in clinical knowledge, and expectations regarding follow-up and lab monitoring. This information must be provided in a manner attentive to the patient's health literacy and comprehension abilities. Examples of GAHT patient education materials are available for further guidance.[16,17]

General principles of GAHT initiation and management

There is no "best" regimen or pathway for gender-affirming medical and surgical interventions. Hormone regimens should be tailored to each patient's goals, including desired changes in physical presentation and/or internal sense of embodiment. Some TGNB people may seek to masculinize or feminize to the fullest extent possible, while others may desire to achieve a mixture of masculine and feminine characteristics. Furthermore, patients' gender-related goals may change throughout their lives. Patients may choose to increase, decrease, stop, and/or restart GAHT for a wide variety of factors; those who stop GAHT rarely report doubt regarding their gender identity as a contributing factor.[20]

Specific changes caused by GAHT, as well as their reversibility, are detailed below. Some effects may be noticeable within the first months, while others may take years for maximum expression. Rate of change is also dependent on individual characteristics, such as age and genetic predisposition. Patients should be counseled that it is impossible to predict how fast or

slow changes will occur for them.[18] It is essential that patients understand the limitations of GAHT and that some characteristics cannot be altered by GAHT, such as height and bone structure.

GAHT may impact fertility. Patients who desire to use their gametes for future family building should be offered sperm or oocyte cryopreservation. Lack of insurance coverage limits the financial feasibility of these procedures for many patients.[21] However, GAHT does not guarantee sterility. Patients at risk for pregnancy, based on current anatomy and sexual activity, should be counseled on contraceptive options. When conducting sexual healthcare for TGNB patients, exams should be conducted using trauma-informed techniques. TGNB anatomy terms and sexual history-taking recommendations are detailed in previous literature.[6]

When monitoring hormone levels, normal total testosterone and estradiol ranges for cisgender men and women are used as reference. Exact ranges vary by lab provider and assay. These reference ranges do not have to represent "goal" levels, depending on desired outcomes. For example, a patient on masculinizing GAHT who desires a slower rate of change may prefer to maintain a total testosterone level above that of a cisgender woman but below that of a cisgender male. Supratherapeutic estradiol and testosterone dosing may increase risk for adverse events.[22] If total testosterone exceeds the normal cisgender male range (masculinizing GAHT) or if estradiol exceeds the normal cisgender female range (feminizing GAHT), testosterone or estradiol dose decreases are recommended. The authors typically confirm supratherapeutic levels with repeat analysis before decreasing GAHT doses, particularly when results seem inconsistent with reported dosing, as sex steroid assays may lack accuracy.[23]

Patients who have undergone complete gonadectomy should continue, at minimum, a low dose of GAHT to maintain bone health. It is not known if hormone doses should be decreased in older patients.[8]

While this article covers major risks associated with GAHT, it is not exhaustive. Please see *WPATH SOC Version 8* for further discussion.[8]

Masculinizing GAHT

Masculinizing GAHT consists of the use of testosterone to create masculine secondary sex characteristics in people assigned female at birth. Providers can review specific changes resulting from masculinizing GAHT and the time course of these changes (see *Expected changes and time course of masculinizing GAHT*). Deepening of the voice, clitoral enlargement, facial and body hair growth, and scalp hair loss are permanent. Masculinizing GAHT will not substantially reduce breast size.[22]

Absolute contraindications to masculinizing GAHT include active hormone-sensitive cancer, pregnancy, and polycythemia with a hematocrit of 54% or higher. When considering treatment of a patient with a prior history of hormone-sensitive cancer, an oncology consult should be sought.[2,24]

Federally, the US Controlled Substances Act lists testosterone as a Schedule III controlled substance.

Testosterone

A variety of testosterone preparations are available, and no one form is superior in achieving masculinizing effects. Commonly used forms include short-acting

Expected changes and time course of masculinizing GAHT*

Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	—[a]
Increased muscle mass/ strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	—[b]
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (46), Asscheman *et al.* (47), Gooren *et al.* (48), Wierckx *et al.* (49).

[a]Prevention and treatment as recommended for biological men.

[b]Menorrhagia requires diagnosis and treatment by a gynecologist.

Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2017;102(11):3869-3903. doi:10.1210/jc.2017-01658

**Table is being reproduced as is from the original source. The authors note that all people using masculinizing GAHT will not necessarily identify as transgender males.*

injectables and topical gels. Testosterone cypionate and testosterone enanthate are short-acting depot formulations injected every 1-2 weeks, and can be self- or office-administered I.M. or subcutaneously.[25] Testosterone gels are applied daily. Individuals using testosterone gel should avoid skin-to-skin contact with others at the application site to avoid transfer. Less commonly used routes of administration include long-acting injectables, patches, and subcutaneous implants. Providers can refer to the University of California San Francisco's *Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People* (*UCSF Guidelines*) for masculinizing GAHT dosing recommendations.[2]

Common adverse reactions of masculinizing GAHT include acne, scalp hair loss, and gynecologic issues.

Common adverse reactions of masculinizing GAHT include acne, scalp hair loss, and gynecologic issues. Management of acne and male-pattern balding is similar to that for cisgender men. Vaginitis, irregular bleeding, and pelvic pain are also common concerns for people on masculinizing GAHT. Atrophic vaginitis, similar to that of menopausal cisgender women, may be induced by testosterone therapy. Patients may complain of recurrent urinary or vulvovaginal symptoms. After ruling out other causes (for example, sexually transmitted infection, urinary tract infection), clinicians may offer vaginal estradiol preparations for symptom relief.[26] Pelvic pain is also frequently reported among people on masculinizing GAHT. Determining the cause of this pain is often challenging. Recommendations for evaluation are available.[2]

Although most patients achieve amenorrhea on masculinizing hormone therapy within 6 months of testosterone initiation, persistence or recurrence of breakthrough bleeding is common. Evaluation and management of breakthrough bleeding has been discussed in the recent literature.[27] Evidence does *not* support an increased risk for endometrial hyperplasia among people on masculinizing GAHT. While some patients seek out hysterectomy and/or oophorectomy for gender-affirmation, patients should be counseled that these procedures are not indicated, in the absence of other risk factors, specifically as prophylaxis for gynecologic cancers of any kind.[28,29]

Monitoring

Monitoring parameters for masculinizing hormone therapy include hemoglobin, hematocrit, and total testosterone levels. Providers should check hemoglobin and hematocrit at baseline; then check hemoglobin, hematocrit, and total testosterone at 3 months, 6 months, 12 months, and then annually. Additional monitoring should be performed 3 months following a dose adjustment, and as needed if evaluating symptoms suspected to be related to testosterone dosing or levels. Other lab testing may be helpful in complex cases and is reviewed in other clinical resources.[2] Masculinizing GAHT causes hemoglobin and hematocrit to increase toward normal cisgender male ranges; this is not a cause for concern. Polycythemia is diagnosed if hemoglobin and/or hematocrit rise above normal cisgender male ranges. Providers should check total testosterone levels in patients with polycythemia, and adjust the patient's testosterone dose if the level is supratherapeutic. Patients with polycythemia may also be evaluated for other secondary causes, and can consider blood donation or therapeutic phlebotomy for management. Transdermal testosterone may be less likely to induce polycythemia compared with injectable methods.[30]

Feminizing GAHT

Feminizing GAHT consists of the use of any combination of estradiol, antiandrogens, and progesterone to create feminine secondary sex characteristics and to suppress masculine secondary sex characteristics in people assigned male at birth. Providers can review expected changes resulting from feminizing GAHT and the time course of these changes (see *Expected changes and time course of feminizing GAHT*). Breast growth and decrease in testicular volume are permanent.[22] There are limited data available with conflicting findings on spermatogenesis and semen quality after cessation of feminizing GAHT.[31] Feminizing GAHT does not change vocal pitch.[2]

Estradiol

The form of estradiol used in feminizing GAHT is 17-beta estradiol, which is chemically identical to estrogen

produced by human ovaries. Ethinyl estradiol is associated with a significantly higher risk for venous thromboembolism (VTE) compared with 17-beta estradiol and should not be prescribed as part of GAHT.[32] While conjugated equine estrogen has been used as part of feminizing GAHT in the past, it is no longer recommended.[2] "*Estradiol*" will refer to *17-beta estradiol* for the remainder of this article.

Estradiol may be administered via oral or sublingual tablets, transdermal patches, and self- or office-administered I.M. injection. Selection of route is largely based on patient preference, although other considerations include risk for VTE, as discussed below. No method is superior to another in terms of achieving desired feminizing effects. Recommended dose ranges for estradiol are available in the *UCSF Guidelines*.[2] No estradiol tablets designed for sublingual administration are available in the US; however, micronized estradiol tablets can be taken sublingually. Sublingual administration results in higher serum estradiol levels compared with oral administration.[33]

Evidence regarding increased risk for VTE due to estradiol use is mixed.[34] Transdermal estradiol has the lowest risk for VTE compared with other routes of administration, with some data showing no increased VTE risk.[35] Tobacco use in combination with estradiol use increases risk for VTE; smokers should be counseled to quit. Patients who use tobacco and/or have other risk factors for VTE (family history of VTE, known hypercoagulable state, or prothrombotic mutation) should be thoroughly counseled about the risk of VTE; transdermal estradiol is the preferred route of administration for these patients. Patients with a personal history of VTE may elect to continue transdermal estradiol following an informed consent discussion of risk. Increased risk for VTE may outweigh benefits of estradiol use for select high-risk patients; the authors recommend shared patient-provider decision-making after a thorough discussion of these risks. Consult the *UCSF guidelines* for further discussion and detailed algorithms on estradiol use in patients with significant VTE risk factors and/or a personal or family history of VTE.[2] As risk factors for VTE increase with age, patients over age 45 on feminizing GAHT may benefit from transition to transdermal estradiol.[8]

The only absolute medical contraindication to estradiol use is an active estrogen-sensitive cancer. In patients with a history of an estrogen-sensitive cancer, consultation with the patient's oncologist is advised.[2]

Expected changes and time course of feminizing GAHT*

Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y[a]
Scalp hair	Variable	—[b]
Voice changes	None	—[c]

Estimates represent clinical observations: Toorians *et al.* (46), Asscheman *et al.* (47), Gooren *et al.* (48).

[a]Complete removal of male sexual hair requires electrolysis or laser treatment or both.

[b]Familial scalp hair loss may occur if estrogens are stopped.

[c]Treatment by speech pathologists for voice training is most effective.

Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2017;102(11):3869-3903. doi:10.1210/jc.2017-01658

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Unlike with oral contraceptive use, migraine with aura is not a contraindication for feminizing GAHT. Some patients with migraines, with or without aura, find that estradiol use exacerbates migraine symptoms. Estradiol level fluctuations may trigger migraines; the transdermal route is preferable for patients with migraines to reduce fluctuations in serum estradiol levels.[36]

Antiandrogens

Androgen-blocking medications, or antiandrogens, reduce masculine features by decreasing testosterone levels. Estradiol itself also has antiandrogen effects.[37] Antiandrogens are typically used in combination with estradiol, but may be used alone if the effects of

estradiol are not consistent with the patient's goals. However, complete androgen blockade without estradiol replacement causes menopause-like symptoms, and in the long-term, bone loss.[38] Antiandrogens can be discontinued following gonadectomy, as endogenous androgen production largely ceases.

In the US, spironolactone is the most commonly used antiandrogen for GAHT due to its efficacy, availability, and low risk for severe adverse reactions. Spironolactone has antiandrogen receptor activity as well as a suppressive effect on testosterone synthesis.[39] Adverse reactions, typically self-limited, may include urinary frequency and orthostasis. Due to risk for hyperkalemia, when administering spironolactone to patients with reduced renal function or those taking other medications with risk for hyperkalemia, potassium levels should be monitored more frequently. Starting spironolactone at lower doses and titrating up as needed may help to minimize adverse reactions.

In the US, spironolactone is the most commonly used antiandrogen for GAHT due to its efficacy, availability, and low risk for severe adverse reactions.

The next most commonly used antiandrogens, 5-alpha reductase inhibitors (such as, finasteride, dutasteride), block the conversion of testosterone to dihydrotestosterone (DHT). DHT is the hormone mainly responsible for scalp hair loss. 5-alpha reductase inhibitors do not directly block testosterone activity or synthesis, and thus are less potent than other antiandrogens.[40] However, they may be beneficial for those who cannot tolerate other options, or for those who have hair loss despite low serum testosterone levels. Recommended dose ranges for spironolactone, finasteride, and dutasteride are available in the *UCSF Guidelines*.[2]

In the US, less commonly used antiandrogens include cyproterone acetate, bicalutamide, and gonadotropin releasing hormone (GnRH) analogues. Cyproterone acetate is not available in the US. Bicalutamide is associated with a small risk for hepatotoxicity.[41] Determining if this risk is justified is a matter of clinician judgment, however, the authors conclude that the risks associated with bicalutamide outweigh the benefits when used for GAHT, when safer alternatives are available. GnRH analogues, more often used for pubertal suppression within the context of TGNB health, are also effective antiandrogens.[42] Use of GnRH analogues is limited by high cost and challenges in obtaining insurance authorization.

Some patients on feminizing GAHT find the decrease in libido and erectile function to be gender-affirming, while others prefer to maintain these traits. Decreasing the androgen blocker dose to allow a small increase in total testosterone may increase libido and erectile function, although patients may be unable to tolerate an increase in other androgenic features. Phosphodiesterase-5 enzyme inhibitors (for example, sildenafil, tadalafil) can be prescribed, if not otherwise contraindicated, to assist with erectile function. Patients with low libido following gonadectomy may benefit from administration of low-dose topical testosterone.[2]

Progesterone

The role of progesterone as part of a feminizing GAHT regimen is less well-defined compared with estradiol and antiandrogens. Many individuals report that the addition of progesterone to their GAHT regimen improves breast development, mood, and libido, while others report a negative effect on mood.[22] Concerns exist regarding increased cardiovascular and breast cancer risk related to progesterone use; however, expert opinion finds minimal risk in progesterone use in the context of feminizing GAHT.[2] Some data suggest increased VTE risk associated with use of progesterone as part of feminizing GAHT regimens.[43]

Oral medroxyprogesterone acetate and micronized progesterone are the most commonly prescribed forms of progesterone for GAHT in the US. Recommended dose ranges for progesterone are available in the *UCSF Guidelines*.[2]

Monitoring

Monitoring parameters for feminizing GAHT include estradiol and total testosterone levels, as well as renal function and potassium levels for GAHT regimens that include spironolactone. Providers should check renal function and potassium at baseline; then, check renal function, potassium, estradiol, and total testosterone levels at 3 months, 6 months, 12 months, and then annually. Additional monitoring should be performed

3 months following a dose adjustment, and as needed if evaluating adverse reactions or symptoms suspected to be related to estradiol or testosterone levels.[2]

Routine monitoring of prolactin is not advised, as there is no evidence for increased risk for prolactinoma with GAHT.[44] Prolactin should only be measured in patients with signs or symptoms of prolactinoma (for example, visual changes, new headache, and galactorrhea).[45] A small amount of galactorrhea, especially early in the course of feminizing GAHT, is common and alone should not be cause for concern for prolactinoma.[2]

Conclusion

TBNB people may present to PCPs seeking GAHT as part of their gender affirmation. Prescribing GAHT is within the primary care scope of practice. Familiarity with the informed consent model of care, changes expected from GAHT, and guidelines for GAHT dosing and monitoring prepare PCPs to offer this life-changing treatment.

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