HHS Public Access

Author manuscript

Handb Exp Pharmacol. Author manuscript; available in PMC 2024 June 09.

Published in final edited form as:

Handb Exp Pharmacol. 2023 ; 282: 41–55. doi:10.1007/164_2023_665.

Clinical pharmacological considerations in transgender medicine

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Abstract

Transgender medicine is a growing clinical field. Hormone therapy (testosterone or estrogen treatment) is part of the standard of gender affirming medical care, yet clinical pharmacological knowledge in transgender medicine is lacking. Herein, we summarize available clinical and pharmacologic data for hormone therapy among transgender and gender diverse people.

Keywords

drug interactions; drug-metabolizing enzymes; drug transport proteins; gender affirming medical care; sex steroid hormones; pharmacology; transgender

1 Introduction

Transgender and gender diverse (TGD) people comprise an increasingly visible population globally. Clinicians may prescribe hormone therapy across the lifespan to support a person's gender expression goals (Coleman et al., 2022), yet TGD people have been underrepresented in most pharmacologic research (Cirrincione et al., 2023). Clinical pharmacological knowledge in transgender medicine is limited.

Sexually dimorphic characteristics may influence the safety and efficacy of certain medications, as described in detail elsewhere in this textbook. Sex steroids affect expression and activity of certain drug metabolizing enzymes and drug transport proteins based on *in vitro* and animal model data (Le et al., 2022). It is largely unknown the extent to which sex-specific predictors of drug safety and effectiveness can be generalized to TGD adults undergoing hormone therapy. Herein, we provide an overview of emerging considerations for clinical pharmacology in transgender medicine.

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1.1 Terminology

Sex: a culturally defined social construct assigned at birth based on appearance of external genitalia. Commonly referred to as biological factors related to male, female, or intersex characteristics including hormonal expression and genitalia. This assignment carries a set of assumptions regarding the underlying internal genital anatomy and the hormone-tissue interactions that will occur with development and aging. This term is descriptive and not prescriptive.

Gender identity: a social construct related to sex assignment that describes behavioral, psychological, and social traits present in a given culture. Gender identity is an individual's personal understanding of their place in that social construct. Gender expression is the outward manifestation of the intersection of gender identity and environment via behavior and dress. Gender, gender identity, and gender expression are linked but may not be congruent.

Sexual orientation: emotional, romantic, and/or sexual attraction to another individual or individuals of a certain gender or sex. This includes lack of emotional, romantic, and/or sexual attraction as well. Sexual orientation and gender identity are non-interchangeable terms and are independent of each other.

Gender-affirming medical care: medications, surgery, or other medical interventions that a person may or may not choose to meet their gender expression goals.

Transgender: A culturally defined social construct describing people whose gender identities differ from the cultural expectation of their sex assigned at birth. Common examples include transgender men or transmasculine individuals, transgender women or transfeminine individuals, and nonbinary people. May or may not be used by an individual to describe themselves.

Cisgender people: people whose gender aligns with the cultural expectation of their sex assigned at birth; not transgender.

Transgender men/transmasculine person: people identifying as men or along the masculine spectrum and assigned female at birth.

Transgender women/transfeminine person: people identifying as women or along the feminine spectrum and assigned male at birth.

Nonbinary people: people with a gender identity outside of the cultural binary of "man" or "woman." Some labels people may use to describe themselves: nonbinary, genderfluid, genderqueer, agender, pangender, bigender, gender nonconforming.

Intersex people: people born with reproductive or sexual anatomy that does not align with binary definitions of female or male due to any of a variety of variations in sex characteristics (VSC). May or may not be used by a given individual to describe themselves.

1.2 US Demographics

Investigators have estimated at least 25 million people globally are TGD (Winter et al., 2016). Based on US Centers for Disease Control and Prevention (CDC) Behavioral Risk Factor Surveillance System (BRFSS) data from 2017 to 2020, 1.6 million US people ages ≥13 years were TGD, 38.5% of whom were transgender women and 35.9% were transgender men (Herman et al., 2022). The remaining respondents (25.6%) were nonbinary (referred to as “gender nonconforming” on BRFSS questionnaires) (Cicero et al., 2020). Respondents identified as straight, lesbian, gay, bisexual or pansexual (Meyer et al., 2017). TGD people living in the US are racially and ethnically diverse. TGD adults identified as Asian (5.8%), American Indian or Alaska Native (1.1%), Black (13%), Native Hawaiian, Pacific Islander, biracial, multiracial, or another race or ethnicity (3.8%), and White (54.7%) (Herman et al., 2022). Twenty-one percent of TGD adults identified as Hispanic or Latinx (where “Latinx” was used as a nonbinary form of Latino or Latina) (Herman et al., 2022). Experts anticipate the number of US TGD older adults will increase over the next few decades (Fredriksen-Goldsen, 2016). Between 2017 and 2020, 0.3% of US adults ≥65 years of age were TGD (Herman et al., 2022).

1.3 Health disparities and co-occurring medical conditions

1.3.1 Barriers to healthcare access—TGD people face social and structural stigma, discrimination, and barriers to healthcare access (Scheim et al., 2022; James et al., 2016). In a 2015 nonprobability survey of approximately 28,000 US transgender adults, nearly one-quarter of respondents avoided seeking necessary medical care within the year prior to completing the questionnaire, largely because of fear of being disrespected or mistreated (James et al., 2016). Among those who reported receiving medical care, many respondents experienced verbal harassment from healthcare providers, encountered clinical providers who refused to offer gender-affirming medical treatment, or needed to teach clinical providers about transgender people to receive appropriate medical care (James et al., 2016).

Anti-transgender stigma and discrimination are associated with poor health outcomes for TGD people (Coleman et al., 2022). Among >400 TGD adult respondents in a statewide US survey, investigators observed that delaying healthcare due to fear of discrimination was predictive of lower self-reported general health relative to respondents who did not delay seeking healthcare ($\beta=-0.26$, $P<0.05$) (Seelman et al., 2017). In a US probability survey of 271 TGD adults and 1162 cisgender adults, TGD respondents had significantly higher age-adjusted odds of reporting poor to fair general health (adjusted odds ratio: 2.50, $P<0.001$), reporting days per month of poor physical health (adjusted odds ratio: 3.87, $P<0.001$), and reporting days per month of poor mental health relative to cisgender respondents (adjusted odds ratio: 7.09, $P<0.001$) (Feldman et al., 2021). Finally, in a separate cohort of approximately 2500 US lesbian, gay, bisexual, and transgender adults ≥50 years of age, transgender people had significantly lower odds of utilizing preventive health screenings relative to cisgender adults, including mammogram, Papanicolaou (Pap) smear, osteoporosis test, and prostate-specific antigen tests (Hoy-Ellis et al., 2022). These factors contribute to highly individualized medical experiences for all TGD people.

1.3.2 Chronic disease burden—Knowledge about the chronic disease burden among TGD people is limited (Rich et al., 2020). Transgender women have at least 49 times higher odds of HIV globally compared with the general population (aged 15-49 years) (Baral et al., 2013). Transgender men have 6.8 times higher odds of HIV relative to the general population (Stutterheim et al., 2021). HIV prevalence among nonbinary people is currently unknown. Several observational studies have characterized cardiovascular disease risk and metabolic disorders among TGD people undergoing hormone therapy (Rich et al., 2020; Defreyne et al., 2019). One retrospective cohort study in a large US-based healthcare system observed two times higher venous thromboembolism incidence among transgender women than cisgender men or cisgender women (Getahun et al., 2018). Limited clinical data suggest type 2 diabetes incidence may be higher among transgender women than cisgender women (hazard ratio: 1.4, 95% confidence interval: 1.1-1.8), although an association with estrogen treatment appears unlikely (Islam et al., 2021). Testosterone treatment is associated with decreased high-density lipoprotein concentrations, but researchers observed mixed effects of testosterone on low-density lipoprotein and triglyceride concentrations for TGD people (Coleman et al., 2022). Hormone therapy is associated with increased quality of life for TGD people (Baker et al., 2021), and it is a key part of the standard of gender-affirming medical care. Thus, experts typically recommend a harm-reduction approach when prescribing hormone therapy in the context of modifiable and non-modifiable cardiovascular risk factors (Deutsch, 2016; Ramsay and Safer, 2022).

Investigators have documented several sex-related and gender-related differences in chronic disease risk and outcomes in the general adult population, ranging from autoimmune disorders and infectious diseases (Klein and Flanagan, 2016), cardiovascular disease (Colafella and Denton, 2018), diabetes (Tramunt et al., 2020), to some neurodegenerative disorders (Ferretti et al., 2018; Gillies et al., 2014). Complex interactions between sex-specific genetic and hormonal factors, gender-specific behaviors, and environmental factors contribute to these differences (F. Mauvais-Jarvis et al., 2020; Khramtsova et al., 2019). Further research is needed to understand how these factors may influence the health and well-being of TGD people.

1.3.3 Considerations across the lifespan—TGD older adults are an increasingly visible population with unmet gaps in medical care. Although social support and having feelings of belonging within the lesbian, gay, bisexual and transgender community were positively associated with perceived physical health among transgender older adults, social support and belonging were lower for TGD older adults than cisgender counterparts (Fredriksen-Goldsen et al., 2014). Several observational studies have suggested TGD older adults may have a higher prevalence of cognitive impairment than the general older adult population (Cheung et al., 2023). For example, in a cross-sectional survey of TGD adults ≥50 years of age, respondents who experienced discrimination in medical settings because of their gender identity had significantly higher odds of subjective cognitive decline compared with TGD older adults who did not (odds ratio: 7.49, 95% confidence interval: 1.71 to 32.79, P=.008) (Lambrou et al., 2022). In an analysis of Medicare fee-for-service data from 2009-2017, the predicted probability of dementia was higher for TGD older adult beneficiaries than cisgender older adult beneficiaries after adjusting for age,

race and ethnicity, census region, and the number of months of enrollment (transgender women vs. cisgender women: 21.3% vs. 13.6%, respectively, P<0.0001; transgender men vs. cisgender men: 20.2% vs. 12.3%, respectively, *P*<.0001) (Hughto et al., 2023). Multiple chronic conditions often translate into increased prescription medication use, polypharmacy, and potential drug-drug interactions among older adults (Cerreta et al., 2023). Studies characterizing the scope of these medication-related issues for TGD older adults are lacking (Gamble et al., 2020). Research addressing this topic is needed.

TGD older adults have diverse gender-affirming medical care experiences across the life course. For example, TGD older adults may start hormone therapy later in life, including 50 years or older (see section 2.2 Overview of hormone therapy) (Gooren and T'Sjoen, 2018; Cheung et al., 2023). Among >200 TGD people who presented for gender-affirming surgery at a large US-based academic medical center, patients ≥40 years of age self-reported longer timeframes before starting hormone therapy and other types of gender-affirming care over their lifetime than patients <40 years of age (average timeframes: 37 years vs. 16 years, respectively, *P*<.001) (Zaliznyak et al., 2021). Because TGD people may continue hormone therapy long-term (Cheung et al., 2023), increased knowledge on managing hormone therapy for TGD older adults is needed (Gooren and T'Sjoen, 2018). Effects of physiologic changes among cisgender older adults on drug safety, including changes in body composition, kidney or liver, are well characterized (Cerreta et al., 2023), but pharmacologic considerations for transgender older adults are an unmet knowledge gap.

2 Pharmacologic considerations for TGD adults undergoing hormone therapy

Scientists have characterized differences in medication safety and effectiveness for cisgender women and cisgender men (Cirrincione and Huang, 2021), but implications for TGD people undergoing hormone therapy are unknown. The remainder of this chapter focuses on hormone therapy for TGD adults. Specifically, we focus on the role of hormone therapy in gender-affirming medical care, its physiologic and pharmacologic effects, and its potential contribution to interindividual variability in pharmacokinetic processes for TGD people.

2.1 TGD-inclusive pharmacologic research

TGD people face certain barriers related to clinical research participation. These barriers may include concerns about privacy and exploitive or opportunistic research (Asquith et al., 2021) and mistrust of medical and research communities (Owen-Smith et al., 2016). TGD and cisgender scientists in HIV research have made progress in engaging TGD communities in Phase 3 clinical trials (Cirrincione et al., 2023) and conducting drug-hormone interaction studies for HIV pharmacologic prevention interventions (Yager and Anderson, 2020). As transgender medicine grows in scope, investigators should prioritize including TGD people in pharmacologic studies in phase 1, 2, and 3 clinical trials across all therapeutic areas (Yager and Anderson, 2020). The effects of hormone therapy on drug metabolism and drug transport of other medications among TGD people are unknown. Clinical mechanistic studies *in vivo* are required to establish the pharmacologic effects of hormone therapy on major drug-handling pathways among TGD people.

2.2 Overview of hormone therapy

The World Professional Association for Transgender Health (WPATH) issued standards of care for the health of TGD people over the past 40 years and published Standards of Care version 8 in 2022 (Coleman et al., 2022). WPATH recommended hormone therapy as part of the standard of medical care for TGD people (Hembree et al., 2017; Coleman et al., 2022). WPATH also endorsed the Endocrine Society professional guidelines, which provided specific clinical guidance for hormone therapy management (including administration routes and dosing) and clinical laboratory monitoring for TGD people taking hormone therapy (Hembree et al., 2017). Broadly, hormone therapy includes either testosterone or estrogen treatment and aligns a person's secondary sex characteristics with their gender identity (Coleman et al., 2022). Clinicians individualize hormone regimen dosing, agents, and administration routes based on a person's gender expression goals and the safety profiles for specific agents (Table 1) (Hembree et al., 2017).

Clinical laboratory values change markedly during hormone therapy (Hembree et al., 2017). For TGD adults undergoing 12 months of testosterone treatment, investigators have observed 15- to 20-fold increased average serum testosterone concentrations (total and free) and 40% decreased serum estradiol concentrations (Cirrincione and Huang, 2021). For TGD adults undergoing estrogen treatment, investigators have observed up to 9-fold increased average serum estradiol concentrations and 93-98% decreased testosterone concentrations (total and free) (Cirrincione and Huang, 2021).

Changes in sex steroid concentrations have direct effects on interpreting other clinical laboratory values. For example, in a longitudinal electronic health record study of hematological changes among nearly 1000 transgender adults, investigators observed markedly increased hemoglobin and hematocrit values for patients undergoing testosterone treatment and markedly decreased values among patients undergoing estrogen treatment (Antun et al., 2020). Based on these findings, investigators proposed using hematologic reference intervals aligned with an individual's gender identity for TGD people undergoing hormone therapy (Antun et al., 2020). These findings highlight the effect of sex steroids on clinical laboratory values, specifically those with sex-specific reference ranges for the general adult population.

2.3 Drug absorption

No clinical studies have examined gastric transit times or changes in drug absorption for TGD people undergoing hormone therapy. As discussed in other chapters, gastric processes differ between cisgender women and cisgender men (Vinarov et al., 2021). Examples include slower gastric emptying time and lower gastric acid secretion among cisgender women (Vinarov et al., 2021). Evidence for sex-related differences in nonoral drug disposition is limited, but data suggest cisgender women may have slower intramuscular absorption of certain medications than cisgender men (Franck Mauvais-Jarvis et al., 2021). Clinical and animal model data suggest estrogens and progestogens, but not androgens, contribute to slow gastric emptying times (Jiang et al., 2019). Investigators have yet to characterize the effects of hormone therapy on oral or nonoral drug absorption for TGD people (Yager and Anderson, 2020).

2.4 Drug distribution

Hormone therapy causes marked body composition changes within the first year of therapy. A meta-analysis of 10 prospective European cohorts (approximately 500 transgender adults total with baseline average body mass indices between 20 kg/m^2 and 25 kg/m^2) reported increased total body weight within the first 12 months of either testosterone or estrogen treatment relative to baseline (up to +1.8 kg compared with measured body weight before hormone therapy) (Klaver et al., 2017). For transgender adults undergoing testosterone treatment (average age 30 years), total body fat decreased significantly from baseline (−2.6 kg, 95% confidence interval: −3.9 to −1.4; P <.0001), whereas lean body weight increased significantly from baseline (+3.9 kg, 95% confidence interval: 3.2 to 4.5; P <.00001). Conversely, transgender adults undergoing estrogen treatment (average age 33 years) had significantly increased total body fat from baseline (+3.0 kg, 95% confidence interval: 2.0 to 3.9; P <.00001), and significantly decreased lean body weight from baseline (−2.4 kg, 95% confidence interval: −2.8 to −2.1; P <.00001) (Klaver et al., 2017). Increased total body fat may increase the volume of distribution for certain fat-soluble medications (e.g., neuromuscular blocking agents vecuronium and rocuronium and the benzodiazepine diazepam) (Soldin and Mattison, 2009).

Limited clinical data for TGD people observed unchanged serum albumin and corticosteroid-binding globulin concentrations during hormone therapy (Cirrincione and Huang, 2021). Sex hormone binding globulin concentrations increased modestly for TGD adults undergoing estrogen treatment (1.3-fold) and decreased markedly for TGD adults undergoing testosterone treatment (51-54%) (Cirrincione and Huang, 2021). These findings have implications for pharmacokinetic modeling (Cirrincione and Huang, 2021).

2.5 Drug metabolism

No clinical studies have investigated the effects of hormone therapy on the apparent activities of major drug-metabolizing enzymes among TGD adults. Several drug-metabolizing enzymes in the cytochrome P450 (CYP) enzyme superfamily exhibit differences in apparent activities between cisgender women and cisgender men (Vo and Paine, 2022). A comprehensive review of sex-related differences in CYP activity and expression is covered elsewhere in this textbook. As one example among phase I drug metabolizing enzymes, investigators observed higher (~35%) apparent CYP3A activity for cisgender women than cisgender men (Cirrincione and Huang, 2021). Supraphysiologic estradiol concentrations increased CYP3A4 protein levels in human hepatocytes *in vitro* (Le et al., 2022). Apparent CYP1A2 activity is lower among cisgender women than cisgender men (Cirrincione and Huang, 2021). Clinical and *in vitro* data suggested estrogen has an inhibitory effect on CYP1A2 activity (Le et al., 2022). The clinical relevance of these findings for TGD people undergoing estrogen treatment remains to be determined. Sex-related differences for other major CYPs (CYP2B6, 2C9, 2C19, 2D6, 2E1) are mixed (Franck Mauvais-Jarvis et al., 2021). Several phase II conjugation enzymes have sex-related differences in expression and activity, including uridine diphosphate-glucuronosyltransferase (UGT) 2B17 and 2B15, glutathione S-transferase A1/A2, and sulfotransferase (SULT) 1A1 and 1E1 (Franck Mauvais-Jarvis et al., 2021). Clinical implications for TGD people, particularly those undergoing testosterone treatment, remain to be determined.

2.6 Drug elimination

The effects of hormone therapy on kidney function is an ongoing area of investigation for TGD people (Krupka et al., 2022). Based on findings from clinical pharmacokinetic studies, plasma concentrations of tenofovir (as tenofovir disoproxil fumarate) and emtricitabine, two anti-HIV agents that are predominantly renally eliminated as unchanged drugs, are 12-27% lower among transgender women undergoing estrogen treatment relative to cisgender men and transgender women not yet taking estrogen treatment (Yager and Anderson, 2020). In a separate analysis, Investigators observed that estimated creatinine clearance was 60% higher among transgender women than cisgender men (P=0.04), and estimated creatinine clearance influenced tenofovir and emtricitabine clearance based on population pharmacokinetic modeling (Tanaudommongkon et al., 2022).

In a meta-analysis of nine clinical cohorts of TGD adults taking hormone therapy, adults undergoing testosterone treatment had markedly increased serum creatinine concentrations after 12 months of treatment (+0.15 mg/dL, 95% confidence interval: 0.00 to 0.29), whereas adults undergoing estrogen treatment had no significant change in serum creatinine concentrations (−0.05 mg/dL, 95% confidence interval: −0.16 to +0.05) (Krupka et al., 2022). Blood urea nitrogen concentrations did not change markedly during either testosterone or estrogen treatment. Researchers have yet to characterize potential changes in other kidney function biomarkers before and during hormone therapy (e.g., cystatin C, albuminuria, proteinuria) (Krupka et al., 2022).

In one small longitudinal clinical cohort study, investigators observed an 18% apparent decrease in estimated glomerular filtration rate among transgender adults after 12 months of testosterone treatment (using creatinine-based estimating equations with a female modifier for both pre-testosterone and post-testosterone estimates) (Fadich et al., 2021). Median serum creatinine increased by 0.12 mg/dL from baseline to follow-up (P=.0006). However, investigators did not assess changes in lean muscle mass, which may have contributed to increased serum creatinine concentrations (see Section 2.3 Drug distribution). Because creatinine-based kidney function estimating equations require the use of stable serum creatinine concentrations and a binary sex modifier (male or female) (Fadich et al., 2021), prospective, longitudinal studies using a gold-standard indicator of glomerular filtration (e.g., iohexol) are needed to characterize potential changes in kidney function and to address altered drug elimination among TGD people undergoing hormone therapy.

2.7 Drug transport

No studies have examined the clinical effects of hormone therapy on drug transporter activities for TGD adults. Sex-related effects on drug transport protein expression are mixed (Vo and Paine, 2022). For example, investigators observed 3-fold higher hepatic expression of P-glycoprotein, an adenosine triphosphate (ATP)-binding cassette efflux transporter, among cisgender men versus cisgender women but no difference in intestinal P-glycoprotein expression (Vo and Paine, 2022). Investigators observed no sex-related differences in the expression of hepatic breast cancer resistance protein (BCRP), an efflux transporter, or organic anion transporting polypeptides (OATP) 1B1, 1B3, 2B1, uptake transporters (Vo and Paine, 2022). Animal model data suggest testosterone treatment activated protein expression

of kidney organic anion transporter 1 and organic cation transporter 2 (Le et al., 2022). The clinical effects of hormone therapy on drug transport proteins for TGD people remain to be determined.

3 Limitations of sex/gender as binary variable in biomedical and pharmacologic research

All sex-related and gender-related pharmacological knowledge relies on a binary male-female framework (Bhargava et al., 2021; Franck Mauvais-Jarvis et al., 2021). However, experts recognize the binary male-female framework fails to capture the spectrum of sex and its associated physiological and behavioral phenotypes, with unclear implications for growing fields, including nanomedicine (Sharifi et al., 2021). As one example, variations in sex characteristics (also described as “intersex”) include several biologic underpinnings such as genetic and hormonal factors (Conway, 2022). Additionally, investigators have noted gaps in how sex-related differences are studied and reported in the literature (Garcia-Sifuentes and Maney, 2021). Appropriately designed studies are needed in pharmacologic research to identify and characterize sex-specific outcomes.

4 Conclusions and Clinical Implications

TGD people may undergo testosterone or estrogen treatment as part of their medical care. Hormone therapy is part of the standard of gender-affirming medical care. Yet, the effects of hormone therapy on the safety and effectiveness of other prescribed medications among TGD people have not been established (Cirrincione and Huang, 2021). Although experimental and animal model data suggest potential hormone-mediated changes in major drug handling proteins may exist for TGD adults undergoing hormone therapy, empirical clinical data for drug-hormone interactions are lacking due to TGD people facing significant barriers and stigma accessing healthcare and participating in clinical research.

Acknowledgement

RC is supported by the National Institute of Health Biological Mechanisms for Healthy Aging Training Grant under Award Number T32AG066574. LRC is supported by the National Institute of General Medical Sciences of the National Institutes of Health under Award Number K23GM147350. The opinions expressed in this manuscript are those of the authors and should not be interpreted as the position of the National Institutes of Health.

Abbreviations

TGD	transgender and gender diverse
VSC	variations in sex characteristics
CDC	Centers for Disease Control and Prevention
BRFSS	Behavior Risk Factor Surveillance System
EHR	electronic health record
WPATH	World Professional Association for Transgender Health

ATP	adenosine triphosphate
CYP	Cytochrome P450 enzymes
BCRP	Breast cancer resistance protein
OATP	Organic anion transporting polypeptides

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Take Home Messages

- TGD people are a diverse and increasingly visible population, and transgender medicine is a growing clinical field.
- Clinical pharmacological data from the general adult population suggest medication safety and efficacy may differ between cisgender women and cisgender men. Yet, the implications for TGD adults, and the role of sex steroids in these findings, are unknown.
- TGD populations are underrepresented in clinical research, and pharmacologic knowledge for TGD people undergoing hormone therapy is lacking.
- Increased pharmacological studies specific to TGD populations or enriched for TGD priority populations are warranted.

Table 1.

Typical agents recommended for TGD adults undergoing hormone therapy

Regimen	Typical Medication Classes	Prescribed Agents
Testosterone treatment		
	• Androgenic agent	• Testosterone (gel, compounded cream, or injection)
Estrogen treatment [a]		
	• Estrogenic agent • Antiandrogenic agent	• 17β-estradiol (tablet, patch, or injection) • Cyproterone acetate [b], spironolactone, or gonadotropin agonist (e.g., leuprolide acetate)

Table modified from Hembree et al., 2017 & Coleman et al., 2022. This table provides an overview of hormone therapies that may be recommended for TGD people. It not a comprehensive list of all agents that might be prescribed in clinical practice.

[a] Clinical providers may add-on oral progestogens (e.g., micronized progesterone) or 5α-reductase inhibitors (e.g., finasteride) to support a person's gender expression goals.

[b] Not approved in the United States.