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UIM: Updates in Gender-Affirming Care

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Disclosures

- AACE Board of Directors
- DynaMed Endocrine Section Editor
- Small amount of personally bought stock in Quest and Doximity

Objectives

- Review terminology, patient-centered history taking, and language that help us better care for an often medically underserved patient population
- Present updates to standards of care (“SOC 8”) as published by the World Professional Association for Transgender Health in 9/2022

WPATH SOC 8

- WPATH began as the Harry Benjamin International Gender Dysphoria Association in 1979
 - SOC 7 was published 2012
 - SOC 8 published 9/2022
- Evidence based, Delphi process, graded recommendations
- Explicit acknowledgement of dominance of perspectives in English (96% of published literature) and global north (99% of literature from Europe, North American, Australia, NZ)
- Understanding that many patients globally do not have access to multidisciplinary teams and DIY is common
- Chapters on Nonbinary (8), Eunuchs (9), Intersex (10)
- <https://www.wpath.org>
- <https://doi.org/10.1080/26895269.2022.2100644>

Terminology: SOC8 Appendix B Glossary

- **GENDER:** Depending on the context, gender may reference gender identity, gender expression, and/or social gender role, including understandings and expectations culturally tied to people who were assigned male or female at birth. Gender identities other than those of men and women (who can be either cisgender or transgender) include transgender, nonbinary, genderqueer, gender neutral, agender, gender fluid, and “third” gender, among others; many other genders are recognized around the world.
- **GENDER-AFFIRMATION SURGERY (GAS)** is used to describe surgery to change primary and/or secondary sex characteristics to affirm a person’s gender identity. **Replaces “SRS”**
- **GENDER EXPRESSION** refers to how a person enacts or expresses their gender in everyday life and within the context of their culture and society. Expression of gender through physical appearance may include dress, hairstyle, accessories, cosmetics, hormonal and surgical interventions as well as mannerisms, speech, behavioral patterns, and names. A person’s gender expression may or may not conform to a person’s gender identity.
- **GENDER IDENTITY** refers to a person’s deeply felt, internal, intrinsic sense of their own gender.
- **GENDER INCONGRUENCE** is a diagnostic term used in the ICD-11 that describes a person’s marked and persistent experience of an incompatibility between that person’s gender identity and the gender expected of them based on their birth-assigned sex.

Gender vs Sex

Replaces “SRS”

Additional Collaborative Definitions

- **SEX:** Sex is assigned at birth based on appearance of external genitalia. This assignment carries a set of assumptions regarding the underlying internal genital anatomy and the hormone-tissue interactions that will occur with aging. It is descriptive, not prescriptive.
- **SYNCHRONIZATION:** Gender, gender identity, gender expression, and biological sex are linked but may not be congruent.
- **GENDER DIVERSE:** Describes individuals with presentations, behaviors, or identities incongruent with sex assigned at birth. Gender-diverse individuals may choose to self-label as transgender, nonbinary, genderqueer, gender fluid, gender creative, gender independent, agender, intergender, ambigender, and non-cisgender (<https://thegenderbook.com>).

Work with Selma Witchel, MD (DOP, Division of Pediatric Endocrinology); Victoria Grieve, PharmD (U of Pitt School of Pharmacy); Janet Leung, MD (DOM, Division of Endocrinology); Bianca Pinto, MD (DOP, Division of Pediatric Endocrinology); Alicyn Simpson (DOP, Division of Adolescent & Young Adult Medicine); Carol Vetterly, PharmD (UPMC CHP, Director of Pharmacy)

Terminology: Nonbinary (Chapter 8)

- Spectrum of gender is not always linear; not all are comfortable with being under “transgender” umbrella (e.g. LGBTQIA2S+)
- Predominantly associated with global north contexts, may/may not encompass indigenous and non-Western genders
- Bigender, agender or neutrois, polygender, demiboy, demigirl, genderfluid, genderqueer
- Pronouns vary: he/him, she/her, they/them, e/em/eir, ze/zir/hir, er/ers/erself
- Can feel even more marginalized and delay care more than binary transgender patients

Statements of Recommendations

8.1- We recommend health care professionals provide nonbinary people with individualized assessment and treatment that affirms their experience of gender.

8.2- We recommend health care professionals consider gender-affirming medical interventions (hormonal treatment or surgery) for nonbinary people in the absence of “social gender transition.”

8.3- We recommend health care professionals consider gender-affirming surgical interventions in the absence of hormonal treatment, unless hormone therapy is required to achieve the desired surgical result.

8.4- We recommend health care professionals provide information to nonbinary people about the effects of hormonal therapies/surgery on future fertility and discuss the options for fertility preservation prior to starting hormonal treatment or undergoing surgery.



Identity Exercise

- Think about three identities that you would use to describe yourself
- For me: endocrinologist, engineer, cook/baker
 - Gender is not one of my top 3 identities and may not be yours
 - But what happens if someone challenges your identity



In the office: Beginning your visit

- Creating a safe space
 - For ALL patients: “Hi, I’m Dr. X, I’m an endocrinologist, and my pronouns are she/her. How would you like to be addressed?”
 - Even SAYING you have pronouns help patients understand you are more open to a non cis-norm
 - Consider changing your template/refresh once you update SOGI in EMR

In the office: Writing your note

- Avoid assuming pronouns based on gender expression
- Avoid assuming legal names are patient's chosen names
- Avoid assuming binary gender identification/affirmation goals
- Avoid gendered honorifics like Mr/Ms/Mrs (unless specifically requested by patient)
- **“Transgender”** should always be used as adjective (as in “trans people”) and never as nouns or verbs

Evolving Standard of Care and Practices

	WPATH SOC7 2012
Terminology	Transsexual, Transgender, Gender Nonconforming
For GAHT	Informed consent, “persistent and well- documented”
For surgery	1 referral for top (prefer 1 year E2 for cosmetic outcome); Genital surgery: 2 referrals + 1 year lived experience and consider 1 yr GAHT
Evidence/ Length	Expert Consensus 72 pg of recs; 21 pg of references (total 120)

Medical Homes

- Primary care remains medical home
- Many will be referred to endocrinologists (or out to Planned Parenthood, etc) when they want medical hormone therapy, however:
 - Gender affirmation does not REQUIRE hormones nor surgery nor gender expression
 - PCP's can absolutely provide gender affirming hormone therapy – diagnose/initiate/continue
 - Watch out for non-standard of care practices (excessive hormones, etc)
- As endo, I'm getting more patients seeking information
- Bonus:
 - Smoking is not a hard contraindication (but counsel!)
 - Don't be afraid of appropriately dosed hormones!

SOC 8: Diagnosis

Statements of Recommendations

5.1- We recommend health care professionals assessing transgender and gender diverse adults for physical treatments:

5.1.a- Are licensed by their statutory body and hold, at a minimum, a master's degree or equivalent training in a clinical field relevant to this role and granted by a nationally accredited statutory institution.

5.1.b- For countries requiring a diagnosis for access to care, the health care professional should be competent using the latest edition of the World Health Organization's International Classification of Diseases (ICD) for diagnosis. In countries that have not implemented the latest ICD, other taxonomies may be used; efforts should be undertaken to utilize the latest ICD as soon as practicable.

5.1.c- Are able to identify co-existing mental health or other psychosocial concerns and distinguish these from gender dysphoria, incongruence, and diversity.

5.1.d- Are able to assess capacity to consent for treatment.

5.1.e- Have experience or be qualified to assess clinical aspects of gender dysphoria, incongruence, and diversity.

5.1.f- Undergo continuing education in health care relating to gender dysphoria, incongruence, and diversity.

5.2- We suggest health care professionals assessing transgender and gender diverse adults seeking gender-affirming treatment liaise with professionals from different disciplines within the field of transgender health for consultation and referral, if required.

SOC 8: Diagnosis (continued)

The following recommendations are made regarding the requirements for gender-affirming medical and surgical treatment (all should be met):

5.3- We recommend health care professionals assessing transgender and gender diverse adults for gender-affirming medical and surgical treatment:

5.3.a- Only recommend gender-affirming medical treatment requested by a TGD person when the experience of gender incongruence is **marked and sustained**.

5.3.b- Ensure **fulfillment of diagnostic criteria** prior to initiating gender-affirming treatments in regions where a diagnosis is necessary to access health care.

5.3.c- Identify and exclude other possible causes of apparent gender incongruence prior to the initiation of gender-affirming treatments.

5.3.d- Ensure that any mental health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed, before a decision is made regarding treatment.

5.3.e- Ensure any physical health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed, before a decision is made regarding treatment.

5.3.f- Assess the capacity to consent for the specific physical treatment prior to the initiation of this treatment.

5.3.g- Assess the capacity of the gender diverse and transgender adult to understand the effect of gender-affirming treatment on reproduction and explore reproductive options with the individual prior to the initiation of gender-affirming treatment.

5.4- We suggest, as part of the assessment for gender-affirming hormonal or surgical treatment, professionals who have competencies in the assessment of transgender and gender diverse people wishing gender-related medical treatment **consider the role of social transition together with the individual**.

5.5- We recommend transgender and gender diverse adults who fulfill the criteria for gender-affirming medical and surgical treatment require a **single opinion** for the initiation of this treatment from a professional who has competencies in the assessment of transgender and gender diverse people wishing gender-related medical and surgical treatment.

5.6- We suggest health care professionals assessing transgender and gender diverse people seeking gonadectomy consider a minimum of **6 months of hormone** therapy as appropriate to the TGD person's gender goals before the TGD person undergoes irreversible surgical intervention (unless hormones are not clinically indicated for the individual).

5.7- We recommend health care professionals assessing adults who wish to detransition and seek gender-related hormone intervention, surgical intervention, or both, utilize a comprehensive multidisciplinary assessment that will include additional viewpoints from experienced health care professional in transgender health and that considers, together with the individual, the role of social transition as part of the assessment process.

DSM 5: Diagnosis

- The DSM-5-TR defines gender dysphoria in adolescents and adults as a marked incongruence between one's experienced/expressed gender and their assigned gender, lasting **at least 6 months, as manifested by at least two** of the following:
- A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
- A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
- A strong desire for the primary and/or secondary sex characteristics of the other gender
- A strong desire to be of the other gender (or some alternative gender different from one's assigned gender)
- A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)
- A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)

ICD 10: Definition

F64 Gender identity disorders

F64.0 Transsexualism

A desire to live and be accepted as a member of the opposite sex, usually accompanied by a sense of discomfort with, or inappropriateness of, one's anatomic sex, and a wish to have surgery and hormonal treatment to make one's body as congruent as possible with one's preferred sex.

F64.1 Dual role transvestism

The wearing of clothes of the opposite sex for part of the individual's existence in order to enjoy the temporary experience of membership of the opposite sex, but without any desire for a more permanent sex change or associated surgical reassignment, and without sexual excitement accompanying the cross-dressing.

Gender identity disorder of adolescence or adulthood, nontranssexual type

Excl.: fetishistic transvestism ([F65.1](#))

F64.2 Gender identity disorder of childhood

A disorder, usually first manifest during early childhood (and always well before puberty), characterized by a persistent and intense distress about assigned sex, together with a desire to be (or insistence that one is) of the other sex. There is a persistent preoccupation with the dress and activities of the opposite sex and repudiation of the individual's own sex. The diagnosis requires a profound disturbance of the normal gender identity; mere tomboyishness in girls or girlish behaviour in boys is not sufficient. Gender identity disorders in individuals who have reached or are entering puberty should not be classified here but in F66.-.

Excl.: egodystonic sexual orientation ([F66.1](#))
sexual maturation disorder ([F66.0](#))

F64.8 Other gender identity disorders

F64.9 Gender identity disorder, unspecified

Gender-role disorder NOS

<https://icd.who.int/browse10/2016/en#/F64.2>




ICD 11: Definition

Foundation URI : <http://id.who.int/icd/entity/90875286>

HA60 Gender incongruence of adolescence or adulthood

All ancestors up to top

- 17 Conditions related to sexual health
 - Gender incongruence
 - HA60 Gender incongruence of adolescence or adulthood

Hide ancestors 

Description

Gender Incongruence of Adolescence and Adulthood is characterised by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other health care services to make the individual's body align, as much as desired and to the extent possible, with the experienced gender. The diagnosis cannot be assigned prior the onset of puberty. Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis.

Exclusions

- Paraphilic disorders (6D30-6D3Z)

SOC 8: Criteria for GAHT

- a. Gender incongruence is marked and sustained;
- b. Meets diagnostic criteria for gender incongruence prior to gender-affirming hormone treatment in regions where a diagnosis is necessary to access health care;
- c. Demonstrates capacity to consent for the specific gender-affirming hormone treatment;
- d. Other possible causes of apparent gender incongruence have been identified and excluded;
- e. Mental health and physical conditions that could negatively impact the outcome of treatment have been assessed, with risks and benefits discussed;
- f. Understands the effect of gender-affirming hormone treatment on reproduction and they have explored reproductive options.

History Taking

- 15.1 - ... Past and present use of hormones, gonadal surgeries, as well as the presence of traditional [CAD and CVD] RF
 - Would ask about binding/tucking practices as well
- 15.3- We recommend health care professionals tailor sex-based risk calculators used for assessing medical conditions to the needs of transgender and gender diverse people, taking into consideration the length of hormone use, dosing, serum hormone levels, current age, and the age at which hormone therapy was initiated.
- 15.4- We recommend health care professionals counsel transgender and gender diverse people about their tobacco use and advise tobacco/nicotine abstinence prior to gender-affirming surgery.
- 15.5- We recommend health care professionals discuss and address aging-related psychological, medical, and social concerns with transgender and gender diverse people

History Taking

- Breast/cervical guideline screening per local guidelines
- 15.12- ... presence of traditional osteoporosis risk factors to assess the optimal age and necessity for osteoporosis screening.
- 15.13- ... discuss bone health with transgender and gender diverse people including the need for active weight bearing exercise, healthy diet, calcium, and vitamin D supplementation.

EPIC: organ inventory (currently not linked to decision making tools)

Sexual Orientation and Gender Identity SmartForm

Patient pronouns:

she/her/hers

he/him/his

they/them/theirs

patient's name

decline to answer

unknown

not listed

Affirmation steps patient has taken, if any:

presentation aligned with gender identity

preferred name aligned with gender identity

legal name aligned with gender identity

legal s

medical or surgical interventions

Patient's future affirmation plans, if any:



Insert SmartText



100%

In your notes, document patient-preferred terms: chest vs breast; chestfeeding vs breastfeeding; cycles or bleed vs period, etc

Organ Inventory

Organs the patient currently has:

+ breasts	—
+ cervix	—
ovaries	—
uterus	—
+ vagina	—
+ penis	—
+ prostate	—
+ testes	—

Organs present at birth or expected at birth to develop:

+ breasts	—
+ cervix	—
+ ovaries	—
+ uterus	—
+ vagina	—
+ penis	—
+ prostate	—
+ testes	—

Organs surgically enhanced or constructed:

+ breasts	—
+ vagina	—
+ penis	—

Organs hormonally enhanced or developed:

+ breasts	—
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SOC 8: Informed Consent (Chapter 5)

The following recommendations are made regarding the requirements for gender-affirming medical and surgical treatment (all should be met):

- 5.3.a- Only recommend gender-affirming medical treatment requested by a TGD person when the experience of gender incongruence is marked and sustained.
- 5.3.b- Ensure fulfillment of diagnostic criteria prior to initiating gender-affirming treatments in regions where a diagnosis is necessary to access health care.
- 5.3.c- Identify and exclude other possible causes of apparent gender incongruence prior to the initiation of gender-affirming treatments.
- 5.3.d- Ensure that any mental health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed, before a decision is made regarding treatment.
- 5.3.e- Ensure any physical health conditions that could negatively impact the outcome of gender-affirming medical treatments are assessed, with risks and benefits discussed, before a decision is made regarding treatment.
- 5.3.f- Assess the capacity to consent for the specific physical treatment prior to the initiation of this treatment.

SOC 8: Informed Consent (Chapter 5)

- 5.3.g- Assess the capacity of the gender diverse and transgender adult to understand the effect of gender-affirming treatment on **reproduction** and explore reproductive options with the individual prior to the initiation of gender-affirming treatment
- 5.5- We recommend transgender and gender diverse adults who fulfill the criteria for gender-affirming **medical and surgical treatment require a single opinion** for the initiation of this treatment from a professional who has competencies in the assessment of transgender and gender diverse people wishing gender-related medical and surgical treatment.
- 5.6- We suggest health care professionals assessing transgender and gender diverse people **seeking gonadectomy** consider **a minimum of 6 months** of hormone therapy as appropriate to the TGD person's gender goals before the TGD person undergoes irreversible surgical intervention (unless hormones are not clinically indicated for the individual).

Timeline of Changes:

- Set expectations re: timeline
- Set expectations on what can be achieved

Table 1. Expected time course of physical changes in response to gender-affirming hormone therapy

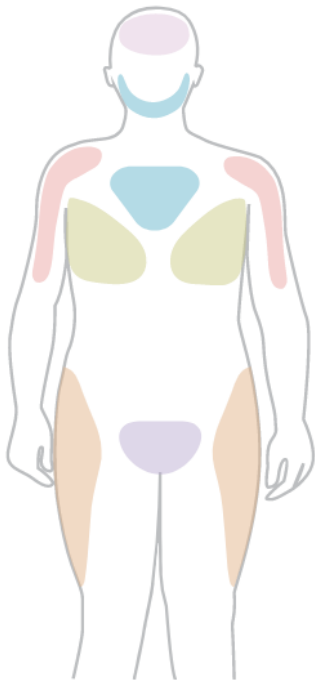
Testosterone Based Regimen		
Effect	Onset	Maximum
Skin Oiliness/acne	1–6 months	1–2 years
Facial/body hair growth	6–12 months	>5 years
Scalp hair loss	6–12 months	>5 years
Increased muscle mass/ strength	6–12 months	2–5 years
Fat redistribution	1–6 months	2–5 years
Cessation of menses	1–6 months	1–2 years
Clitoral enlargement	1–6 months	1–2 years
Vaginal atrophy	1–6 months	1–2 years
Deepening of voice	1–6 months	1–2 years
Estrogen and testosterone-lowering based regimens		
Effect	Onset	Maximum
Redistribution of body fat	3–6 months	2–5 years
Decrease in muscle mass and strength	3–6 months	1–2 years
Softening of skin/ decreased oiliness	3–6 months	Unknown
Decreased sexual desire	1–3 months	Unknown
Decreased spontaneous erections	1–3 months	3–6 months
Decreased sperm production	Unknown	2 years
Breast growth	3–6 months	2–5 years
Decreased testicular volume	3–6 months	Variable
Decreased terminal hair growth	6–12 months	> 3 years
Increased scalp hair	Variable	Variable
Voice changes	None	

Adapted from Hembree et al., 2017.

Timeline of Changes: Visualization

Effects and expected time course

Hover over the coloured regions to view expected information on the reversibility, onset^a and maximum effects^a of physical changes



PHYSICAL EFFECTS	REVERSIBILITY	TIME COURSE (YEARS)					
		0	1	2	3	4	5
Softening of skin/decreased oiliness	Reversible	[Progressive bar from 0 to 5 years]					
Body fat redistribution	Reversible/Variable	[Progressive bar from 0 to 3 years]					
Decreased muscle mass/strength	Reversible	[Progressive bar from 0 to 2 years]					
Thinned/slowed growth of body/facial hair	Reversible	[Progressive bar from 1 to 5 years]					
Scalp hair loss (loss stops, no regrowth)	Reversible	[Progressive bar from 0 to 5 years]					
Breast growth	Irreversible	[Progressive bar from 0 to 2 years]					
Decreased testicular volume	Variable	[Progressive bar from 0 to 3 years]					
Decreased libido	Variable	[Progressive bar from 0 to 1 year]					
Decreased spontaneous erections	Variable	[Progressive bar from 0 to 1 year]					
Decreased sperm production	Variable	[Progressive bar from 0 to 5 years]					
Reduced erectile function	Variable	[Progressive bar from 0 to 5 years]					

<https://www.rainbowhealthontario.ca/TransHealthGuide/gp-femht.html>

Treatment Options

- Use transdermal E for women >40, smokers
- Subq testosterone works as well as IM and is patient preferred (PMID: 28379417; review at 34698352)

Table 4. Hormone regimens in transgender and gender diverse adults*

Estrogen-based regimen (Transfeminine)

Estrogen

Oral or sublingual

Estradiol 2.0-6.0 mg/day

Transdermal

Estradiol transdermal patch 0.025-0.2 mg/day

Estradiol gel various ‡ daily to skin

Parenteral

Estradiol valerate or cypionate 5-30 mg IM every 2 weeks
2-10 IM every week

Anti-Androgens

Spirololactone 100–300 mg/day

Cyproterone acetate 10 mg/day**

GnRH agonist 3.75–7.50 mg SQ/IM monthly

GnRH agonist depot formulation 11.25/22.5 mg SQ/IM 3/6
monthly

‡ Amount applied varies to formulation and strength

Testosterone-Based Regimen (Transmasculine)

Transgender males

Testosterone

Parenteral

Testosterone enanthate/
cypionate 50–100 IM/SQ weekly or
100–200 IM every 2 weeks

Testosterone undecanoate 1000 mg IM every 12 weeks or
750 mg IM every 10 weeks

Transdermal testosterone

Testosterone gel 50-100 mg/day

Testosterone transdermal patch 2.5–7.5 mg/day

*Doses are titrated up or down until sex steroid hormone levels are in the therapeutic range. Hormone regimens do not reflect all formulations that are available in all pharmacies throughout the world. Hormone regimens may have to be adapted to what is available in local pharmacies.

**Kuijpers et al (2021).

Anti-Androgens

- I personally love spiro (fellowship research/exposure to negative effects of mineralocorticoid-receptor activation)
- Patient forums have a lot of negative preconceptions re: spiro – “spiro belly” . Other anti-androgens include dutasteride, finasteride. I do not recommend bicalutamide

Alternatives to Spiro	MoA	T effects
Finasteride	5 alpha reductase inhibitor: blocks T->DHT	Increases testosterone levels (15-25%)
Dutasteride	Dual 5-reductase inhibitor: blocks T->DHT	Increases T levels (20%)
Bicalutamide	Selective AR antagonist; reported fulminant liver failure	Increases T and E levels 1.5-2.5x if intact testes
Cyproterone (not available in US)	Progestogen and AR antagonist	Decreases T 50-70%
GnRH agonist	Central suppression	Can fully suppress T

Hormone Monitoring Recs (adapted from endo society)

Table 5. Hormone monitoring of transgender and gender diverse people receiving gender-affirming hormone therapy (Adapted from the Endocrine Society Guidelines)

Transgender male or trans masculine (including gender diverse/nonbinary) individuals

1. Evaluate patient approximately every 3 months (with dose changes) in the first year and 1 to 2 times per year thereafter to monitor for appropriate physical changes in response to testosterone.
2. Measure serum total testosterone every 3 months (with dose changes) until levels are at goal
 - a. For parenteral testosterone, the serum total testosterone should be measured midway between injections. The target level is 400-700 ng/dL. Alternatively, measure peak and trough peaks to ensure levels remain in the range of reference men.
 - b. For parenteral testosterone undecanoate, testosterone should be measured just before injection. If the level is < 400 ng/dL, adjust the dosing interval.
 - c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 week of daily application (at least 2 hours after application of product).
3. Measure hematocrit or hemoglobin concentrations at baseline and approximately 3 months (with dose changes) for the first year and then one to two times a year.

Transgender Female or trans feminine (including gender diverse/nonbinary) individuals

1. Evaluate patient approximately every 3 months (with dose changes) in the first year and one to two times per year thereafter to monitor for appropriate physical changes in response to estrogen.
 - a. Serum testosterone levels should be less than 50 ng/dL.
 - b. Serum estradiol should be in the range of 100-200 pg/mL.
 2. For individuals receiving spironolactone, serum electrolytes, in particular potassium, and kidney function, in particular creatinine, should be monitored.
 3. Follow primary care screening per primary care chapter recommendations
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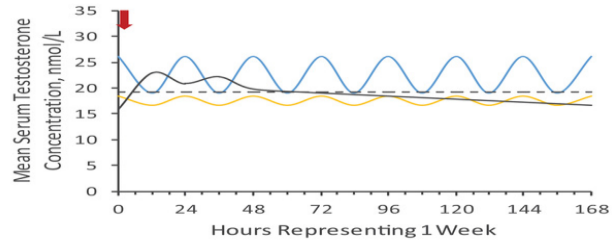
- Lipids for patients on testosterone removed, now states per PCP

Testosterone dosing and options same as in cis-gender men

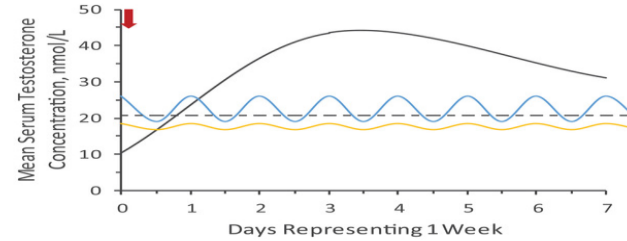
- Topical qAM (lowest effect on Hct)
- Transdermal no longer on market
- IM testosterone qweek
- Subq testosterone qweek
 - In transgender men: Spratt DS. J Clin Endocrinol Metab 2017 <https://doi.org/10.1210/jc.2017-00359>
 - Figueiredo MG, Gagliano-Juca T, Basaria S. J Clin Endocrinol Metab. 2022 Mar; 107(3): 614–626. PMID: [34698352](https://pubmed.ncbi.nlm.nih.gov/34698352/)
- Lacking long-term data even in cis-gender males:
 - Oral testosterone undecanoate (Jatenzo), testosterone undecanoate (Aveed, q10 weeks), pellets

Pharmacokinetics of testosterone tx vs diurnal variation

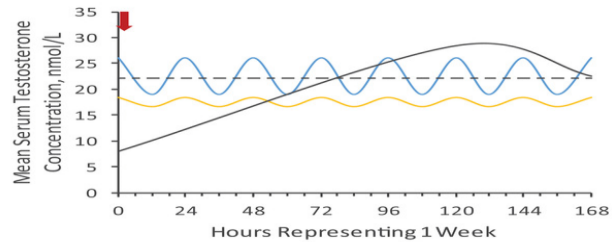
A. Subcutaneous



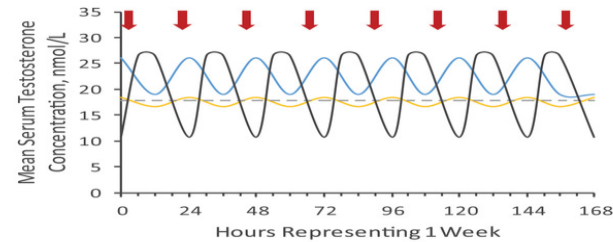
B. Intramuscular



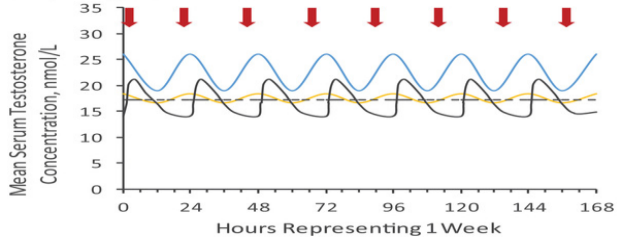
C. Subdermal pellets



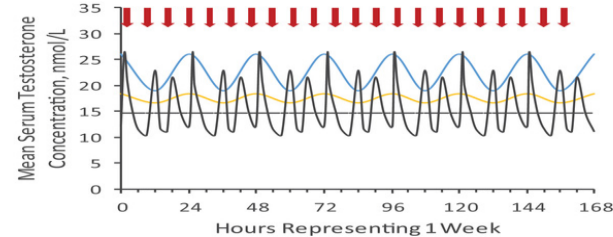
D. Transdermal patch



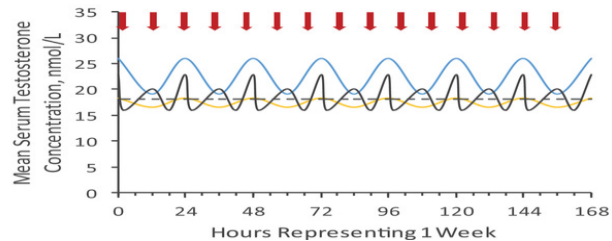
E. Topical gels and solutions



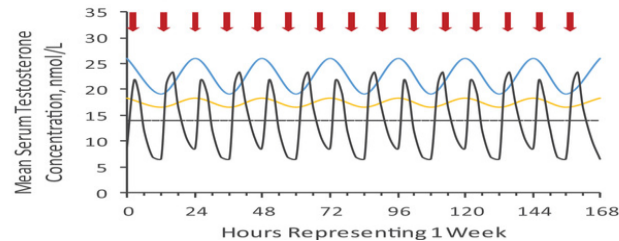
F. Nasal gel



G. Buccal mucoadhesives



H. Oral capsules



Blue = physiologic age 23-28

Yellow = physiologic age 58-82

Black = medication

Testosterone: Labs -- Harmonization and LC-MS/MS

- 1133 laboratories using 14 different assays measured TT concentrations using the same quality control sample from a **single hypogonadal man**, the measured values ranged from 45 to 365 ng/dL (1.6 to 12.7 nmol/L)

Bhasin. JCEM 2018; 103(5): 1715-1744

- Starting in 2010, attempts to harmonize reference range developed, with move to more accurate testosterone by LC-MS/MS for diagnosing hypogonadism
- “Harmonized normal range in a healthy nonobese population of European and American men, 19 to 39 years, is 264 to 916 ng/dL”

Travison TG et al. J Clin Endocrinol Metab. 2017 Apr 1; 102(4): 1161–1173.

Testosterone: when to measure

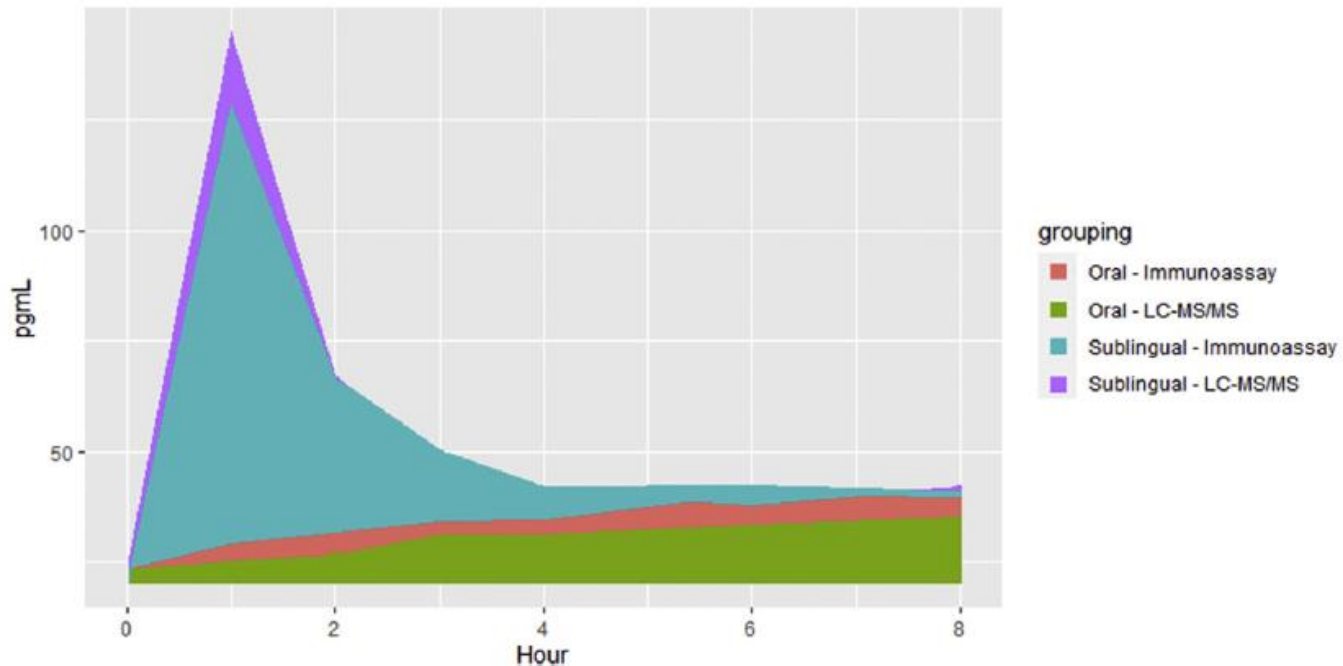
- Monitor labs 3 months after adjustments – target serum T in mid-normal range (also measure Hct)
- No long need to measure LFTs if physiologic dosing
Stangl et al. Eur J Endocrinol . 2021 Apr;184(4):513-520
- Consider **midcycle** vs trough vs peak
- Based on patient symptoms (does patient feel peaks and valleys? Consider dosing frequency)

Estradiol: when to measure? At steady state, after the peak

- Estradiol patch (BIW-weekly): peak 8-12 hours, $t_{1/2}$ 24 hour
- Estradiol tablet oral: peak 2-4 hours, $t_{1/2}$ 12 hour
 - Sublingual peaks at 1-2 hours (Doll et al. Endocr Pract . 2022 Mar;28(3):237-242)
- Estradiol gel/spray (in Europe): peak 4-6 hours, $t_{1/2}$ 36 hours
- Estradiol IM: peak 2-4 hours, $t_{1/2}$ 7-14 days
- (Estradiol subq)

Estradiol: sublingual or oral

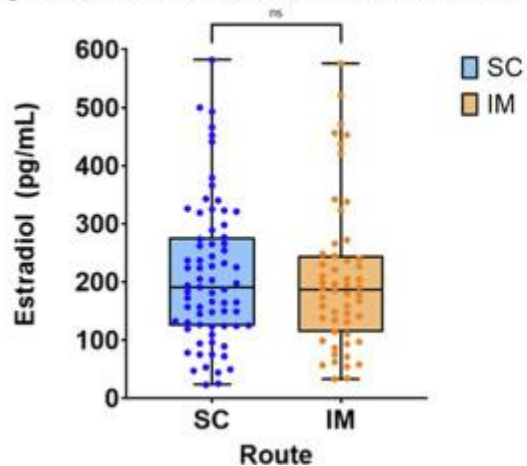
- n = 10 (8 white, 1 Black, 1 Hispanic)
- New to GAHT; 1 week washout. Mean age 24 +/- 8; mean BMI 33
- 1 mg E2 as oral vs SL, monitored to 8 hours (oral E2 $t_{1/2}$ = 12-20 hours)
- Immunoassay vs LC-MS/MS – max difference 10-20% at the low end



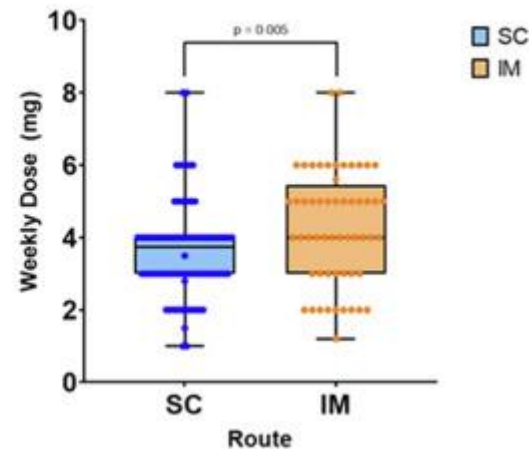
Estradiol IM vs Subq

- Mayo clinic, n= 74 SC, n = 56 IM, retrospective cohort on EC or EV, from 2011-2022
- Weekly subq 3.75 mg (IQR 3-4) vs weekly IM 4 mg (IQ 3-5.15), $p = 0.005$, but estradiol and testosterone levels same ($p = 0.69$, $p = 0.9$)
- Better liked by patients

A Achieved Serum Estradiol Concentrations



B Weekly Dose of Parenteral Estradiol



Safety/AE

Table 2. Risks associated with gender affirming hormone therapy (bolded items are clinically significant) (Updated from SOC-7)

RISK LEVEL	Estrogen-based regimens	Testosterone-based regimens
Likely increased risk	Venous Thromboembolism Infertility Hyperkalemia ^s Hypertriglyceridemia Weight Gain	Polycythemia Infertility Acne Androgenic Alopecia Hypertension Sleep Apnea Weight Gain Decreased HDL Cholesterol and increased LDL Cholesterol
Likely increased risk with presence of additional risk factors	Cardiovascular Disease Cerebrovascular Disease Meningioma ^c Polyuria/Dehydration ^s Cholelithiasis	Cardiovascular Disease Hypertriglyceridemia
Possible increased risk	Hypertension Erectile Dysfunction	
Possible increased risk with presence of additional risk factors	Type 2 Diabetes Low Bone Mass/ Osteoporosis Hyperprolactinemia	Type 2 Diabetes Cardiovascular Disease
No increased risk or inconclusive	Breast and Prostate Cancer	Low Bone Mass/ Osteoporosis Breast, Cervical, Ovarian, Uterine Cancer

^ccyproterone-based regimen

^sspironolactone-based regimen

SOC 8

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen

Very high risk of adverse outcomes:

- Thromboembolic disease

Moderate risk of adverse outcomes:

- Macroprolactinoma
- Breast cancer
- Coronary artery disease
- Cerebrovascular disease
- Cholelithiasis
- Hypertriglyceridemia

Endo Society

Transgender male: testosterone

Very high risk of adverse outcomes:

- Erythrocytosis (hematocrit > 50%)

Moderate risk of adverse outcomes:

- Severe liver dysfunction (transaminases > threefold upper limit)
- Coronary artery disease
- Cerebrovascular disease
- Hypertension
- Breast or uterine cancer



Outcomes (non-randomized, various HRT regimens)

	Transwomen	Transmen
QoL	Mixed to ↑	Mixed to ↑
Depression	↓ sx	– to ↓ sx
VTE	4-5x vs both cismen and ciswomen	No Δ
MI	2-3x vs ciswomen, similar to cis-men	↑3.7-4x ciswomen at >3 yr, ~ cismen In older population, ≤ 2x cis-men?
CVA	2x vs both references	No difference
Bone	Stable to ↑ at L-spine	Stable at 1-2 yrs
Mortality	↑ (driven by CVD, lung cancer, HIV, suicide)	↑ vs cis-women, similar to cis-men, (driven by non-natural causes)

Kotamarti J Sex Med 2021. PMID 34140253

De Blok. Lancet Diabetes Endocrinol 2021. PMID 23381559

Alzaharni Circ Cardiovasc Qual Outcomes 2019. PMID: 30950651



Hormones and bone health

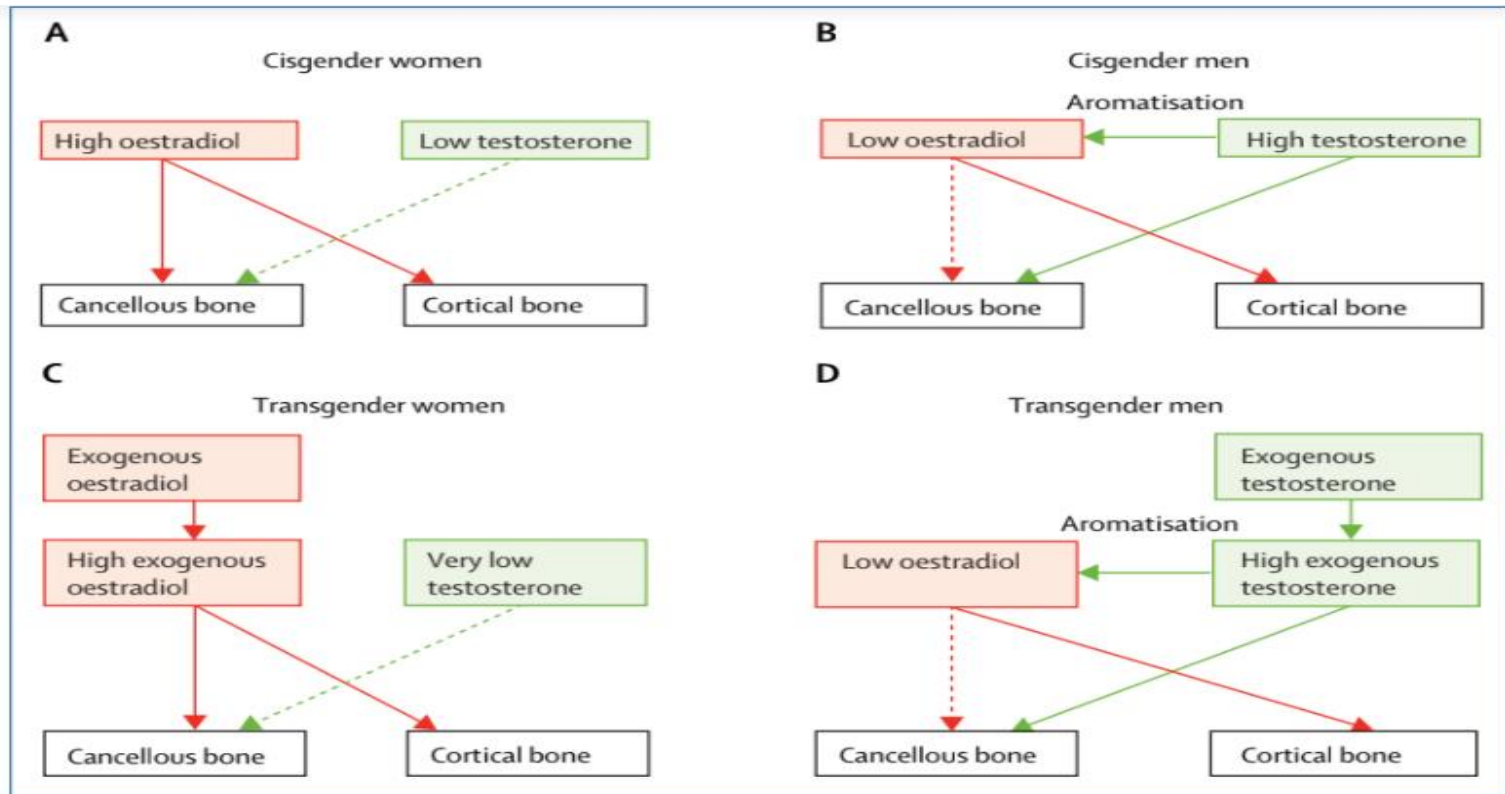


Figure: Working model for sex steroid action on cancellous versus cortical bone in cis gender women (A) and cisgender men (B) and the analogous models in transgender women (C) and transgender men (D) placing the models in the context of exogenous hormone therapies. Red indicates oestrogen effects and green indicates testosterone effects, with dashed lines showing relatively small effects.

Cortical bone = peripheral
Cancellous = trabecular = spine

Khosla S et al. Lancet Diabetes Endocrinol 2019
 Dec;7(12):893-895.

Progesterone (hiding in 12.15)

- With the exception of cyproterone acetate (note this is not approved for use in the US because of concerns of potential hepatotoxicity), **the use of progestins in hormone therapy regimens remains controversial.** To date, there have been no quality studies evaluating the role of progesterones in hormone therapy for transgender patients.
- We are aware some practitioners who prescribe progestins, including micronized progesterone, are under the impression there may be improvements in breast and/or areolar development, mood, libido, and overall shape for those seeking it along with other benefits yet to be demonstrated (Deutsch, 2016a; Wierckx, van Caenegem et al., 2014). However, these improvements remain anecdotal, and there are no quality data to support such progestin use. **An attempted systematic review we commissioned for this version of the SOC failed to identify enough data to make a recommendation in favor of any progestins.**
- Instead, existing data suggest harm is associated with extended progestin exposure (Safer, 2021).... Potential adverse effects of progestins include weight gain, depression, and lipid changes.
- If, after a discussion of the risks and benefits of progesterone treatment [micronized progesterone], there is a collaborative decision to begin a trial of progesterone therapy, the prescriber should evaluate the patient within a year to review the patient's response to this treatment.

Gender Affirming Surgeries

- No increased VTE risk in continuing HRT through surgery vs stopping x 1-4 weeks pre/post
 - Kozato A et al. JCEM 2021 Mar 25;106(4):e1586-e1590. doi: 10.1210/clinem/dgaa966.
- Ask patients about what they mean by GAS to help plan screenings/physical exams:
 - simple orchiectomy, TAH-BSO? Vaginoplasty, phalloplasty?
 - mastectomy -- check to see if total or if subtotal (and thus still recommended breast exams)

Fertility and Sexual Health (Chapter 16, 17)

- Ask about sexual behaviors, HIV/STI screening/need for PREP, counsel on body changes
- Document fertility desires and continue to readdress
- Ask about reproductive organs in sex partners and about contraception
- Bank sperm/eggs, but with hormone discontinuation, fertility can return for many if not s/p surgery

- Nice review at PMID: 31380227
 - E2 is NOT contraception in sperm producing people – up to 24% still made sperm
 - Testosterone is not contraception in people with uteruses -- unintentional pregnancies

Goals of GAHT monitoring

- Evaluate for attainment of patient goals and consider surgical/SLP/electrolysis/laser referral
- Evaluate for side effects and safety
- For hormone labs: evaluate dosing for peaks/valleys/steady state
- Consider formulation
 - Estradiol:
 - For higher risk CAD/CVD/VTE, >40-45 yo: transdermal preferred
 - Not much data on IM (or), oral vs sublingual
 - Testosterone – transdermal, ?undeconate has lower Hct?

Bonus: What to do in older adults?

- WPATH SOC 8, Chapter 12
- “While GAHT is customized to meet the individual needs of the TGD person, typically hormone levels are maintained at a concentration sufficient to support good bone health and are not supraphysiologic (Hembree et al., 2017; Rosen et al., 2019).... It is not known if doses of GAHT should be reduced in older TGD people.”
- In patients who still have testes, long term E2 needed to suppress androgen. What about those s/p orchiectomy? How much E2?
- In transgender men, do we decrease T doses slightly to mimic natural aging?

Final Thoughts

- Active field of research and growth – more and more evidence!
- Informed consent for all interventions (just like in all of our other medical conditions)
- Discuss and document fertility and contraception
- Manage CAD/CVD, bone, VTE risk factors
- Counsel on surger(ies) and implications
- Consider referrals for SLP, skin, mental health
- Continue stable GAHT whenever possible and desired by patient
- Continue age/gender/hormone-based f/u for cancer screenings, etc (I recommend chose the more conservative option until more data)
- Consider what to do as patients age