Medical care of gender expansive patients

Gender Care in the Heartland 2023

Alex Dworak MD

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Objectives

- Disclosures
- Brief review of terminology
- Informed consent model
- Review medical and nonmedical gender affirmation
- Briefly review surgical gender affirmation
- Discuss fertility options
- Provide resources for further learning and slides/links for reference
- Discuss current regulations as per 2023 NE LB574 on youth care

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Disclosures

- I have no financial conflicts of interest to disclose.
- I will be discussing off label use of medications.
- I am a provider of gender care and have testified and advocated repeatedly in 2023 to the Nebraska State Senate in that capacity.
- I will mention a local clinic to whom I refer patients, but with whom I have no formal or informal financial relationship of any kind.
- I have attended the Fenway/Harvard Advancing Excellence in Transgender care in Boston numerous times for my CME on this topic, most recently October 27-29 2023.
- I can be presumed to be actively restraining myself from a terrible impression of a Boston accent for the duration of this lecture.

A sign at the post office in Massachusetts.

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Medical gender affirmation

- Recall that all patients have unique goals and that not all trans and nonbinary people need or want medical or gender services
- All trans and nonbinary people need primary and preventive care (just like all cisgender people, aka literally everyone)
- Being welcoming is extremely important—thank you for your commitment to that!
- Not making your patient teach you how to care for them is also as it should be—thank you for your commitment to that too!

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Medical gender affirmation

- General categories of medical gender affirmation include:
- Estrogen prescribing, with or without testosterone blockade
- Testosterone prescribing, which inherently suppresses estrogen
- GnRH agonist therapy, to stop progression of puberty as well as to suppress testosterone in select cases
- Regulation of menses
- Primary care, screening, counseling on healthy behaviors, lab monitoring, and management of any concurrent health concerns with a focus on the patient's overall well being

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Brief review of definitions and terms

- Source: HRC https://www.hrc.org/resources/sexual-orientation-and-gender-identity-terminology-and-definitions
- **Sexual orientation:** An inherent or immutable enduring emotional, romantic or sexual attraction to other people. Note: an individual's sexual orientation is independent of their gender identity.
- **Gender identity:** One's innermost concept of self as male, female, a blend of both or neither – how individuals perceive themselves and what they call themselves. One's gender identity can be the same or different from their sex assigned at birth.

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Brief review of definitions and terms

- **Transgender:** An umbrella term for people whose gender identity and/or expression is different from cultural expectations based on the sex they were assigned at birth. Being transgender does not imply any specific sexual orientation. Therefore, transgender people may identify as straight, gay, lesbian, bisexual, etc.
- **Gender transition:** The process by which some people strive to more closely align their internal knowledge of gender with its outward appearance. Some people socially transition, whereby they might begin dressing, using names and pronouns and/or be socially recognized as another gender. Others undergo physical transitions in which they modify their bodies through medical interventions
- **Gender dysphoria:** Clinically significant distress caused when a person's assigned birth gender is not the same as the one with which they identify.

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Informed consent

- Best practice in all areas of medicine is to utilize informed consent, and gender care is no different
- For adults: Medical informed consent; I use written informed consent
  - Most patients have already done extensive reading and are not surprised with any of the information, but it is always good to offer time for questions and discussion
- For people under the age of majority in your state:
  - Written informed consent of the patient and any/all parents/legal guardians mandatory
- Letter of support needed for minors from a qualified mental health professional; also often requested by surgeons prior to operating
- Example forms at the end of the presentation

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Medical gender affirmation: Estrogen therapy

- Estrogen prescribing, with or without testosterone blockade
- Options include oral (PO), sublingual (SL), transdermal (TD) and injectable (intramuscular/IM and subcutaneous/SQ)
- No option is known to be superior to any other in terms of effects
- Target is usually average physiologic feminine range for your reference lab, plus/minus T blockade per patient goals. Do not go supratherapeutic.
- Treatment should be individualized:
  - Active patients or those with skin conditions may not do well with patch
  - Patients with needle phobias of course may prefer non-injectable options
  - Forgetful or overly busy patients may struggle with pill adherence just like anyone else

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Medical gender affirmation

- Data for subcutaneous administration was historically limited and mainly anecdotal
- 2023 study compared subQ vs IM at a tertiary care center
- Both were found to give equal levels, although further pharmacokinetic study warranted
- https://pubmed.ncbi.nlm.nih.gov/36868378/

Comparison of the Subcutaneous and Intramuscular Estradiol Regimens as Part of Gender-Affirming Hormone Therapy

Justine S Herndon [1], Arvind K Maheshwari [2], Todd B Nippoldt [3], Sara J Carlson [3], Caroline J Davidge-Pitts [3], Alice Y Chang [4]

Abstract

Objective: Gender-affirming hormone therapy guidelines describe the estradiol (E2) doses for intramuscular (IM), but not subcutaneous (SC), routes. The objective was to compare the SC and IM E2 doses and hormone levels in transgender and gender diverse individuals.

Methods: This is a retrospective cohort study at a single-site tertiary care referral center. Patients were transgender and gender diverse individuals who received injectable E2 with at least 2 E2 measurements. The main outcomes were the dose and serum hormone levels between the SC and IM routes.

Results: There were no statistically significant differences in age, body mass index, or antiandrogen use between patients on SC (n = 74) and those on IM (n = 56). The weekly doses of SC E2, 3.75 mg (IQR, 3-4 mg), were statistically significantly lower than those of IM E2, 4 mg (IQR, 3-5.15 mg) (P =.005); however, the E2 levels achieved were not significantly different (P =.69), and the testosterone levels were in the cisgender female range and not significantly different between routes (P =.92). Subgroup analysis demonstrated significantly higher doses in the IM group when the E2 and testosterone levels were >100 pg/mL and <50 ng/dL, respectively, with the presence of the gonads or use of antiandrogens. Multiple regression analysis demonstrated that the dose was significantly associated with the E2 levels after adjusting for injection route, body mass index, antiandrogen use, and gonadectomy status.

Conclusion: Both the SC and IM E2 achieve therapeutic E2 levels without a significant difference in the dose (3.75 vs 4 mg). SC may achieve therapeutic levels at lower doses than IM .

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Medical gender affirmation: Estrogen

- Estrogen prescribing: PO
- Estradiol is preferred (17-beta estradiol)
- Premarin was previously used and a rare patient may occasionally present for care still taking it and request to continue it, but it is not normally recommended over estradiol recommended due to mildly increased thrombogenicity
- Ethinyl estradiol, despite its widespread use for OCPs for cis women, has been shown to have over 8x higher risk of VTE when used for gender affirming care and should be actively avoided for this purpose

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Medical gender affirmation: Estrogen

- Transdermal estradiol
- Applied in the form of patches
- Advantage is avoidance of both first pass hepatic metabolism and also the peak/trough "roller coaster" effect that happens with IM injections (not all patients are bothered by that phenomenon, to be clear)
- Preferred option in
  - patients who are >age 45
  - Patients who smoke
  - Especially patients with prior history of VTE

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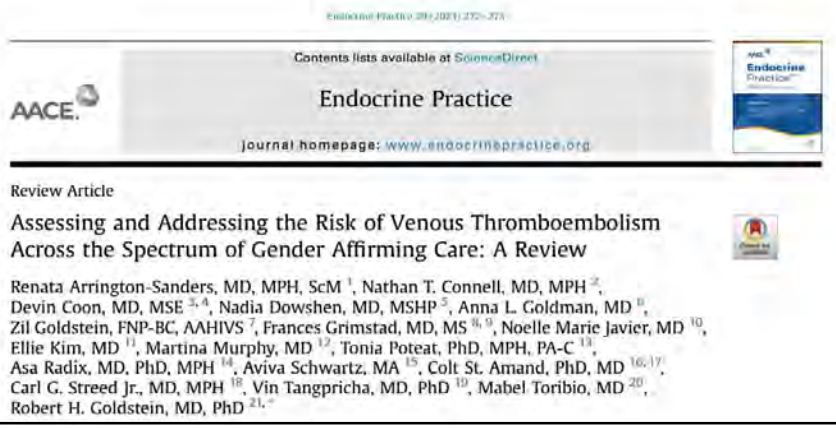
Medical gender affirmation: VTE risk with estrogen therapy

- Detailed review: https://www.endocrinepractice.org/article/S1530-891X(22)00898-9/fulltext



Contents lists available at ScienceDirect

Endocrine Practice

journal homepage: www.endocrinepractice.org

Review Article

Assessing and Addressing the Risk of Venous Thromboembolism Across the Spectrum of Gender Affirming Care: A Review

Renata Arrington-Sanders, MD, MPH, ScM [1], Nathan T. Connell, MD, MPH [2], Devin Coon, MD, MSE [3,4], Nadia Dowshen, MD, MSHP [5], Anna L. Goldman, MD [6], Zil Goldstein, FNP-BC, AAHIVS [7], Frances Grimstad, MD, MS [8,9], Noelle Marie Javier, MD [10], Ellie Kim, MD [11], Martina Murphy, MD [12], Tonia Poteat, PhD, MPH, PA-C [13], Asa Radix, MD, PhD, MPH [14], Aviva Schwartz, MA [15], Colt St. Amand, PhD, MD [16,17], Carl G. Streed Jr., MD, MPH [18], Vin Tangpricha, MD, PhD [19], Mabel Toribio, MD [20], Robert H. Goldstein, MD, PhD [21,*]

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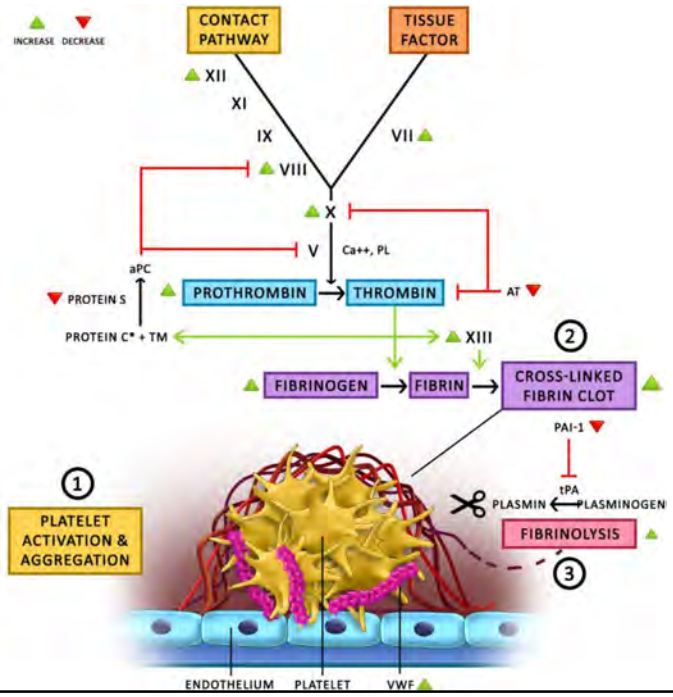
Estrogen and Thrombosis: a Bench to Bedside Review

Mouhamed Yazan Abou-Ismail, Divyaswathi Citla Sridhar, and Lalitha Nayak

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC734144



- This diagram demonstrates our current understanding of the effects of estrogen on hemostasis & thrombosis. 1) The exact effect of estrogen on platelet activation and aggregation remains unclear, with conflicting reports in the literature showing altered platelet behavior. Estrogen is known to increase VWF levels which plays a central role in platelet adhesion and activation. 2) Estrogen leads to increased thrombin generation and fibrin clot formation by increasing the levels of variable coagulation proteins (green arrowheads) and decreasing the levels of anticoagulant proteins (red arrowheads). 3) Conversely, estrogen has also been shown to be associated with increased fibrinolysis due to decreased PAI-1 levels, which does not seem to balance out the increase in coagulation. **Thus the net effect overall, has been shown to be prothrombotic.**
- aPC = activated Protein C
- AT = anti-thrombin
- PAI-1 = plasminogen activator inhibitor 1
- PL = phospholipid
- TM = thrombomodulin
- tPA = tissue plasminogen activator
- VWF = von Willebrand Factor

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Medical gender affirmation: Testosterone blockade

- For patients desiring binary feminine/estrogen dominant hormone profile:
- Spironolactone: Potassium sparing diuretic with antiandrogen properties
  - Used at higher doses than in HTN, CHF
  - Avoid if CKD or using other K+ sparing/raising meds like ACE/ARB
- Finasteride/Dutasteride: 5-alpha reductase inhibitors
  - Blocks activation to 5-DHT; will NOT change T levels on labs
- Leuprolide: Very effective with Rx estrogen added back; expense and IM need make it tertiary option for those on Rx estrogen

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Medical gender affirmation: Testosterone blockade

- Progesterone
  - Anecdotal reports of breast development assistance, improved libido
  - May lead to weight gain (can be affirming as increased breast and hip fat with estrogen gives more classically femme body contour), mood changes same as cis women. NOT a direct testosterone blocker, considered an adjunct which has hypothalamic-pituitary-gonadal axis inhibition properties
  - Minimal data, but minimal chance of harm; bioidentical micronized progesterone preferred over medroxyprogesterone acetate if chosen
- Bicalutamide
  - Nonsteroidal androgen antagonist approved for prostate cancer; NOT recommended due to rare but nonzero chance of fulminant hepatic failure
- Orchiectomy
  - Not recommended solely for this purpose and obviously permanent, but eliminates need for blockers if patient chooses it as part of overall affirmation

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Effects of estrogen gender treatment

- Breast development
- Decreased (not absent) facial and body hair
- Decreased libido (for most)
- Testicular atrophy
- Decreased (not necessarily absent) fertility
- Softer, less oily skin
- Decreased muscle mass and hematocrit
- Increased body fat percentage (diet and exercise otherwise remaining unchanged)

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Things estrogen and testosterone blockade will NOT do

- Change height
- Change voice pitch
- Completely prevent fertility—family planning counseling needed
- Reverse any male pattern hair loss which has already occurred, or reverse any already present facial and body hair growth
- Alleviate the need for screening and diagnostic workup of present organs according to cisgender people's recommendations (i.e. breast cancer screening as for cis women, prostate symptom workup according to cis male recommendations)

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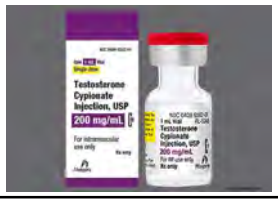
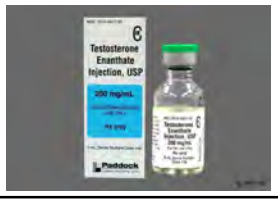
Medical gender affirmation: Testosterone

- Testosterone prescribing
- Inherently suppresses estrogen to normal male physiologic levels at therapeutic doses, and thus aromatase inhibitors or other estrogen suppressors are not needed (Chan et al 2018, https://doi.org/10.4158/EP-2017-0203)







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Medical gender affirmation: Testosterone

- Testosterone prescribing
- Options include (for cis and trans guys):
- SubQ or IM testosterone cypionate or enanthate
- Transdermal testosterone in the form of gel
- Less commonly used due to expense: buccal testosterone
- No longer on the market: testosterone patches
- Now available in USA: PO testosterone undeconoate (BID with food)
- Maintenance option: subcutaneous pellets which are replaced every 3-6 months as a minor office procedure

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Medical gender affirmation: Testosterone

- Lab monitoring: Every 3 months during the first year or until at target dose, then every 6-12 months
- Target is no higher than upper limit of normal male physiologic range
- Monitor CBC and avoid polycythemia due to stroke risk
- Monitor lipids at baseline and then usually annually
- Estrogen monitoring optional; usually will not change management
- Excessive T will get aromatized back to undesired E (just like in cis men)
- Maintain vigilance for obstructive sleep apnea as this risk increases with both weight gain (if it occurs) and with T presence, all other things being equal.

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Benefits/effects of testosterone treatment

- Virilization of voice: pitch deepens, although may not reach the same level as someone who went through testosterone puberty natally
- Increase in muscle mass (although may be marginal if no exercise)
- Male pattern hair loss vs never having T present (recall not all cis men lose hair at the same rate so this will vary)
- Facial hair growth (see above re: cis men, variable)
- Oilier skin, increased body odor
- Acne may occur

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Medical gender affirmation: Puberty blockade

- GnRH agonist therapy, to stop progression of puberty as well as to suppress testosterone in select cases
- Available as:
  - Leuprolide IM depot injections (requires RN administration)
  - Histrelin subcutaneous implant (placed by a trained provider)
- Works by continuous stimulation of GnRH receptors, thus disrupting the physiologic pulsatile secretion of FSH and LH
- FDA approved for central precocious puberty as well as endometriosis and prostate cancer (ie situations where sex hormones cause inappropriate or harmful effects), off label for gender dysphoria

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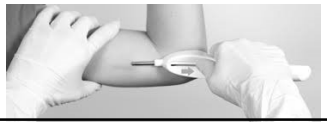
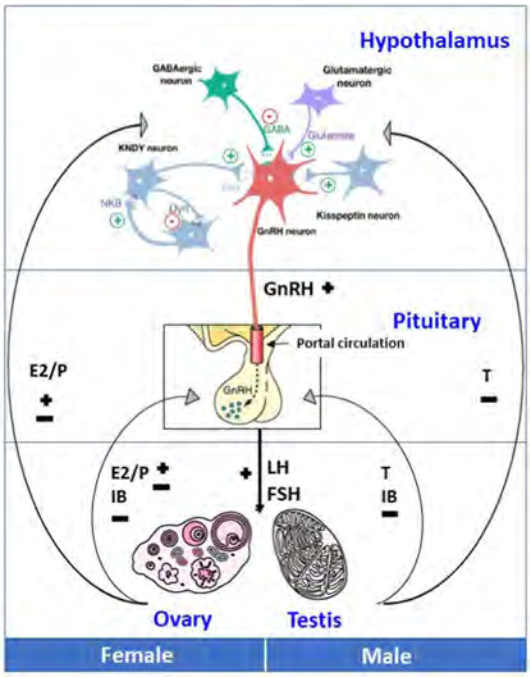
Medical gender affirmation: Puberty blockade/T blockade

- Pulsatile GnRH release leads to sex steroid release
- Blockers continuously stimulate the receptors—initial surge of hormones followed by sex steroid deprivation
- Leuprolide injections, histrelin subcutaneous implant--identical agents used for central precocious puberty for which they are FDA approved





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Medical gender affirmation: Benefits of puberty blockade

- AMAB: Prevent voice deepening, slow growth of facial and body hair, limit growth of genitalia (penis, testicles, scrotum), limit need for facial harmonization surgery by avoiding testosterone effects on face
- AFAB: Stops menstruation, limits breast growth which may avoid need for chest surgery depending on timing and individual patient characteristics
- In appropriately selected patients suffering from gender dysphoria, this can improve mental health, ease social interactions and prevent bullying by limiting physically obvious gender incongruity
- Buys time for therapy and additional processing and discussion between patient, parent(s)/guardian(s) and appropriate health professionals (PCP and any relevant medical and mental health specialists, individualized to the patient's needs)

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Medical gender affirmation: Benefits of puberty blockade: mental health

- "Using a cross-sectional survey of 20,619 transgender adults aged 18 to 36 years, we examined self-reported history of pubertal suppression during adolescence. Using multivariable logistic regression, we examined associations between access to pubertal suppression and adult mental health outcomes, including multiple measures of suicidality.
- **RESULTS:**
- Of the sample, 16.9% reported that they ever wanted pubertal suppression as part of their gender-related care. Their mean age was 23.4 years, and 45.2% were assigned male sex at birth. Of them, 2.5% received pubertal suppression. After adjustment for demographic variables and level of family support for gender identity, **those who received treatment with pubertal suppression, when compared with those who wanted pubertal suppression but did not receive it, had lower odds of lifetime suicidal ideation** (adjusted odds ratio = 0.3; 95% confidence interval = 0.2–0.6)." (*emphasis added—ATD MD)*

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Medical gender affirmation: Risks of puberty blockade

- Possible osteoporosis if prolonged state of sex steroid deprivation
  - Usual limit is 3 years prior to Rx hormones or stopping to permit natal puberty
  - Variable, may occur within 3-6 months; most associated with long term use
  - Time dependent and also influenced by other factors—per Lexicomp:
    - Treatment duration
    - Family history of osteoporosis
    - Concurrent administration of medications associated with bone loss (eg, antiseizure medications, long-term corticosteroids, aromatase inhibitors)
    - Lifestyle factors (eg, chronic tobacco or alcohol use, **sedentary nature**)
    - Low calcium intake
    - Vitamin D deficiency
    - Hypogonadism

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Medical gender affirmation: Risks of puberty blockade

J Endocr Soc. 2020 Sep 1; 4(9): bvaa065.
Published online 2020 Jul 2. doi: 10.1210/jendso/bvaa065
PMCID: PMC7433770
PMID: 32832823

Low Bone Mineral Density in Early Pubertal Transgender/Gender Diverse Youth: Findings From the Trans Youth Care Study

Janet Y Lee,[1,2] Courtney Finlayson,[3] Johanna Olson-Kennedy,[4] Robert Garofalo,[5] Yee-Ming Chan,[6] David V Glidden,[7] and Stephen M Rosenthal[1]

- Exercise and adequate calcium intake significant factors in protecting bone mineral density
- BMD needs to be reviewed and potential risk balanced against benefit, but is NOT a reason to withhold treatment especially with Ca++ and exercise being intervenable targets

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Medical gender affirmation: Risks of puberty blockade

- If begun early in puberty i.e. SMR/Tanner stage 2 (as opposed to somone presenting and consenting later in adolescence or adulthood) and patient proceeds to gender affirming cross sex hormones without undergoing puberty with natal hormones affecting gonads, ability to have genetically related children likely to be precluded
  - This can be optimal for mental health and physical/social presentation in the appropriate case—pros are always weighed vs. cons in informed consent model
- ALWAYS discuss as part of informed consent and offer referral to fertility specialist (stay tuned for a later slide!)

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Medical gender affirmation: Risks of puberty blockade

- AMAB: Surgical options for bottom surgery (vaginoplasty) may be more limited if blockers and then cross sex hormones limit genital development—less skin and tissue to work with
- Seizure risk (per package insert, obtained from Lexicomp):
  - There are postmarketing reports of **seizures** with the use of long-acting leuprolide.
  - Reports were mostly in females (average age 25 years) receiving therapy for endometriosis; there are 2 reports of seizure in pediatric patients with preexisting brain damage; resolution of seizure activity occurred with discontinuation of leuprolide therapy and initiation of treatment
  - *Mechanism*: Postulated to be dose-related; related to pharmacological action. Potentially same mechanism as catamenial seizures since leuprolide causes transient increase in hormones

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Medical gender affirmation: Regulation of menses

- Menses can be quite dysphoric for some
- May also be painful, inconvenient or lead to anemia just like for cis women
- Progesterone only contraceptives can be used from early puberty through menopause; PO, IM, LARC/hormonal IUD (same as for cis folks)
- Leuprolide would also work as is used for endometriosis, but is not generally used due to availability of less expensive options with fewer side effects
- Hysterectomy not indicated solely for this purpose, but obviously very effective if patient chooses it as part of their afffirmation

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Medical gender affirmation: Primary Care

- Primary care, screening, counseling on healthy behaviors, lab monitoring, and management of any concurrent health concerns with a focus on the patient's overall well being
- Offering emotional support, behavioral heath consultation as needed, assistance with medicolegal forms, helping navigate specialist referrals for both gender affirming and general healthcare needs
- Advocacy

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Nonmedical gender affirmation

- Speech and voice therapy both for social presentation, internal harmony and to treat/prevent muscle tension dysphonia
- Laser hair removal and electrolysis as needed
- Counseling on safer use of binders, tucking and other specific clothing
- Counseling on exercise modalities to support health and pursuit of aesthetic goals (just like cis people)
- Registered Dietitian referral as above

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Surgical gender affirmation

- Brief overview:
- "Top surgery:" either augmentation or reduction mammoplasty in line with the patient's individual goals
- "Bottom surgery:" different options based on patient's anatomy, which is usually in line with sex assigned at birth:
  - AMAB: Orchiectomy, vaginoplasty
  - AFAB: Hysterectomy/oophorectomy, metoidioplasty, phalloplasty
- ENT and facial plastics procedures: facial harmonization surgery for patients who have experienced a testosterone driven puberty, tracheal shave ("Adam's apple" reduction)

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Fertility considerations

- All patients should have fertility options reviewed in a non-judgmental way which neither presumes desire for fertility or desire for infertility—allow patients to make their own decisions
- Fertility is never expected to be better than prior to starting gender affirming therapy (recall that some cis people have reduced fertility and infertility, which may impact gender expansive clients prior to medical therapy as well)
- I advise patients of fertility specialist consultation option either when doing initial visits, or when patients transfer care to me (unless status post gonadectomy)

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Fertility considerations

- Sperm producers:
  - Cryopreservation before starting hormones
  - Decreasing or interrupting hormone therapy to allow spermatogenesis to resume; variable time and efficacy
- Egg producers:
  - Oocyte harvesting with IVF—does NOT require testosterone to be stopped
  - Decreasing and stopping T to allow menses to resume and pursue natural conception—recall that T is teratogenic and requires active efforts to prevent pregnancy, and pursuing pregnancy on T is absolutely contraindicated

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Fertility considerations

- Heartland Reproductive
- Omaha and Lincoln offices
- Offers sperm cryopreservation prior to starting hormones at no cost for as many times as needed to freeze up to 6 vials (cost to clinic is $2000 per cryo event
- Offers oocyte cryopreservation prior to hormone therapy at the same discounted rates we offer it to individuals before chemotherapy, which is 1/2 the normal cost.
- Only clinic in the country (to our knowledge) that offers discounted rates for sperm/egg cryo for trans people (most places do for cancer diagnosis only).

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Resources for further learning

- https://www.tandfonline.com/doi/pdf/10.1080/26895269.2022.2100644 WPATH SOC 8
- https://transcare.ucsf.edu/guidelines Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People. UCSF Transgender Care. Madeline Deutsch, MD MPH editor and Medical Director, UCSF Gender Affirming Health Program
- https://transline.zendesk.com/hc/en-us/articles/229373288-TransLine-Hormone-Therapy-Prescriber-Guidelines A collaborative project by: Lyon-Martin Health Services, Fenway Health, Chase Brexton Health Center, Howard Brown Health, Mazzoni Center, Baystate Health, Cooley Dickinson Hospital, Callen-Lorde Community Health Center, The LA LGBT Center, Whitman-Walker Health, Apicha Community Health Center, Legacy Community Health, Care Resource

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Informed consent and general resources

- Fenway Clinic Resources and National LGBTQIA+ Education Center
- https://fenwayhealth.org/documents/medical/transgender-resources/Fenway_Health_Consent_Form_for_Feminizing_Therapy.pdf
- https://fenwayhealth.org/wp-content/uploads/Consent_Form_for_Masculinizing_Therapy.pdf
- https://fenwayhealth.org/wp-content/uploads/Hormone-Blocker-Consent.doc

- https://www.lgbtqiahealtheducation.org/resources/

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Gender Affirming Hormone Therapy Guidelines

TRANSGENDER MEDICAL CONSULTATION SERVICE
TRANSLINE

Trans Masculine: Exogenous Testosterone Dosing

Medication	Start/Usual Dose	Typical Max Dose	Frequency	Pros	Cons	Notes
Intramuscular or Subcutaneous[1] Injectable Testosterone (Testosterone Cypionate or Testosterone Enanthate)	50mg – 80mg (0.25mL - 0.4mL of 200mg/mL solution or 0.5mL - 1.0mL of 100mg/mL solution)	100mg (0.5mL of 200mg/mL solution)	Weekly[2]	• Less frequent administration compared with transdermal • Peak of irritability may better suppress endogenous hormone production	• Peak/trough fluctuation effect • Self-injection or frequent in-office injections • Needle use	• Cypionate formulated in cottonseed oil (use if allergic to sesame) • Enanthate formulated in sesame oil (use if allergic to cottonseed) • Enanthate has slightly shorter half life than cypionate
Transdermal Testosterone Topical Gel (Androgel, Axiron, Testim)	20mg – 62.5mg • Androgel 1%, 12.5mg/actuation, 2-5 pumps • Androgel 1.62%, 20.25mg/actuation, 1-3 pumps • Axiron, 30mg/actuation, 1-2 pumps • Testim, 50mg/5g, 2.5g-5g	100mg • Androgel 1%, 12.5mg/actuation, 8 pumps • Androgel 1.62%, 20.25mg/actuation, 5 pumps • Axiron, 30mg/actuation, 3 pumps • Testim, 50mg/5g, 10 g	Daily	• No needle use • Less fluctuation in levels • Good for more gradual effects	• Slower to stop menses and may not fully stop at lower doses • Risk of transferring to others/pets so must instruct how to apply per package insert • Some products are scented and may not be appropriate for those with scent sensitivities • Daily application • May be expensive if not covered by insurance	• Consider using higher doses for those with more adipose tissue
Transdermal Testosterone Patch (Androderm)	2mg – 4mg (1 - 1x 2mg patches)	8mg (2x 4mg patches)	Daily	• No needle use • Less fluctuation in levels • Good for more gradual effects • Less risk of transfer to others	• Slower to stop menses and may not fully stop at lower doses • Adhesive irritation, can fall off with sweat • Daily application • May be expensive if not covered by insurance	• Consider using higher doses for those with more adipose tissue
Testosterone Pellets (Testopel)	450mg – 600mg (6 - 8x 75mg pellets)	750mg (10x 75 mg pellets)	Every 3-4 months	• No needle use • Less frequent administration • Less fluctuation in levels	• More invasive, requires minor surgery to implant • May be expensive if not covered by insurance	• Lab draw frequency: Baseline draw prior to starting, once at 1 month then at 3 months prior to next insertion • Consider using higher doses for those with more adipose tissue
Testosterone Undecanoate IM (Aveed)	750mg (3mL of 750mg/3mL solution)	NA	Initial injection at 4 weeks, then every 10 weeks thereafter	• Less frequent injection • Less fluctuation in levels	• Pulmonary oil embolism risk • PCP and facility need registration • May be expensive and unlikely to be covered by insurance at present	• Formulated in castor oil
Testosterone Undecanoate Oral (Jatenzo)	316mg – 474mg (1x 158mg capsules BID, 1x 158mg capsules BID + 1x 237mg capsules BID)	790mg (1x 158mg + 1x 237mg capsules BID)	Daily	• No needle use • Less fluctuation in levels	• First pass metabolism • Daily dose	• Recommend divided doses (BID) to decrease first pass effect and hepatotoxicity • Starting dose 237mg BID, then adjust dose to min of 158mg BID, with a max of 395mg BID
Testosterone Nasal Gel (Natesto)	33mg (2 pump actuations, one 5.5mg actuation per nostril = 11mg TID)	NA	Daily	• No needle use • Less fluctuation in levels	• Administration three times per day	• Not recommended for use with other nasally administered drugs, other than sympathomimetic decongestants

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Gender Affirming Hormone Therapy Guidelines

TRANSGENDER MEDICAL CONSULTATION SERVICE
TRANSLINE

Testosterone Formulations: Approximate Dose Equivalent Chart

Injectable	Transdermal Patch	Transdermal Gel	Pellets
50mg weekly (0.25mL of 200mg/mL solution weekly)	2-4mg	20-50mg	37.5mg (5x 75mg pellets)
80mg weekly (0.4mL of 200mg/mL solution weekly)	6mg	50-75mg	62.5mg (7x 75mg pellets)
100mg weekly (0.5mL of 200mg/mL solution weekly)	8mg	75-100mg	75mg (10x 75mg pellets)
120mg weekly (0.6mL of 200mg/mL solution)			90mg (12x 75mg pellets)

Trans Masculine: Medications to Supplement Testosterone

Medication	Start/Usual	Typical Max	Frequency	Pros	Cons	Notes
Finasteride Oral (Proscar, Prupecia)	1mg (¼ of 1.1mg pill or 1x 1mg pill)	5mg (1x 4.4mg pill)	Daily	• Prevent or slow balding due to androgenic alopecia	• May slow other DHT-dependent changes like secondary hair growth and clitoral growth, so this should be discussed with patients, especially if considering using at the beginning of testosterone use, unless they are deliberately trying to prevent above mentioned changes	• 4.4mg are cheapest then 1mg, can split 4.4mg into quarters
Dutasteride Oral (Avodart)	0.5mg (1x 0.5mg tablet)	0.5mg (1x 0.5mg tablet)	Every 3 days	• Slows and prevents balding due to androgenic alopecia • Can take every 3 days rather than every day with Finasteride	• Same as Finasteride Cons	
Compounded Testosterone Cream (applied to genitalia)	12.5mg –50mg* (0.25g –1g of 5% cream)	100mg (2g of 5% cream or 1g of 10% cream)	Daily	• Clitoral enlargement • Can also be used as a cheaper transdermal alternative to Androgel	• May worsen balding due to androgenic alopecia	• Some surgeons may suggest the topical application of testosterone to the clitoris as an adjunct to growth. There is no definitive evidence for this practice, however if undertaken, this applied dose should be subtracted from the client's total testosterone dosage (if it is used in addition to another formulation of T). Contact compounding pharmacy to determine equivalent amount to be subtracted from total dose, as equivalency depends greatly on what chemicals testosterone is compounded with. Long-term efficacy is not well established.
Compounded Dihydrotestosterone (DHT) Cream (applied to genitalia)	5mg over course of day 20mg of 10% cream	5mg over course of day 20mg of 10% cream	Apply 2mg 3x per day	• Clitoral enlargement	• May worsen balding due to androgenic alopecia	• Same as Compounded Testosterone Cream Notes • Not sold or FDA approved in the US, very expensive, and illegal to import due to being a schedule III drug • Overseas this is available as an alcohol-based gel, which, when used on mucous membranes can result in a burning sensation after topical application
Leuprolide Acetate IM (Lupron, Eligard)	11.25mg (1 IM shot of 1.25mg/1.5mL diluent)	22.5mg (2 IM shots of 11.25mg/1.5mL diluent)	Every 3 months	• GnRH receptor agonist, very effective to suppress endogenous hormone production • Typically only used for client for puberty suppression, can use either alone or with exogenous hormones	• May be expensive if not covered by insurance • Not ideal for long term use due to bone density loss*	
Vaginal Estradiol (Estrace, Premarin, Estring, Vagifem)	Dosing same as post-menopausal cis-women	N/A	N/A	• Treats vaginal atrophy, pain with penetration and unsatisfactory cytology result on pap smear		• If just used in preparation for vaginal exam and/or pap smear, short two week course prior can help with pain during exam as well as obtaining satisfactory cytology • Approach discussion with sensitivity as some may not feel comfortable using estrogen due to gender dysphoria

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Medroxyprogesterone Acetate IM (Depo-Provera)	150mg (1mL of 150mg/mL solution)	150mg (1mL of 150mg/mL solution)	Every 3 months	• Stops persistent vaginal bleeding on T* • Contraception		• 3 month course, then re-evaluate
Medroxyprogesterone Oral (Provera)	5mg (1 5mg tablet daily)	10mg (1 10mg tablet daily)	Daily	• Stops persistent vaginal bleeding on T*		• Short 7-10 day course to as long as a 3 month course
Anastrozole (Anmidex)	1mg	1mg	Daily	• Stops persistent vaginal bleeding on T*	• Not ideal for long term use due to bone density loss*	• 3 month course • May cause menopausal symptoms
Levonorgestrel Intrauterine Device (Mirena, Skyla, Kyleena)	20mcg/day (Mirena) 14mcg/day (Skyla) 19.5 mg/day (Kyleena)	N/A	N/A	• Stops persistent vaginal bleeding on T* • Contraception		• Mirena lasts 5 years • Skyla lasts 3 years • Kyleena lasts 4 years

Trans Masculine: Exogenous Testosterone Monitoring

This is in addition to any PCP visits or lab work indicated to monitor other health risks, disease states or standard medical screening.

Baseline	Once Amenorrheic (or 2-3 months after start)	After change in dose (1-3 months after change)	6 months after first estimated maintenance dose (OPTIONAL, esp if otherwise young and healthy)	12 months after achieving stable maintenance dose (unless other concerns)	When to draw testosterone?
CBC, CMP	Testosterone (total)	Testosterone (total)	CBC, Testosterone (total)	CBC, Testosterone (total), CMP, Lipids**	Injectable: One week after injection Transdermal: Through client apply it on the day of the draw, or wear gloves when administering on day of draw to avoid contaminating sample) Oral: 8 hours after morning dose at least 7 days after starting or adjusting dose
PCP exam, BP, UPT*	PCP check in & BP	PCP check in & BP	PCP check in & BP	PCP check in & BP	

*Only if at risk for pregnancy
**In all patients, check lipids one time at 12 months after starting, and repeat every 12 months if there is a concern of fatty liver, chronic liver disease, high cholesterol, otherwise ok to just check once.

Total Testosterone Reference Range:

- Use cisgender male suggested reference range. Reference ranges may vary depending on lab.
- The goal is to be around or below mid-normal range for a cisgender male, but also it depends on transition goals of the client.
- If testosterone is supraphysiologic, before making major adjustments, review administration technique to ensure correct dosing and re-check level. If persistently supraphysiologic, decrease dose and re-check again.
- Recommended mid-cycle draw reference ranges vary:
  - Fenway: 300-700ng/dl
  - Endocrine Society: 400-700ng/dl
  - UCSF: a bit 1100ng/dl unless in setting of symptoms like migraines, pelvic cramping or mood swings, in which case recommends peak and trough draw may be helpful. If supraphysiologic, consider change to transdermal or decreasing injection interval

Secondary Polycythemia:

- Use CBC reference range for cisgender men
- Hematocrit >54 is ideal
- >54 indicates polycythemia, which increases the risk of hypercoagulation and thrombosis
- First rule out pulmonary disease cause such as asthma, smoking, COPD, etc, or JAK2 mutation. EPO level can also be checked to determine if it's primary or secondary polycythemia.
- If polycythemia is actually secondary to testosterone use, there are a few treatment options to choose from other than just decreasing the dose. Since HH elevation is often due to high peaks of testosterone with injectable, consider:
  - Changing to weekly injection schedule if currently on an every two week injection schedule
  - Changing from injectable to transdermal
  - Stay on current dose/formulation and do therapeutic phlebotomy
- Re-check labs for normalization 1-3 months after change is made

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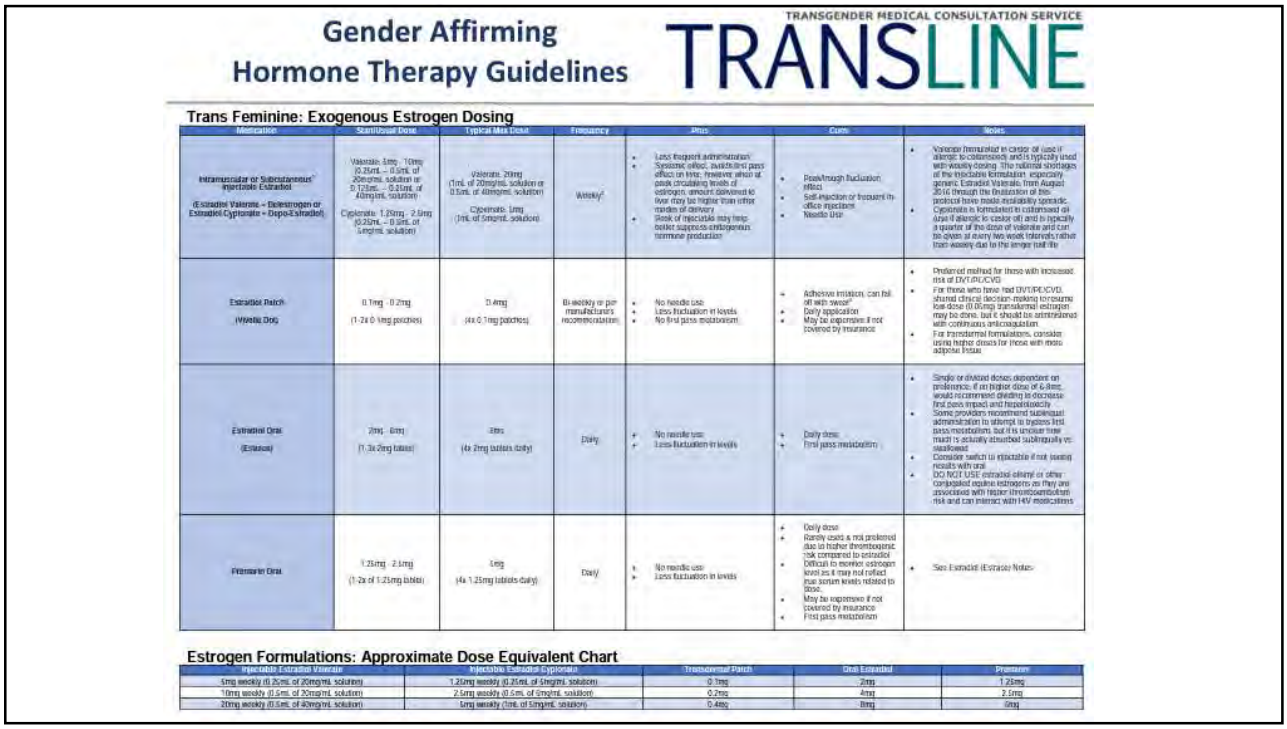

Gender Affirming Hormone Therapy Guidelines

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Trans Feminine: Exogenous Estrogen Dosing

Medication	Start/Usual Dose	Typical Max Dose	Frequency	Pros	Cons	Notes
Intramuscular or Subcutaneous[1] Injectable Estradiol (Estradiol Valerate – Delestrogen or Estradiol Cypionate – Depo-Estradiol)	Valerate: 5mg - 10mg (0.25mL – 0.5mL of 20mg/mL solution or 0.125mL – 0.25mL of 40mg/mL solution) Cypionate: 1.25mg - 2.5mg (0.25mL – 0.5mL of 5mg/mL solution)	Valerate: 20mg (1mL of 20mg/mL solution or 0.5mL of 40mg/mL solution) Cypionate: 5mg (1mL of 5mg/mL solution)	Weekly[2]	• Less frequent administration • Systemic effect, avoids first pass effect on liver; however, when at peak circulating levels of estrogen, amount delivered to liver may be higher than other modes of delivery • Week of injectable may help better suppress endogenous hormone production	• Peak/trough fluctuation effect • Self-injection or frequent in-office injections • Needle Use	• Valerate formulated in castor oil (use if allergic to cottonseed) and is typically used with weekly dosing. The national shortages of the injectable formulation, especially generic Estradiol Valerate, from August 2016 through the finalization of this protocol have made availability sporadic. • Cypionate is formulated in cottonseed oil (use if allergic to castor oil) and is typically a quarter of the dose of valerate and can be given at every two week intervals rather than weekly due to the longer half-life
Estradiol Patch (Vivelle Dot)	0.1mg - 0.2mg (1-2x 0.1mg patches)	0.4mg (4x 0.1mg patches)	Bi-weekly or per manufacturer's recommendation	• No needle use • Less fluctuation in levels • No first pass metabolism	• Adhesive irritation, can fall off with sweat[3] • Daily application • May be expensive if not covered by insurance	• Preferred method for those with increased risk of DVT/PE/CVD • For those who have had DVT/PE/CVD, shared clinical decision-making to assume low-dose (0.05mg) transdermal estrogen may be done, but it should be antithrombins with continuous anticoagulation • For transdermal formulations, consider using higher doses for those with more adipose tissue
Estradiol Oral (Estrace)	2mg - 6mg (1-3x 2mg tablet)	8mg (4x 2mg tablets daily)	Daily	• No needle use • Less fluctuation in levels	• Daily dose • First pass metabolism	• Single or divided doses dependent on preference. If on higher dose of 6-8mg, would recommend dividing to decrease first pass impact and hepatotoxicity • Some providers recommend sublingual administration to attempt to bypass first pass metabolism, but it is unclear how much is actually absorbed sublingually vs. swallowed • Consider switch to injectable if not seeing results with oral • DO NOT USE estradiol-ethinyl or other conjugated equine estrogens as they are associated with higher thromboembolism risk and can interact with HIV medications
Premarin Oral	1.25mg - 2.5mg (1-2x of 1.25mg tablet)	5mg (4x 1.25mg tablets daily)	Daily	• No needle use • Less fluctuation in levels	• Daily dose • Rarely used, is not preferred due to higher thromboganic risk compared to estradiol • Difficult to monitor estrogen level as it may not reflect true serum levels related to dose. • May be expensive if not covered by insurance • First pass metabolism	• See Estradiol (Estrace) Notes

Estrogen Formulations: Approximate Dose Equivalent Chart

Injectable Estradiol Valerate	Injectable Estradiol Cypionate	Transdermal Patch	Oral Estradiol	Premarin
5mg weekly (0.25mL of 20mg/mL solution)	1.25mg weekly (0.25mL of 5mg/mL solution)	0.1mg	2mg	1.25mg
10mg weekly (0.5mL of 20mg/mL solution)	2.5mg weekly (0.5mL of 5mg/mL solution)	0.2mg	4mg	2.5mg
20mg weekly (0.5mL of 40mg/mL solution)	5mg weekly (1mL of 5mg/mL solution)	0.4mg	8mg	5mg

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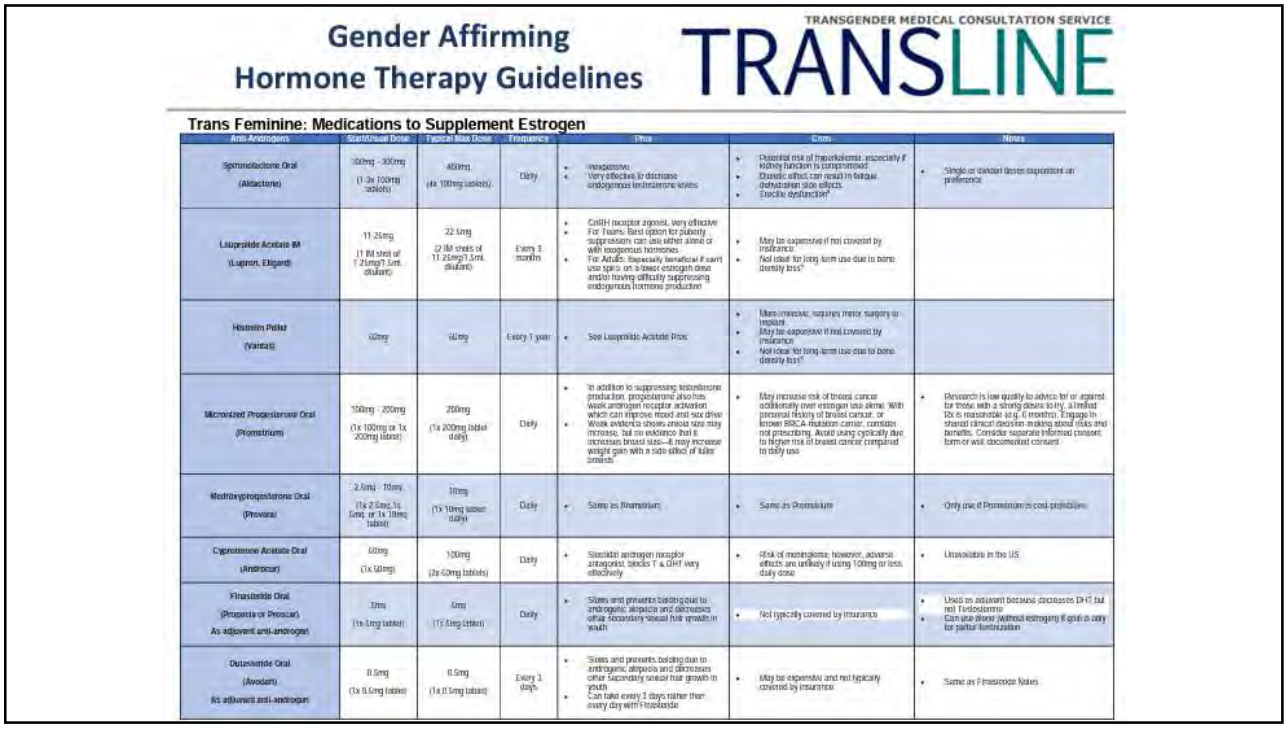

Gender Affirming Hormone Therapy Guidelines

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Trans Feminine: Medications to Supplement Estrogen

Anti-Androgens	Start/Usual Dose	Typical Max Dose	Frequency	Pros	Cons	Notes
Spironolactone Oral (Aldactone)	100mg - 300mg (1-3x 100mg tablets)	400mg (4x 100mg tablets)	Daily	• Antiandrogenic • Very effective at decrease endogenous testosterone levels	• Potential risk of hyperkalemia, especially if kidney function is compromised • Diuretic effect can result in fatigue, dehydration side effects • Erectile dysfunction[4]	• Single or divided doses dependent on preference
Leuprolide Acetate IM (Lupron, Eligard)	11.25mg (1 IM shot of 11.25mg/1.5mL diluent)	22.5mg (2 IM shots of 11.25mg/1.5mL diluent)	Every 3 months	• GnRH receptor agonist, very effective • For Teens: Best option for puberty suppression; can use either alone or with exogenous hormones • For Adults: Especially beneficial if can't use spiro, on a lower estrogen dose and/or having difficulty suppressing endogenous hormone production	• May be expensive if not covered by insurance • Not ideal for long-term use due to bone density loss[5]	
Histrelin Pellet (Vantas)	50mg	50mg	Every 1 year	• See Leuprolide Acetate Pros	• More invasive, requires minor surgery to implant • May be expensive if not covered by insurance • Not ideal for long-term use due to bone density loss[5]	
Micronized Progesterone Oral (Prometrium)	100mg - 200mg (1x 100mg or 1x 200mg tablet)	200mg (1x 200mg tablet daily)	Daily	• In addition to suppressing testosterone production, progesterone also has weak antiandrogen receptor activation which can improve mood and sex drive • Weak evidence shows breast size may increase, but no evidence that it increases breast size—it may increase weight gain with a side effect of fuller breasts	• May increase risk of breast cancer additionally over estrogen use alone. With personal history of breast cancer, or known BRCA mutation carrier, consider not prescribing. Avoid using cyclically due to higher risk of breast cancer compared to daily use	• Research is low quality to advise for or against for those with a strong desire to try. Limited Rx is reasonable (e.g. 6 months). Engage in shared clinical decision-making about risks and benefits. Consider separate informed consent form or well documented consent
Medroxyprogesterone Oral (Provera)	2.5mg - 10mg (1x 2.5mg, 1x 5mg, or 1x 10mg tablet)	10mg (1x 10mg tablet daily)	Daily	• Same as Prometrium	• Same as Prometrium	• Only use if Prometrium is cost-prohibitive
Cyproterone Acetate Oral (Androcur)	50mg (1x 50mg)	100mg (2x 50mg tablets)	Daily	• Steroidal androgen receptor antagonist, blocks T & DHT very effectively	• Risk of meningioma; however, adverse effects are unlikely if using 100mg or less daily dose	• Unavailable in the US
Finasteride Oral (Propecia or Proscar) As adjuvant anti-androgen	1mg (1x 1mg tablet)	5mg (1x 5mg tablet)	Daily	• Slows and prevents balding due to androgenic alopecia and decreases other secondary sexual hair growth in youth	• Not typically covered by insurance	• Used as adjuvant because decreases DHT but not Testosterone • Can use alone (without estrogen) if goal is only for partial feminization
Dutasteride Oral (Avodart) As adjuvant anti-androgen	0.5mg (1x 0.5mg tablet)	0.5mg (1x 0.5mg tablet)	Every 3 days	• Slows and prevents balding due to androgenic alopecia and decreases other secondary sexual hair growth in youth • Can take every 3 days rather than every day with Finasteride	• May be expensive and not typically covered by insurance	• Same as Finasteride Notes

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Impact of 2023 NE LB574 and current status of regulations on youth care

- https://www.nebraska.gov/rules-and-regs/regsearch/Rules/Health_and_Human_Services_System/Title-181/Chapter%208%20Emergency%20Rule%20Effective%20Until%2012-30-2023.pdf

- Public comment: Tuesday November 28 from 7 AM to 7 PM in Lincoln at the Lancaster County Event Center in Lincoln.
- Comments may also be emailed to mailto:dhhs.regulations@nebraska.gov. DHHS reports equal weight will be given to emailed and written comments.

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Questions

https://webbtelescope.org/contents/media/images/2023/128/01H449193V5Q4Q6GFBKXAZ3S03

Rho Ophiuci is full of “dark rivers” which are from collisions of gas clouds which function as stellar nurseries. These will become planetary systems of the future. Out of this darkness, chaos and collision will come the seeds of new stellar life.

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