Gender Affirming Hormone Therapy

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Continuing Medical Education Disclosure

- **Program Faculty:** Timothy Cavanaugh, MD
- **Current Positions:**
- **Disclosure:**
  - I have no financial relationships with a commercial entity producing healthcare-related products and/or services.
  - The use of medications for cross-sex hormone therapy is off-label use.

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OBJECTIVES

- Be aware of the prevalence of transgender and non-conforming persons and appreciate the heterogeneity in this population
- Familiarize oneself with the use of cross-sex hormones for the purpose of gender affirmation
- Understand the short and potential long-term effects and consequences of cross-sex hormone therapy
Alternative Constructs of Gender Identity:

- If gender is determined by anatomic sex/the genitals...then binary understanding of gender....gender “reassignment” or “transition”

- If gender is determined by the brain/ one’s internal identity....then spectrum of gender identity....gender “affirmation”
The criteria for hormone therapy are as follows:

- Persistent, well-documented gender dysphoria;
- Capacity to make a fully informed decision and to consent for treatment;
- Age of majority in a given country (if younger, follow the Standards of Care outlined in section VI);
- If significant medical or mental health concerns are present, they must be reasonably well controlled.
Standard vs. Informed Consent Model (WPATH SOC7)

Standard Model of Care

▪ Initiation of hormone Rx after psychosocial assessment by “qualified mental health professional”
▪ Recommendation for team care or collaborative model
▪ Psychotherapy not required
▪ Experienced hormone prescribing medical provider may meet requirement
▪ Informed consent
Informed Consent Model

- Requires healthcare provider to effectively communicate benefits, risks and alternatives of treatment to patient.
- Requires healthcare provider to judge that the patient is able to understand and consent to the treatment.
- WPATH SOC7 states protocols using informed consent model are consistent with SOC7.
  - Applies to hormone therapy.
- Informed consent model does not preclude mental health care.
- Recognizes that prescribing decision ultimately rests with clinical judgment of provider working together with the patient.
  - Informed consent is not equivalent to treatment on demand.

(Deutsch, 2012)
Gender Affirming Hormone Therapy

- Many patients have taken self-prescribed hormones
  - 2013 Ontario survey: 25% had ever used and 6.4% were currently using
  - 2009 NYC study: 23% of transwomen currently using
  - 2007 Virginia Trans Health Initiative Survey: 60% of transwomen and 23% of transmen had ever used
  - 2001 San Francisco Study: 29% of transwomen and 3% of transmen in the past 6 months
  - 2000 Washington, DC Transgender Needs Assessment Study: 58% had used at some time in the past
Initial Visits

- Review history of gender experience
- Document prior hormone use
- Obtain sexual history
- Review patient goals
- Address safety concerns
- Assess social support system
- Assess readiness for gender transition
- Review risks and benefits of hormone therapy
- Obtain informed consent
- Order screening laboratory studies
- Provide referrals
Gender Affirming Hormone Therapy

- Heredity and age limit the tissue response to hormones
- More is not always better
Which one is a transman?

If you can't tell, why should he?
Masculinizing Treatment Options

**Injectable Testosterone**
- Testosterone Enanthate or Cypionate IM or SC q 1 or 2 weeks,
- standard dose is 50 – 100 mg weekly
- Testosterone undeconoate (Aveed) 750 mg initial, 4 weeks, then q10 weeks

**Transdermal Testosterone**
- Androderm (2 and 4 mg patches) 2-8mg daily
- Topical testosterone gels in packets and pumps, 50 – 100 mg daily, Androgel pump 1.62% gives 20.25 mg per pump, Androgel or Testim packets provide 25 mg (2.5 gm) or 50 mg (5 gm)
  Axiron 2% pump gel for axillary application 1 pump (30 mg) to each axilla daily

**Testosterone Pellet**
- Testopel- implant 6-10 pellets q 3 to 6 months

**Buccal Testosterone**
- Striant 30 mg buccal system q 12 hours
Other Treatment Considerations for Transmasculine People

- Testosterone cream in aquaphor for clitoral enlargement
- Estrogen vaginal cream for atrophy
- Rogaine or Finasteride for male pattern baldness
- Use of Progesterone – may help to reduce estrogen levels and aid in cessation of menses before or after starting testosterone therapy.
Other Treatment Considerations for Transmasculine People

- Aromatase Inhibitors, e.g. anastrozole (Arimidex) and letrozole (Femara) – block the conversion of androgen to estrogen
- Selective Estrogen Receptor Modulators, e.g. raloxifene (Evista) – estrogen antagonist in breast and uterus, estrogen agonist in bone

May be of use in treating persistent uterine bleeding despite adequate testosterone levels
## Masculinizing Effects of Testosterone

<table>
<thead>
<tr>
<th>Effect</th>
<th>Onset (months)</th>
<th>Maximum (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin oiliness/acne</td>
<td>1-6</td>
<td>1-2</td>
</tr>
<tr>
<td>Fat redistribution</td>
<td>1-6</td>
<td>2-5</td>
</tr>
<tr>
<td>Cessation of Menses</td>
<td>2-6</td>
<td></td>
</tr>
<tr>
<td>Clitoral enlargement</td>
<td>3-6</td>
<td>1-2</td>
</tr>
<tr>
<td>Vaginal atrophy</td>
<td>3-6</td>
<td>1-2</td>
</tr>
<tr>
<td>Emotional changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased sex drive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Masculinizing Effects of Testosterone

<table>
<thead>
<tr>
<th>Effect</th>
<th>Onset (months)</th>
<th>Maximum (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deepening of voice</td>
<td>3-12</td>
<td>1-2</td>
</tr>
<tr>
<td>Facial/Body Hair Growth</td>
<td>6-12</td>
<td>4-5</td>
</tr>
<tr>
<td>Scalp Hair Loss</td>
<td>6-12</td>
<td></td>
</tr>
<tr>
<td>Increased Muscle Mass &amp; Strength</td>
<td>6-12</td>
<td>2-5</td>
</tr>
<tr>
<td>Coarser Skin/ Increased Sweating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Gain/Fluid Retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Breast Atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakening of Tendons</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Risks of Testosterone Therapy

- Lower HDL and Elevated triglycerides
- Increased homocysteine levels
- Polycythemia
- Possible worsened migraine
- Male pattern baldness
- Variable effects on mood
- ? Increased risk of sleep apnea
- Chronic pelvic pain
- Mental health effects
- (Hepatotoxicity)
- Unknown effects on breast, endometrial, ovarian tissues
- Infertility
Drug Interactions - Testosterone

- Increases the anticoagulant effect of warfarin
- Increases clearance of propranolol
- Increases the hypoglycemic effects of sulfonylureas
Laboratory Monitoring for Transmasculine Patients on Testosterone

- **Baseline:**
  - CBC (Hgb/Hct)
  - Lipid Profile, only as clinically indicated
  - Liver Enzymes, only if evidence of underlying liver disease
  - Fasting Glucose, only if clinically indicated
  - ? Screen for PCOS
Laboratory Monitoring for Transmasculine Patients on Testosterone

- After 3 to 6 months, then every 6 to 12 months
  - CBC

- Every 6 to 12 months
  - Lipid Profile, as clinically indicated
  - Fasting Glucose or HbA1c, as clinically indicated
Laboratory Monitoring for Transmasculine Patients on Testosterone

- Serum testosterone levels
  - At 6 to 12 months, then as clinically indicated
  - May be checked 6 to 12 weeks after dosage change
  - about 350-700 ng/dl

- Estradiol levels? (should be less than 50 pg/ml)
Feminizing Treatment Options

- **Oral Estrogens**
  - Estradiol (estrace) 2-8 mg PO or SL daily (can be divided into BID dosing)
  - Premarin (conjugated estrogens) 1.25-10mg PO daily (can be divided into BID dosing)

- **Transdermal Estrogens**
  - Estradiol patch 0.1-0.4mg twice weekly, may start lower in patients at risk of side effects. Maximum single dose patch available is 0.1 mg

- **Injectable Estrogens**
  - Estradiol valerate 5-20mg IM q2 weeks
  - Estradiol cypionate 2-10mg IM weekly

- **Antiandrogens**
  - Spironolactone (aldactone) 50-400mg PO daily (can be divided into BID dosing)
  - Finasteride (Proscar) 2.5-5mg PO daily
Feminizing Treatment Options

- Cyproterone Acetate (not available in US)
- GnRH agonist: Goserelin Acetate, Leuprolide
- Flutamide an androgen receptor blocker, associated with severe liver toxicity
- Bicalutamide (Casodex), used in treatment of prostate CA, ? Less liver toxicity, still with anecdotal reports of severe liver toxicity
Feminizing Treatment Options

Progestins:

- Benefit on breast development, mood, sexual function
- associated with increased risk of cardiovascular events and breast cancer in WHI, but how does this translate to trans women?
- also risk of weight gain and depression

Feminizing Treatment Options

- Prometrium 100 – 200 mg po daily
- Depo-Provera 150 mg IM q 3 months
- Provera 2.5 to 10 mg PO daily*
- * Consider dosing 10 days each month cyclically with po form to minimize risk
Feminizing Treatment Options

- Hydroquinone
  - Topical treatment for pigmentation caused by estrogen therapy

- Hair Removal
  - Eflornithine (Vaniqa) cream
  - Electrolysis
  - Laser hair removal
Feminizing Treatment Options

- “Bio-identical” hormone therapy
  - A compounded mixture of plant-based steroids, often administered as small implantable pellets
- These treatments are often expensive and often based on measurement and monitoring of multiple forms of estrogen and other sex hormones
- There are no studies in either cis- or transgender women that have shown these treatments to be safer or more effective than traditional allopathic hormone therapy
- Pharmacodynamics are not well studied
- Not regulated
Transfeminine patients over 40 yo or at risk of VTE

- Consider adding ASA or other anticoagulant to regimen
- Transdermal estradiol therapy strongly recommended
- Stop smoking!
### Feminizing Effects of Estrogens & Antiandrogens

<table>
<thead>
<tr>
<th>Effect</th>
<th>Onset (months)</th>
<th>Maximum (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Libido</td>
<td>1-3</td>
<td>3-6</td>
</tr>
<tr>
<td>Decreased Spontaneous Erections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Growth</td>
<td>3-6</td>
<td>24-36</td>
</tr>
<tr>
<td>Decreased Testicular Volume</td>
<td>3-6</td>
<td>24-36</td>
</tr>
<tr>
<td>Decreased Sperm Production</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Redistribution of Body Fat</td>
<td>3-6</td>
<td>24-36</td>
</tr>
<tr>
<td>Decrease in Muscle Mass</td>
<td>3-6</td>
<td>12-24</td>
</tr>
<tr>
<td>Softening of Skin</td>
<td>3-6</td>
<td>Unknown</td>
</tr>
<tr>
<td>Decreased Terminal Hair</td>
<td>6-12</td>
<td>&gt;36</td>
</tr>
</tbody>
</table>

**NOTE:** Possible slowing or cessation of scalp hair loss, but no regrowth
No change in voice
Risks of Estrogen Therapy

- Venous thrombosis/thromboembolism
- Increased risk of cardiovascular disease
- Weight gain
- Decreased libido
- Hypertriglyceridemia
- Elevated blood pressure

- Decreased glucose tolerance
- Gallbladder disease
- Benign pituitary prolactinoma
- Mental health effects
- ? Breast cancer
- Infertility
Risks of Spironolactone Therapy

- Increased urinary frequency
- Hyperkalemia
- Hypotension
- Renal insufficiency
Drug Interactions

Estradiol, Ethinyl Estradiol, Testosterone levels are DECREASED by:

- Lopinavir
- Rifampin
- Phenytoin
- Carbamazepine
- Progesterone
- Phenobarbital
- Dexamethasone
- Phenylbutazone
- Naphthoflavone
- Benzo-flavone
- Sulfamide
- Sulfinpyrazone
Drug Interactions

Estradiol, Ethinyl Estradiol, Testosterone levels are INCREASED by:

- Nefazodone
- Fluvoxamine
- Indinavir
- Sertraline
- Diltiazem
- Cimetidine
- Itraconazole
- Fluconazole
- Clarithromycin
- Grapefruit
- Isoniazid
- Fluoxetine
- Efavirenz
- Paroxetine
- Verapamil
- Astemizole
- Ketoconazole
- Miconazole
- Erythromycin
- Triacetyloleandomycin
Drug Interactions

Estrogen levels are DECREASED by:

- Smoking cigarettes
- Nelfinavir
- Nevirapine
- Ritonavir
Drug Interactions

Estrogen levels are INCREASED by:

- Vitamin C
Lab Monitoring for Transfeminine Patients

- Baseline:
  - Renal panel, if on spironolactone
  - Lipids, if indicated clinically
  - Fasting Glucose, if indicated clinically
  - Testosterone level, if suspicion for hypogonadism
  - Prolactin level, if on medication or sx of prolactinoma
  - Liver Enzymes, if suspicion for underlying liver disease
Lab Monitoring for Transfeminine Patients

- If on spironolactone, serum electrolytes 2 to 8 weeks after start/dosage change, then every 3 months in first year, then yearly

- Lipids, glucose, LFTs only as clinically indicated

- Prolactin level ??

- Hgb/Hct will often drop into the normal female range in women on CSHT
Lab Monitoring for Transfeminine Patients

- Serum testosterone level (at 6 to 12 months)
  - Should be less than 55 ng/dl

- Serum Estradiol Levels (?)
  - Ideal level is the mean daily level for premenopausal women (about 100 to 200 pg/ml)
Follow-Up Care on Hormone Therapy

- Assess masculinization or feminization
- Review medication use
- Monitor mood cycles and adjust medication as indicated
- Discuss social impact of transition
- Counsel regarding sexual activity
- Review surgical options
- Plans change of name and gender marker on legal forms
- Review CAD risk factors
- ASSESS SAFETY
Is hormone therapy effective?

2010 meta-analysis (Murad, et al) of studies on hormone therapy

- 80% with improvement in gender dysphoria
- 78% with improvement in psychological symptoms
- 80% improved quality of life
- 72% improved sexual functioning
2015 US Trans Survey

- 8% of respondents reported having “de-transitioned” at some point in time
  - 5% because they realized that gender transition was not for them
  - 4% because initial transition did not reflect the complexity of their gender identity
  - 2% for medical reasons
  - Most because of pressure from other persons or issues connected with social transition
  - 62% were again living as their internalized gender
Further questions

▪ Treating adolescents

▪ Hormone therapy in elderly trans patients.

▪ How to best manage persons who do not identify on a gender binary?
Hormone Therapy in Aging Patients

- Self-assessment of emotional and physical well-being
- Polypharmacy and interactions with hormone therapy
- Stopping or adjusting hormone doses as patients age
- Risk of cardiovascular disease in trans women
- Risk and management of diabetes
- Risk of osteoporosis
- Risk of breast cancer, uterine cancer, cervical cancer, prostate cancer and other tumors
Hormone Therapy in Aging Patients

- Adjustments of the dose of sex hormones may be necessary; the new doses must be adequate to maintain the sex characteristics of the new sex.
- There is as yet no evidence of harmful effects of testosterone on cardiovascular effects in transgender men.
- Maintenance of bone mineral density with aging in both sexes is of great importance.
- Remarkably, with aging, cardiovascular mortality is higher in Transgender women than in transgender men. The underpinnings of this reversed sex difference have not yet been clarified but cardiovascular risks should be aggressively addressed in transgender woman.

(from Gooren and T’sjoen, 2018)
Non-binary, Genderqueer, Gender Fluid, Neutrois

- Affirmation through use of chosen name and (non-binary) pronouns
- Gender expression through clothing, hair, make-up, non-medical measures
- For patients on transfeminine spectrum
  - Spironolactone or GnRH agonist alone
  - Low dose estradiol
  - Limited courses of estradiol
  - ? SERMs
- For patients on the transmasculine spectrum
  - Low dose testosterone
  - Limited courses of testosterone
  - Hormonal or surgical suppression/cessation of menses
- Surgical gender affirmation without hormonal gender affirmation
More on Hormone Safety
Testosterone Treatment for Transmasculine People

- Despite changes in CAD risk factors, no increase in cardiovascular morbidity and mortality in 876 FTM patients. Gooren, et al, 2008

  - No difference in overall or cause-specific mortality
  - Only 1 MI in 72 yo patient on T for 42 years
  - No increase in over-all cancer mortality. No breast CA
  - 1 death by illicit drug use
## Estrogen Therapy for Transfeminine People

- **Women’s Health Initiative:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio</th>
<th>Increased Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD event</td>
<td>1.29</td>
<td>7/10,000</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.32</td>
<td>7/10,000</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.18</td>
<td>1/10,000</td>
</tr>
<tr>
<td>PE</td>
<td>2.13</td>
<td>8/10,000</td>
</tr>
<tr>
<td>CVA</td>
<td>1.41</td>
<td>8/10,000</td>
</tr>
<tr>
<td>DVT</td>
<td>2.07</td>
<td>13/10,000</td>
</tr>
</tbody>
</table>

- Total mortality not increased, but increase in breast cancer.
Estrogen Therapy for Transfeminine People

▪ HERS (HRT in patients with prior coronary event)
  ▪ Treatment with Premarin and Provera
  ▪ 1380 patients in treatment and control groups
  ▪ No significant difference in primary outcomes
  ▪ Lower LDL and higher HDL in treatment group
  ▪ More events in treatment group in year 1, but fewer in years 4 and 5
  ▪ Increased risk of VT (32 vs 12 cases)
Estrogen Therapy for Transfeminine People

- Coronary Drug Project, 1966 – 1975:
  - Men aged 30 to 64 with previous MI
  - Treated with high-dose conjugated estrogen, 2.5 or 5 mg
  - High-dose group discontinued after 5 years because of increased coronary events
  - Low-dose group discontinued because of increased risk of cancers
Estrogen Therapy for Transfeminine People

- ESPRIT (Estrogen for the Prevention of Re-Infarction Trial)
  - 1017 women ages 50 to 69, after first MI, randomised to 2 mg estradiol po daily or placebo, between 1996 and 2000
  - Oral estradiol provided neither a beneficial nor a detrimental effect in the incidence of ischemic heart disease, any heart disease or stroke
Estrogen Therapy for Transfeminine People

- Gooren, et al (2008), 2236 MTF patients
  - Increased weight, visceral fat, impaired glucose sensitivity, small increase in BP; increased HDL, decreased LDL
  - NO increased in cardiovascular morbidity or mortality
  - Increased incidence of VT (6-8%) but only in patients treated with ethinyl estradiol
Estrogen Therapy for Transfeminine People

  - Meta-analysis of 16 eligible studies, 1471 MTF
  - Very few reported cardiovascular events
  - Quality of evidence is very low
  - No meaningful assessment of clinical outcomes like death, stroke, MI or VT. SUGGESTS a higher incidence in MtF, BUT most were from one center using “fairly high estrogen dose”
Estrogen Therapy for Transfeminine People

  - 996 MtF patients, 18.5 years follow-up
  - current but not past use of EE associated with 3x risk of CV death
  - about 2x rate of CV death in 40-64 yo
  - Ischemic HD death in 18 subjects, 11, had been using EE, 5 had suffered previous MI
  - stroke in 5 subjects, in younger subjects, all had used EE
  - in over 65 yo, total mortality was not increased
  - higher lipid levels and higher rates of smoking in MtF
Estrogen Therapy for Transfeminine People

- Venous thromboembolism

- In the Dutch cohorts, rates of 2.6% annually in first year, falling to 0.4% thereafter, with 1 – 2% risk of death from PE, BUT all but 1 of these patients was using oral ethinyl estradiol.
Estrogen Therapy for Transfeminine People

  - Cohort of transgender women treated with transdermal estradiol and cyproterone acetate
  - 8% (13/162) with pro-thrombotic mutation
  - NO occurrence of VT with a mean follow-up of 49.6 months
Estrogen Therapy for Transfeminine People

  - MTF patients treated with Premarin
  - Increased levels of anti-oxidant and decreased levels of inflammatory markers suggesting cardiovascular BENEFIT
  - Oral estrogen resulted in a transient increase in inflammatory markers and clotting factors (within 2 to 4 months but returning to baseline by 6 months); transdermal estrogen showed no such changes
Estrogen Therapy for Transfeminine People

  ▪ Chemical markers of coagulability in MTF patients on EE, oral estradiol and transdermal estradiol
  ▪ Oral and transdermal estradiol groups were similar in all measures of pro-thrombotic variables, and did not differ in the baseline levels seen in natal females
  ▪ An earlier study had shown the incidence of VT was 20 x higher in oral EE versus transdermal estradiol
Estrogen Therapy for Transfeminine People

- 214 traswomen taking various forms of estrogen for an average of 7.7 years
  - Prevalence of DVT/PE  60.7/1000 case
  - Prevalence of MI  18.7/1000, higher than in control cis-women, but not significantly different than in cis-men
  - Prevalence of TIA/CVA  18.7/1000, higher than in cis-men, but not significantly different than cis-women
Estrogen Therapy for Transfeminine People

- 2842 transfeminine patients on various formulations and doses of estradiol, average 4.0 years follow-up
  - VTE 5.5/1000 about twice the rate seen in both cis-men and cis-women
  - MI 2.9/1000 about twice the rate in cis-women, no difference from cis-men
  - Ischemic stroke 4.8/1000 about the same as in cis-men and cis-women
- Unlike studies on cardiovascular events in cis-women on hormone therapy, that show an early increase in risk for cardiovascular events followed by a decline in incidence, the risk of VTE and stroke seemed to increase over time on transfeminine patients
Unfortunately, there are no studies that include significant numbers of patients on injectable estradiol or compare injectable estradiol with any other forms of estrogen.
Resources

• Transgender Medical Consultation Service
  https://transline.zendesk.com/home

• WPATH SOC v.7
  http://www.wpath.org/documents/Standards%20of%20Care%20V7%20-%202011%20WPATH.pdf

• Endocrine Society Clinical guidelines
  cem.endojournals.org J Clin Endocrinol Metab. September 2009, 94(9):3132-3154

• UCSF Center of Excellence for Transgender Health
  http://transhealth.ucsf.edu/trans?page=protocol-00-00

• National LGBT Health Education Center
  http://www.lgbthealtheducation.org