Transgender Medicine – beyond the guidelines.

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Overview

- Definitions and history
- Review of hormonal treatment of transgender patients
- Discussion of risks of transgender hormone therapy (with a focus on two)
- Discussion of some unresolved issues
  - use of progesterone
  - the aging transgender patient
Definitions

- **Gender Non-conforming**: A term for individuals whose gender expression is different from societal expectations related to gender.

- **Transgender**: an umbrella term used by many different groups. Most often refers to those who feel comfortable in a gender to which they were not assigned at birth. *(Transsexual)*

- **Gender Identity**: an individual’s internal sense of being male, female, or something else.
  - Male-to-female (MTF)/transgender woman/transwoman/affirmed female.
  - Female-to-male (FTM)/transgender man/transman/affirmed male.
Terminology

- **Transition**: The time when a person begins living as the gender with which they identify rather than the gender they were assigned at birth.
  - Often includes changing one’s first name and dressing and grooming differently.
- Might include
  - taking hormones,
  - having surgery
  - changing identity documents (e.g. driver’s license, Social Security record) to reflect one’s gender identity.
- Medical and legal steps are often difficult for people to afford.
History

- Harry Benjamin International Gender Dysphoria Association (HBIGDA), now the World Professional Association of Transgender Health (WPATH) founded in 1979

- “Standards of Care” now on 7th edition.

- 2009 “Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline”.

- Updated Endocrine Society Guidelines are being developed.
DSM-5 Gender Dysphoria

A marked incongruence between one’s experienced/expressed gender and assigned gender, of at least 6 months’ duration, 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).
2009 Endocrine Society guidelines recommend that the diagnosis be made by a Mental Health Professional

- “The Letter”
  - Accurate diagnosis
  - Address psychosocial or psychiatric problems
  - Readiness criteria.

- Emerging informed consent model
Goals of hormone therapy:

- Induce the secondary sex characteristics of the desired gender while reducing those of the natal sex.

- Provide relief from gender dysphoria
  - Studies have generally found a positive response to hormone therapy
  - 2016 systematic review found low quality evidence (no RCTs) that hormone therapy leads to improvements in psychological functioning.
Hormone Therapy MtF
2009 Endocrine Society Guidelines

- **Estrogen**
  - Oral estradiol (17β-estradiol) 2-6 mg/d
  - Transdermal estradiol patch 0.1 – 0.4 mg twice weekly
  - Parenteral estradiol valerate/cypionate 5-20 mg IM every 2 weeks or 2-10 mg IM every week.

- **Antiandrogens**
  - Spironolactone 100 – 200 mg/day
  - Cyproterone acetate 50 – 100 mg/day
  - GnRH agonist – 3.75 mg sc monthly
Medical conditions that can be exacerbated by cross-sex hormone therapy with estrogen

- Very high risk of serious adverse outcomes:
  - Thromboembolic disease

- Moderate to high risk of adverse outcomes:
  - Macroprolactinoma
  - Severe liver dysfunction (transaminases >3X ULN)
  - Breast cancer
  - Coronary artery disease
  - Cerebrovascular disease
  - Severe migraine headaches.
Feminizing effects in MTF
2009 Endocrine Society Guidelines

<table>
<thead>
<tr>
<th>Effect</th>
<th>Onset</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redistribution of body fat</td>
<td>3-6 months</td>
<td>2-3 yr</td>
</tr>
<tr>
<td>Decrease muscle mass and strength</td>
<td>3-6 months</td>
<td>1-2 yr</td>
</tr>
<tr>
<td>Softening of skin/decreased oiliness</td>
<td>3-6 months</td>
<td>Unknown</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>1-3 months</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Decreased spontaneous erections</td>
<td>1-3 months</td>
<td>3-6 months</td>
</tr>
<tr>
<td>Male sexual dysfunction</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Breast growth</td>
<td>3-6 months</td>
<td>2-3 yr</td>
</tr>
<tr>
<td>Decreased testicular volume</td>
<td>3-6 months</td>
<td>2-3 yr</td>
</tr>
<tr>
<td>Decreased sperm production</td>
<td>Unknown</td>
<td>&gt;3 yr</td>
</tr>
<tr>
<td>Decreased terminal hair growth</td>
<td>6-12 months</td>
<td>&gt;3 yr</td>
</tr>
<tr>
<td>Scalp hair</td>
<td>No regrowth</td>
<td></td>
</tr>
<tr>
<td>Voice changes</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
Hormone Therapy MtF

- **Estrogen**
  - Oral estradiol (17β-estradiol) 2-6 mg/d
  - Transdermal estradiol patch 0.1 – 0.4 mg twice weekly
  - Parenteral estradiol valerate/cypionate 5-20 mg IM every 2 weeks or 2-10 mg IM every week.

- **Antiandrogens**
  - Spironolactone 100 – 200 mg/day
  - Cyproterone acetate 50 – 100 mg/day
  - GnRH agonist – 3.75 mg sc monthly
Not mentioned in the Endocrine Society Guidelines.
- Use of finasteride
- Use of progesterone.
Hormone Therapy FtM
2009 Endocrine Society Guidelines

- Oral testosterone undecanoate – 160 – 240 mg/d
- Parental Testosterone enanthate/cypionate – 100 – 200 mg im every 2 weeks or 50% weekly.
- Testosterone undecanoate 1000 mg every 12 weeks
- Transdermal
  - testosterone gel 1% 2.5 – 10 g/d
  - testosterone patch 2.5 – 75 mg/d
Medical conditions that can be exacerbated by cross-sex hormone therapy with testosterone.

- Very high risk of serious adverse outcomes
  - Breast or uterine cancer
  - Erythrocytosis (hematocrit >50%)
- Moderate to high risk of adverse outcomes
  - Severe liver dysfunction – transaminases >3X ULN
## Masculinizing effects in FTM

2009 Endocrine Society Guidelines

<table>
<thead>
<tr>
<th>Effects</th>
<th>Onset</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin oiliness/acne</td>
<td>1-6 months</td>
<td>1-2 yr</td>
</tr>
<tr>
<td>Facial/body hair growth</td>
<td>6-12 months</td>
<td>4-5 yr</td>
</tr>
<tr>
<td>Scalp hair loss</td>
<td>6-12 months</td>
<td></td>
</tr>
<tr>
<td>Increased muscle mass/strength</td>
<td>6-12 months</td>
<td>2-5 yr</td>
</tr>
<tr>
<td>Fat redistribution</td>
<td>1-6 months</td>
<td>2-5 yr</td>
</tr>
<tr>
<td>Cessation of menses</td>
<td>2-6 months</td>
<td>**</td>
</tr>
<tr>
<td>Clitoral enlargement</td>
<td>3-6 months</td>
<td>1-2 yr</td>
</tr>
<tr>
<td>Vaginal atrophy</td>
<td>3-6 months</td>
<td>1-2 yr</td>
</tr>
<tr>
<td>Deepening of voice</td>
<td>6-12 months</td>
<td>1-2 yr</td>
</tr>
</tbody>
</table>
- Oral testosterone undecanoate – 160 – 240 mg/d

- Parental Testosterone enanthate/cypionate – 100 – 200 mg im every 2 weeks or 50% weekly.

- **Testosterone undecanoate** 1000 mg every 12 weeks

- Transdermal
  - testosterone gel 1% 2.5 – 10 g/d
  - testosterone patch 2.5 – 75 mg/d
There is almost no literature directly comparing different hormone regimens for transgender patients in terms of efficacy, satisfaction and safety. (No RCTs)
Safety/Risks

- What are the safety concerns in cross-sex hormone therapy?
Wierckx K et al., 2014: Multicenter 1-year prospective study in 53 transmen and 53 transwomen who started cross-sex hormone therapy (CSHT) between 2010 and 2012

Transmen received IM testosterone undecanoate 1000 mg every 3 months

Transwomen received 50 mg cyproterone acetate and 4 mg oral estradiol valerate (<45 yo) or 100 µg/24 hours transdermal estradiol (≥ 45 yo).

Female-to-Male/Transmen results.

- No deaths or severe adverse events.
- 2 transmen developed erythrocytosis (hct >52) and 2 had transient elevation in liver enzymes.
- Increases reported in acne and clitoral pain.
- Cholesterol and LDL-C increased and HDL-C decreased.
Short-term Safety

Male-to-Female/transwomen results:

- 3 transwomen had transient elevations in liver enzymes.
- Significant increases in breast tenderness, hot flashes, emotionality and low sex-drive.
- Increases in fasting insulin, total body fat mass and prolactin levels.
- One woman discontinued therapy because of depression.
- No thromboembolic events were seen.
Asscheman H. et al. 2011: Cohort study with median follow-up of 18.5 years at a university gender clinic.

966 MtF (mean age 31.4) and 365 FtM (mean age of 26.1) who started cross-sex hormone therapy before 1997 followed up to 2007 or date of death.

Mortality risk expressed as standardized mortality ratio adjusted for age and biological sex.

Long-term Safety

- MtF patients received a variety of estrogen regimens and cyproterone acetate 100 mg/day.
- FtM patients received parenteral or oral testosterone or testosterone gel.
Table 2  SMR adjusted for age and period of follow-up on hormone treatment by biological sex in 1331 male-to-female and female-to-male transsexual subjects.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Male-to-female transsexuals</th>
<th>Female-to-male transsexuals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed cases</td>
<td>SMR (95% CI)</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>28</td>
<td>0.98 (0.88–1.08)</td>
</tr>
<tr>
<td>Lung</td>
<td>13</td>
<td>1.35 (1.14–1.58)</td>
</tr>
<tr>
<td>Digestive tract</td>
<td>3</td>
<td>0.42 (0.28–0.60)</td>
</tr>
<tr>
<td>Hematological</td>
<td>6</td>
<td>2.58 (1.97–3.30)</td>
</tr>
<tr>
<td>Brain</td>
<td>2</td>
<td>1.59 (0.95–2.46)</td>
</tr>
<tr>
<td>Other: kidney, melanoma, bone, and prostate in MtF. In FtM: leiomyosarcoma</td>
<td>4</td>
<td>0.79 (0.57–1.07)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>18</td>
<td>1.64 (1.43–1.87)</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>5</td>
<td>1.26 (0.93–1.64)</td>
</tr>
<tr>
<td>AIDS</td>
<td>16</td>
<td>30.20 (26.0–34.7)</td>
</tr>
<tr>
<td>Endocrine/diabetes</td>
<td>2</td>
<td>0.85 (0.41–1.32)</td>
</tr>
<tr>
<td>Respiratory system diseases</td>
<td>4</td>
<td>0.85 (0.61–1.14)</td>
</tr>
<tr>
<td>Digestive system diseases</td>
<td>3</td>
<td>1.01 (0.68–1.45)</td>
</tr>
<tr>
<td>Genitourinary system disease (ESRD)</td>
<td>1</td>
<td>1.21 (0.58–2.17)</td>
</tr>
<tr>
<td>Nervous system disease (MS)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>External causes</td>
<td>24</td>
<td>7.67 (6.84–8.56)</td>
</tr>
<tr>
<td>Illicit drugs use</td>
<td>5</td>
<td>13.20 (9.70–17.6)</td>
</tr>
<tr>
<td>Suicide</td>
<td>17</td>
<td>5.70 (4.93–6.54)</td>
</tr>
<tr>
<td>Unknown/ill-defined symptoms</td>
<td>21</td>
<td>4.00 (3.52–4.51)</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>1.51 (1.47–1.55)</td>
</tr>
</tbody>
</table>

ESRD, end-stage renal disease; MS, multiple sclerosis.
Long-term Safety

- Overall 51% relative increased mortality rate in MtF compared to the general population.
  - Mainly due to suicide, illicit drugs, AIDS, cardiovascular disease and unknown causes.
- No significant increase overall in FtM
  - Should be noted that they were younger in the beginning.
  - Sample size of older patients was much smaller
Long-term Safety

- Cardiovascular disease mortality in MtF patients
  - Smokers.
  - Ethinyl estradiol – the increased risk was found only in those who were on this.
    - No increased risk was found in former users who had changed to other formulations and lower doses of estradiol.

- No breast cancer seen in either group.
Long-term safety

- Wierckx et al. 2013: Cross-sectional study of 214 transwomen and 138 transmen with an age-matched population.

- Transgender subjects were compared to both control men and women.

- Participants on CSHT an average of 7.4 years.

- Hormone therapies were quite variable.

In transwomen:
- Increased risk of venous thromboembolism and/or PE. Incidence was 5.1%.
- Increased risk of cerebrovascular disease compared to control men
- Increased risk of MI compared to control women and similar to control men.

Both groups had an increased risk of type 2 diabetes. (screening effect?).

No increased risk of cancers in either group
- Venous Thromboembolism?

- Cardiovascular disease?
A 1989 study from Amsterdam reported a 45-fold increase in the incidence of VTE among 303 MtF subjects treated with oral ethinyl estradiol 0.1 mg daily + cyproterone acetate. (Asscheman)

13/19 cases had no known risk factors

Risk clearly associated with age (2.1% < 40 years, 12% >40 years of age).

Venous Thromboembolism

- This led to use of transdermal estradiol (patches) in MtF people over age 40.
Venous Thromboembolism

- 1997 Van Kesteren et al published a larger study with longer follow-up

- Only one VTE event diagnosed in patients using transdermal estradiol.

- VTE incidence was still 20-fold increased in the ethinyl estradiol users.

- NOTE: In both the 1989 and 1997 studies the majority of VTE was diagnosed in the first year of estrogen treatment (77% in 1989 and 58% in 1997).
Venous Thromboembolism

- By the early-to-mid 2000’s providers were **no longer prescribing ethinyl estradiol** for transition.

- How much, if any, difference between oral and transdermal 17-beta estradiol?

- First-pass metabolism vs formulation.

- Use of cyproterone acetate.
Arnold JD, et al. A retrospective chart review of 676 transgender women receiving oral estradiol-based CSHT for a total of 1,286 years of hormone treatment and a mean of 1.9 years per patient showed a very low incidence of VTE.

- One individual. 0.15% of the population, incidence of 7.8 events per 10,000 person-years.
- Limitations of a retrospective study and small sample size.
- One of very few US-based studies.

Table 1. Baseline characteristics of transgender women (N = 676)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>33.2 ± 10.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.6 ± 6.8</td>
</tr>
<tr>
<td>White</td>
<td>339 (50.0)</td>
</tr>
<tr>
<td>African American</td>
<td>170 (25.1)</td>
</tr>
<tr>
<td>Race unreported or refused to report</td>
<td>95 (14.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>25 (3.7)</td>
</tr>
<tr>
<td>&gt;1 race</td>
<td>14 (2.1)</td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>9 (1.3)</td>
</tr>
<tr>
<td>HIV positive</td>
<td>154 (22.8)</td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m²</td>
<td>160 (23.6)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>143 (21.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>88 (13.0)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>59 (8.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>43 (6.4)</td>
</tr>
<tr>
<td>Renal disease (eGFR ≤ 60)</td>
<td>11 (1.6)</td>
</tr>
</tbody>
</table>

BMI = body mass index; eGFR = estimated glomerular filtration rate.

*Data are presented as mean ± SD or number (percentage).
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral estradiol</td>
<td>676 (100%)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>634 (93.8%)</td>
</tr>
<tr>
<td>Finasteride</td>
<td>112 (16.6%)</td>
</tr>
<tr>
<td>Conjugated equine estrogens</td>
<td>42 (6.2%)</td>
</tr>
<tr>
<td>Oral progesterone</td>
<td>27 (4.0%)</td>
</tr>
<tr>
<td>Intramuscular medroxyprogesterone acetate</td>
<td>3 (0.4%)</td>
</tr>
</tbody>
</table>
Ott et al. 2010: Retrospective cohort study in a transgender specialty clinic

Standard treatment for MtF patients was with transdermal estradiol and cyproterone acetate. Screening for thrombophilic disorders standard.

Out of 162 MtF patients 8% were found to have thrombophilic defects.

None developed venous thromboembolism during a mean duration of 49.6 months of follow up.

Venous Thromboembolism

- At this time, transdermal estradiol is viewed as the treatment of choice for:
  - Older patients
  - Smokers
  - Known CAD or history of venous thromboembolism
  - Other risk factors: hypertension, hyperlipidemia, diabetic, obesity

- For others oral estradiol is a reasonable option.

- NOTE: there is very little literature about using injectable estradiol.
Initially a surprising finding.

Studies are from Europe.
- Ethinyl estradiol, conjugated equine estrogens
- Smokers
- Almost all were taking cyproterone acetate.
- Studies have had subpopulations of women who were older when they started hormone therapy.
Cardiovascular Risk

- Timing hypothesis – effects may depend on the individual’s cardiovascular health at the start of therapy.
  - Estrogen therapy could aggravate pre-existing CV disease in older transwomen.

- Underlying genetic or epigenetic differences between males and females?

- Still an unsettled question and cardiovascular risk factors should be closely monitored especially in transwomen starting HRT at a later age.
Progesterone

- Not discussed in the 2009 Endocrine Society guidelines.

- Sometimes used to suppress testosterone levels in transgender women or to stop menstrual bleeding in transgender men.

- Many transwomen will request progesterone because they believe it will enhance breast development.
Review of 11 studies between 1974 -2012 looked at breast development in transwomen.

1 case report, 4 cross-sectional, 2 retrospective and 4 prospective. No placebo-controlled studies. All small.

Used different estrogen and anti-androgen regimens. No studies focused solely on the question of progesterone.

Overall, studies did not find a difference in final breast tissue circumference among different types of estrogens.

A majority of trans women in several different studies elected to undergo breast augmentation. (66% and 70%)

One study found no difference between a regimen that used GnRH analog + estradiol vs. cyproterone + ethinyl estradiol in terms of breast outcomes.
The available evidence does not provide support adding progestins to cross-sex hormone administration in trans women for the purpose of increasing breast size.

However the quality and amount of available evidence really doesn’t answer the question.

The studies do indicate that it is important to set realistic goals.
Why not use progesterone?

- Increased risk of thromboembolism
- Breast cancer
- Weight gain/fluid retention
Aging Transgender Patients

- Should cross-sex hormones be continued in aging transgendered individuals?
- What to do with the transgender patient who presents at a more advanced age?
Two articles in the literature and both are basically opinion pieces. Nothing evidence based.

Should cross-sex hormones be continued in aging transgendered individuals?

- Parallels with older people receiving sex steroid treatment.
  - Withdrawing estrogen therapy from a transwoman who has undergone orchiectomy is like surgical menopause.
  - Males who undergo complete androgen deprivation for prostate CA tx may develop metabolic syndrome and bone loss.
- They recommend continuing therapy though at a lower dose.
- Probably makes sense to switch from oral to transdermal estrogen.
What to do with the transgender patient who presents at a more advanced age?

“No good reasons to withhold cross-sex hormone treatment” from older subjects just because of age.
Summary

- There are guidelines to help with cross-sex hormone treatment of transgender patients and updated guidelines on the way.

- Overall risks of CSHT seem to be low but more studies are needed – special attention to cardiovascular risk in transwomen.

- It is not clear which hormonal regimens are best for treating transgender patients.

- There are many other unanswered questions as well.
Thank you