Gender Dysphoria, an Endocrine Condition, not a Publicity Stunt
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Disclosure
I have no relevant financial relationships with the manufacturers(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity.

I intend to discuss off label use of generic GnRH analogs as recommended by the Endocrine Society Clinical Practice Guidelines in my presentation.

Outline
• Terminology
• Prevalence
• Should gender dysphoria be medicalized?
• Risks of treatment
• Overlap between DSD and GD
• 2 Cases that overlap
• Data on possible biologic mechanism in gender dysphoria
Terminology

Gender and Sexual Minorities (GSM)

Gender dysphoria
Disorders of Sex Development (DSD)
LGB

DSD Definitions

• Disorders of Sex Development: multiple chromosomal and hormonal conditions resulting in anatomic changes—ambiguous genitalia or complete sex reversal.
Gender Identity Terminology

- **Gender Identity**: a person’s deeply held internal sense of being male or female or somewhere on the male/female spectrum (who you are in your soul).
- **Gender Dysphoria**: incongruence between one’s expressed gender and assigned gender.
- **Transgender**: (an adjective, not a noun or a verb) A broad term that describes people with gender dysphoria who desire surgery and some who don’t.
- **Transsexual**: an older adjective for people with gender dysphoria who desire gender conversion (surgical numbers used to be used to determine prevalence).

- **Cisgender**: agreement between assigned and preferred gender.

<table>
<thead>
<tr>
<th>1994 (DSM-IV)</th>
<th>2013 (DSM-V)</th>
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<tr>
<td>Gender Identity Disorder (outmoded because of the term disorder)</td>
<td>Gender dysphoria</td>
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Gender Acronyms

- **MTF**: (adj.) natal male to female, trans female
- **FTM**: (adj) natal female to male, trans male
- **GSM**: Gender and Sexual Minorities
- **LGBTQIA**: Lesbian, Gay, Bisexual, Transgender, Questioning, Intersex, Allies

More Terms

- **Target gender**: preferred gender
- **Gender Fluidity**: changing gender identity
- **Persisters and Desisters**: people whose dysphoria persists or not
- **Gender confirmation surgery**: Formerly called sex reassignment surgery (SRS)
- **Blending**: Newer term for “passing”

Who has gender dysphoria and who is just a tomboy or going through a phase?

- **Persistence**
- **Insistence**
- **Consistency**
How to address patients

- Patients usually come to GPS with known preferred names.
- Providers should ask patients which pronouns they prefer.
- Don’t go by the pronouns the parents use.
- It is respectful to use the preferred pronouns throughout the clinic note.

Prevalence: ~1 in 200 in U.S.


Gender dysphoria has almost nothing to do with sexuality and little to do with sexual attractions.

People with Gender Dysphoria can be heterosexual, homosexual, bisexual, asexual, presexual.
Example of prepubertal gender dysphoria

- 3 year old child asks her parents, "If I died and went to heaven would I come back in the right body?"

WPATH: World Professional Association of Transgender Health

Version 6: Do not pathologize
Version 7: Do not psychopathologize


But there may be medical and legal advantages in "medicalizing" gender dysphoria...not psychologically pathologizing but in keeping it medicalized.

1. Health risks associated with gender dysphoria
2. Medical treatments available and associated with risks
Suicide rate in GD

- If left untreated, 28-41% of patients with gender dysphoria attempt suicide.


Endocrine Society Clinical Practice Guidelines


- Co-Sponsoring Associations: European Society of Endocrinology, European Society for Paediatric Endocrinology, Lawson Wilkins Pediatric Endocrine Society, and World Professional Association for Transgender Health (WPATH).

2009 Consensus statement on Gender Dysphoria

- Gender dysphoria now under the realm of pediatric endocrinologists.
Some Consensus Recommendations

- Adolescents who fulfill eligibility and readiness criteria for gender reassignment should undergo treatment to suppress pubertal development. (GnRH analogs reduce unwanted secondary sexual characteristics, reduce the need for and/or extent of surgical procedures later, and eliminates voice change).

- Suppression of pubertal hormones should start when girls and boys first exhibit physical changes of puberty, but no earlier than Tanner stage 2-3.

More recommendations

- Pubertal development of the desired opposite sex be initiated at about the age of 16 yrs.

- Defer surgery until the individual is a least 18 yrs old.

- All patients should be informed and counseled regarding options for fertility prior to treatment with sex hormones of the desired sex.

Other Recommendations

Given the high rate if remission of GD after the onset of puberty, we recommend against a complete social role change and hormone treatment in prepubertal children with GD.

Our clinic has no objections to early social transition in cases of strong dysphoria.
Mental Health Outcomes

After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved. Well-being was similar to or better than same-age young adults from the general population.


Initial Assessment (Adults)

- **History**: Family history, general health, sexual health, and psychosocial history
- **Physical examination**: Body weight, BMI, blood pressure, palpation of liver and breast masses
- **General laboratory tests**: Full blood count, creatinine, urea, electrolytes, liver function tests, fasting glucose, lipid profile, UA
- **Hormonal profile**: FSH, LH, total testosterone, 17B-estradiol, PRL
- **Sexual transmitted diseases**: HBV, HCV, HIV, TPHA


Initial Assessment (Adults)

- **Genetic Assessment**: Karyotype
- **Bone Mineral Density**: If osteoporosis risk factors are present
- **EKG**: If cardiovascular risk factors are present
- **FIM**: Cervical cancer screening
  - Lower abdomen US for ovarian morphology
- **MIF**: Venous system examination
  - Screening for inherited thrombophilia with family history of thromboembolic events
  - Protein C, protein S, ATIII, Factor V mutations, prothrombin G mutations, MTHFR mutations
  - Prostate cancer screening

Risks Associated with hormone therapy in transgender patients

Likely increased risk
Likely increased risk with additional factors
Possible increased risk
Possible increased risk especially with additional risk factors
No increased risk or inconclusive

Bold are clinically significant


Risks Associated with androgen therapy in FTM patients

Likely increased risk
- Polycythemia
- Weight gain
- Acne
- Androgenic alopecia (balding)
- Sleep apnea


Risks Associated with androgen therapy

- Possible increased risk with or without additional risk factors
- Elevated liver enzymes
- Hyperlipidemia
- Destabilization of certain psychiatric disorders
- Cardiovascular disease
- Hypertension
- Type 2 diabetes
- Loss of bone density
- Cancer (breast, cervical, ovarian, uterine)

Risks Associated with Feminizing hormones

- Likely increased risk
  - Venous thromboembolic disease
  - Gallstones
  - Elevated liver enzymes
  - Weight gain
  - Hypertriglyceridemia

- Possible increased risk especially with additional risk factors
  - Cardiovascular disease
  - Hypertension
  - Hyperprolactinemia
  - Type 2 diabetes
  - Breast Cancer

- No increased risk or inconclusive

What is the overlap?

DSD

Gender Dysphoria

Percent of patients assigned female by diagnosis

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Gender Dysphoria in DSD

- Gender dysphoria can be as high as 80% in microphallus and 63% in some testosterone synthesis defects.

Gender Dysphoria also varies with the condition based on the assigned gender.
Gender dysphoria (conversion) in CAH

- 5.2% in those raised as female
- 12.1% in those raised as male


Published literature on Chromosomal abnormalities

- Overall chromosomal abnormalities 1.5%
- 2.9% in the FTM
- 0.6% in the MTF


But how many patients with gender dysphoria have DSDs and vice-versa?
CMH Experience
2 multidisciplinary Clinics

• GUIDE (for DSD) (135 patients)

• GPS (for gender dysphoria) (150 patients)

Gender Pathways Services (GPS) Clinic for GD

Jill Jacobson, M.D. (Endocrinology)
Angela Tuteur, M.D. (Endocrinology)
Christine Moser, Ph.D. (Psychology)
Anna Egan, Ph.D. (Psychology)
Rachel Bartel, A.P.R.N. (Adolescent Medicine)
Heather McQueen, LMSW (S.W.)
Sharon Keating, R.N. (Nursing)
Child Life
Nutrition
Psychiatry (Bob Batterson, M.D.)
Adolescent Medicine (Daryl Lynch, M.D.)

CMH DSD experience

• To date, no patient in GUIDE clinic has undergone gender conversion.
• What percentage of patients with gender dysphoria may have unrecognized DSDs?

CMH Gender dysphoria experience

• A minority of gender dysphoric patients appear to have DSDs.
Case 1 MTF patient
• 28 year old woman from China who was born male.
• Reports that she entered puberty at age 12.
• At age 12 was attacked by classmates.
• Puberty never progressed after that.

Labs:
• LH < .1
• FSH < .1

Differential Diagnosis
• Kallman syndrome?
• Pituitary damage from the attack?
Whole exome sequencing

• Mutation in LHX4 gene

• A transcriptional regulator and be involved in control of differentiation and development of the pituitary gland.

Case 2 FTM patient

• 19 y.o. natal female with feelings of being a boy (man).

• He also has a history of recurrent abdominal pain and primary amenorrhea.

• SOCIAL HISTORY: He began identifying himself as transgender as a sophomore in high school. As a child, he was always playing sports, collecting football cards and dressing like a male. He told his parents 2 months ago and Dad describes it as "dropping a bomb in the living room." Both parents say they are completely supportive and referred to him as a "he". He says he has felt much relief since telling his parents.
Surgical Findings
At the time of surgery, he was found to have findings of Mayer Rokitansky Kuster Hauser syndrome (MRKH), a form of DSD. He had vaginal agenesis. Laparoscopy revealed bilateral uterine horns with significant gross endometriosis and tubal swelling. Bilateral ovaries were visible. Significant endometriosis.

Kindred affected with gender dysphoria, ambiguous genitalia and autism
- 8 year old natal female proband who had ambiguity at birth identifies as male and is autistic.
- 13 year old natal male sibling who identifies as female and has ambiguous genitalia.
- 14 year old natal male sibling who is gender fluid and autistic.
- Father who has undergone gender conversion to female.

All affected family members have an extra copy of 6q16.216.3, a Prader-Willi like syndrome with ambiguous genitalia and autistic features.
What about more common endocrine conditions in gender dysphoria?

- Many of our FTM patients have features of PCOS such as menstrual irregularity, acne, hirsutism that seem to be more common as patients get older.
- Many FTM patients have mothers with PCOS.

Transgender Patients

- 33 MTF
- 57 FTM
Adrenal abnormalities in FTM patients

- N=57 FTM
- 62% with abnormal steroid profile

2009 Consensus statement states that there are no consistent lab abnormalities (failed to reference a 1998 paper showing hormonal abnormalities).

Hyperandrogenism in FTM in Germany

- 83.4% of FTM patients have high androstenedione, DHEA, DHEAS, or testosterone.
- 1/3 thought to have "nonclassical CAH".
• A 2011 Japanese study on FTM transsexual patients demonstrated that 32% had hyperandrogenism associated with PCOS and that 30% were insulin-resistant [Baba, 2011].

• 2014 publication from Spain demonstrated a 49% prevalence of hyperandrogenism in female to male (FTM) transsexuals in Spain [Becerra-Fernadez, 2014].
CAH screening in FTM transgenderism

- 17-OHP levels > 120 ng/dL in 29% of our pediatric patients
- 17 OHP levels > 200 ng/dL in 14% of patients.
- Subsequent testing with ACTH stimulation tests suggests that a subset of these patients may be carriers for 21α-hydroxylase deficiency.

Conclusions

- There are health advantages in medicalizing gender dysphoria.
- There is overlap between GD and DSDs
- Hyperandrogenism and symptoms of hyperandrogenism are common in FTM patients with gender dysphoria.
- Research opportunities exist.
Helpful Resources

- Human Rights Campaign
- National Center for Transgender Equality
  [www.transequality.org/issues/youth-students](http://www.transequality.org/issues/youth-students)
- Gender Spectrum
  [www.genderspectrum.org/resources](http://www.genderspectrum.org/resources)
- Trans Youth Equality Foundation
  [www.transyouthequality.org](http://www.transyouthequality.org)
- Welcoming Schools
  [www.welcomingschools.org](http://www.welcomingschools.org)
- Gay, Lesbian, & Straight Education Network
  [www.glsen.org](http://www.glsen.org)
- WPATH
  [www.wpath.org](http://www.wpath.org)
- Endocrine society guidelines

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