

ENDOCRINE SOCIETY



Endocrine Treatment of Gender-Dysphoric/
Gender-Incongruent Persons:
*An Endocrine Society Clinical Practice
Guideline*

Education Module
June, 2017

Introduction

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Disclosures

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Guideline Task Force Chair

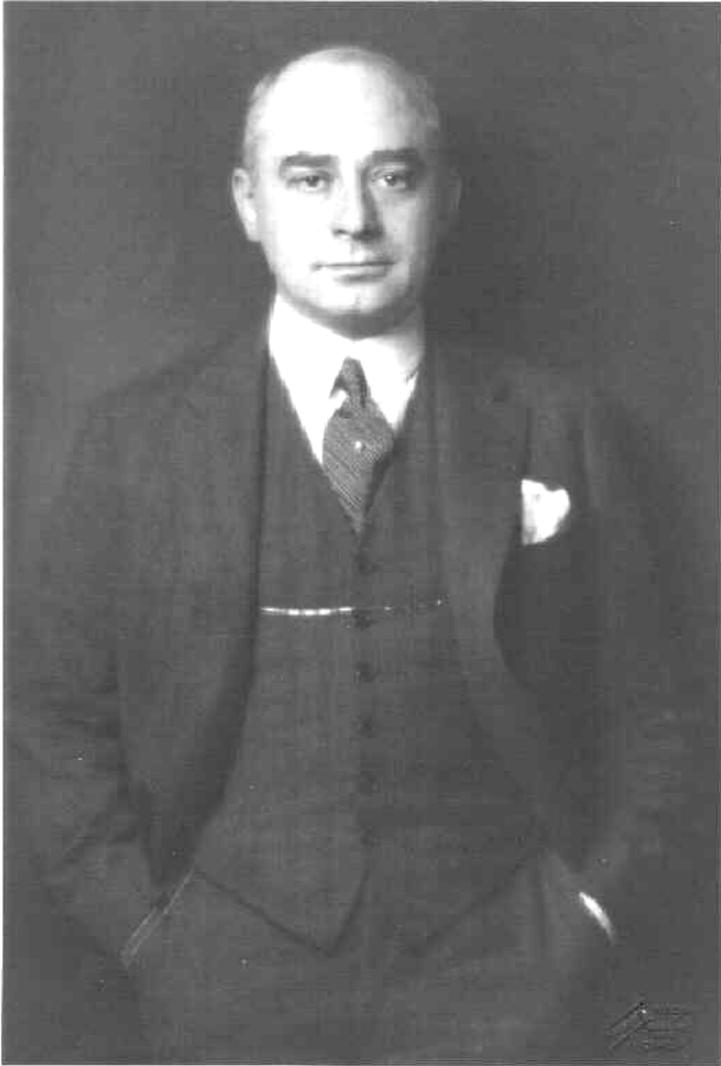
Financial or Business/Organizational Interests:

- None

Significant Financial Interest or Leadership Position:

- None

1963



The TRANSSEXUAL
PHENOMENON



Harry Benjamin, M.D.

ILLUSTRATED WITH PHOTOGRAPHS



THE JULIAN PRESS, INC.

PUBLISHERS

New York

1995 - 1999

Transgender Health: Findings from Two Needs Assessment Studies in Philadelphia.

by Gretchen P. Kenagy

Table of Contents

The Washington, DC Transgender Needs Assessment Survey

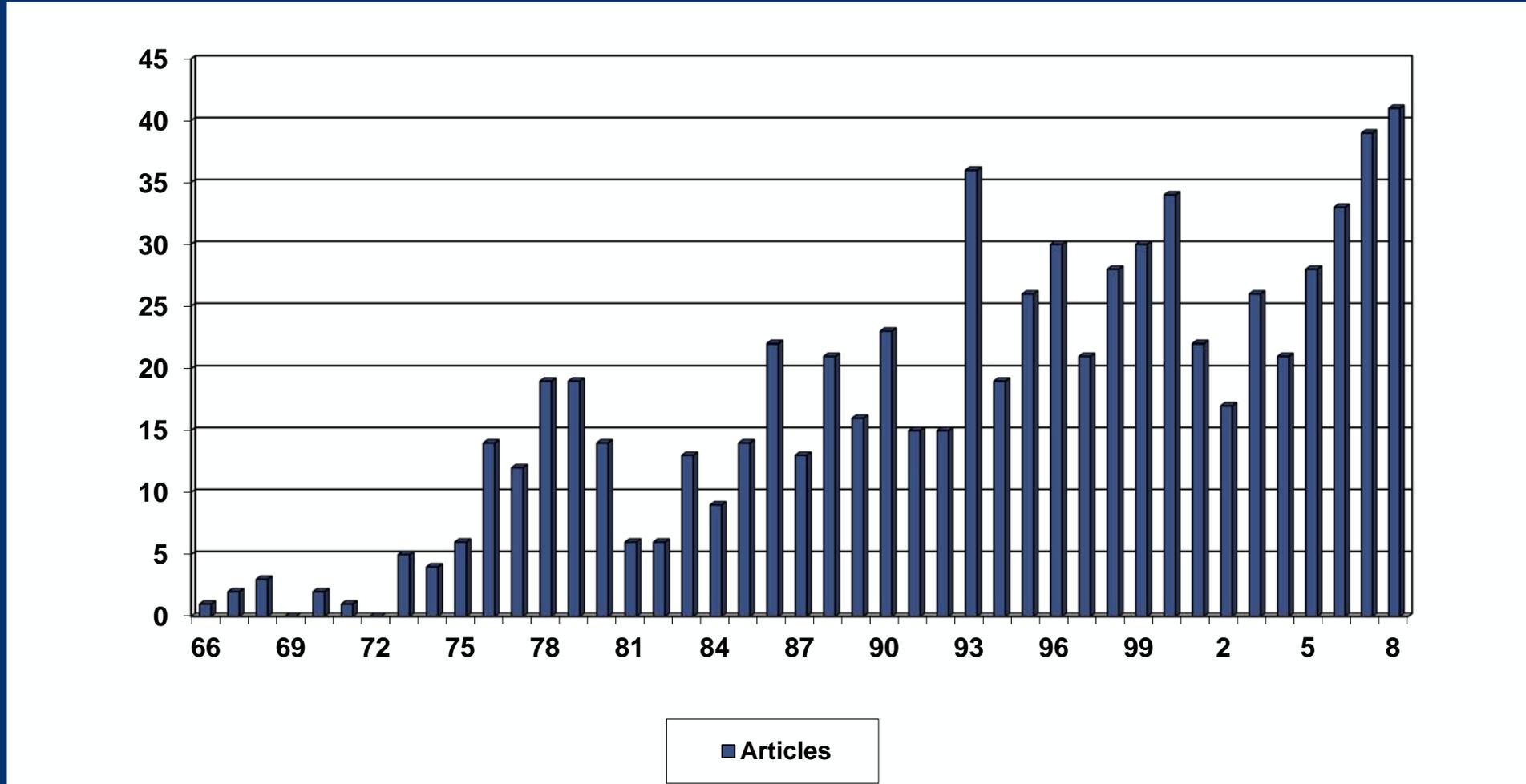
Final Report for Phase Two:

Tabulation of the survey questionnaires; Presentation of Findings and Analysis of the Survey Results; and Recommendations

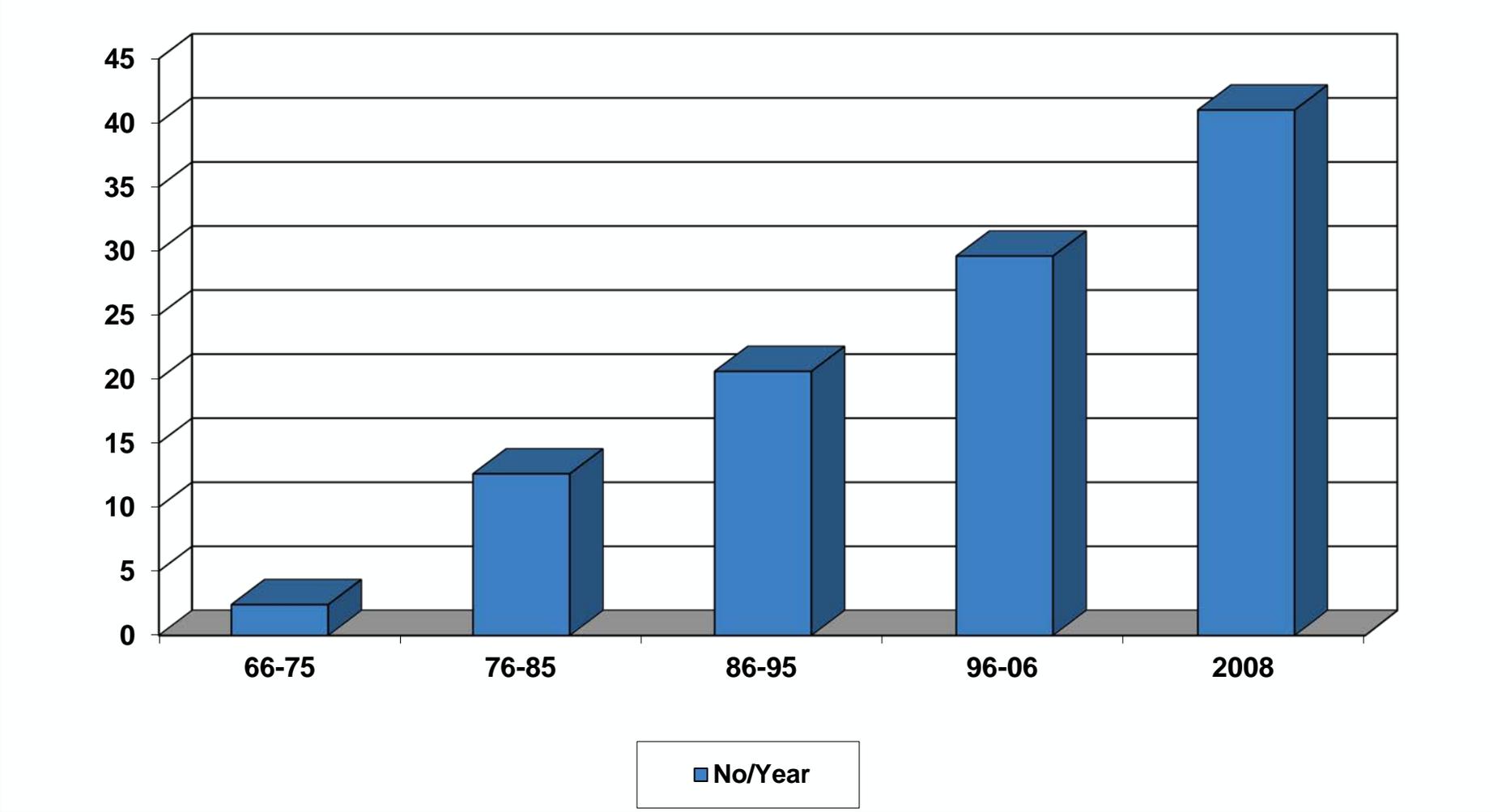
TRANSGENDER NEEDS ASSESSMENT
December 1999

THE HIV PREVENTION PLANNING UNIT
of
THE NEW YORK CITY DEPARTMENT OF HEALTH
212-693-1065

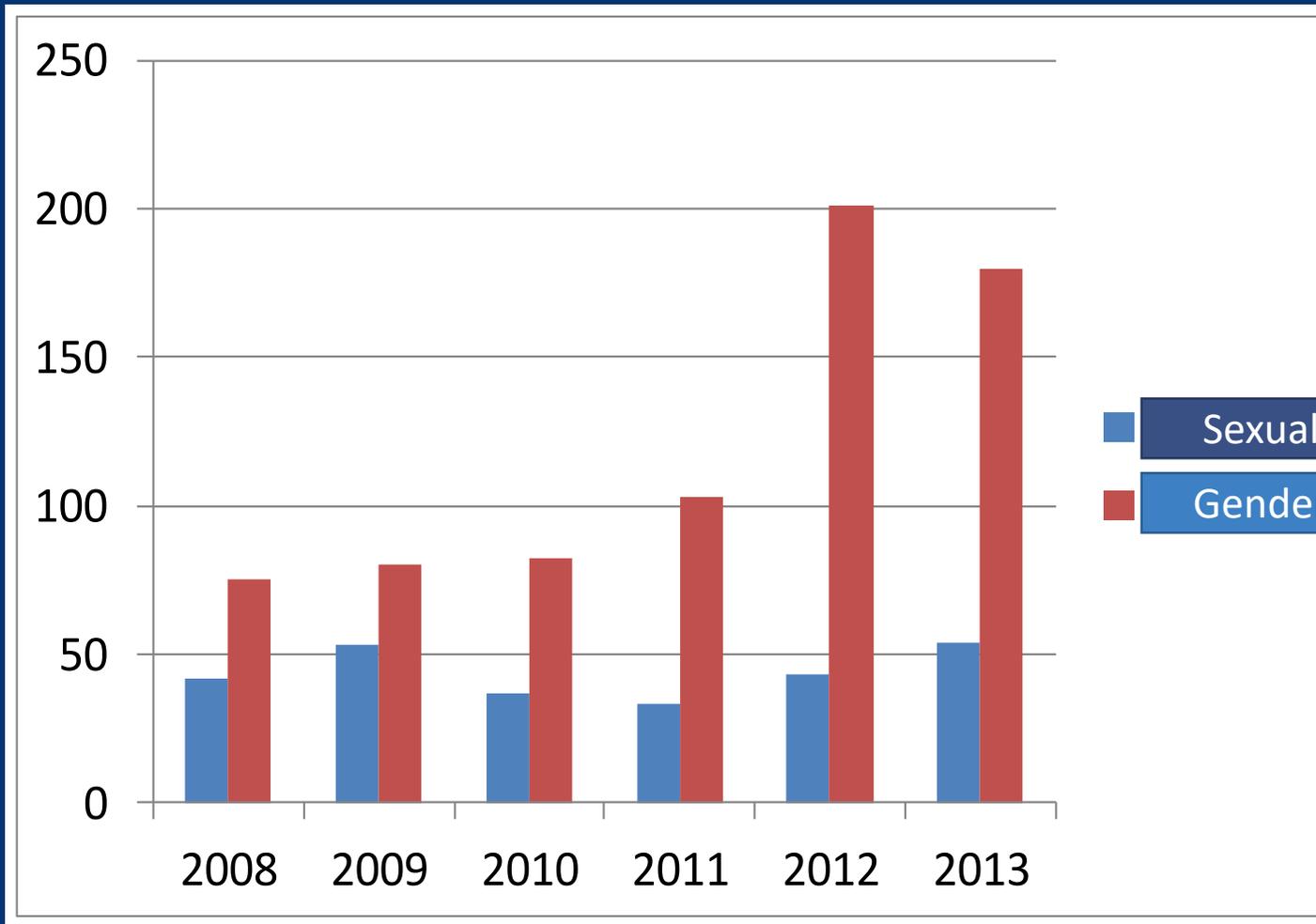
Articles Published 1966-2008 PubMed



Average Number Articles/Year PubMed

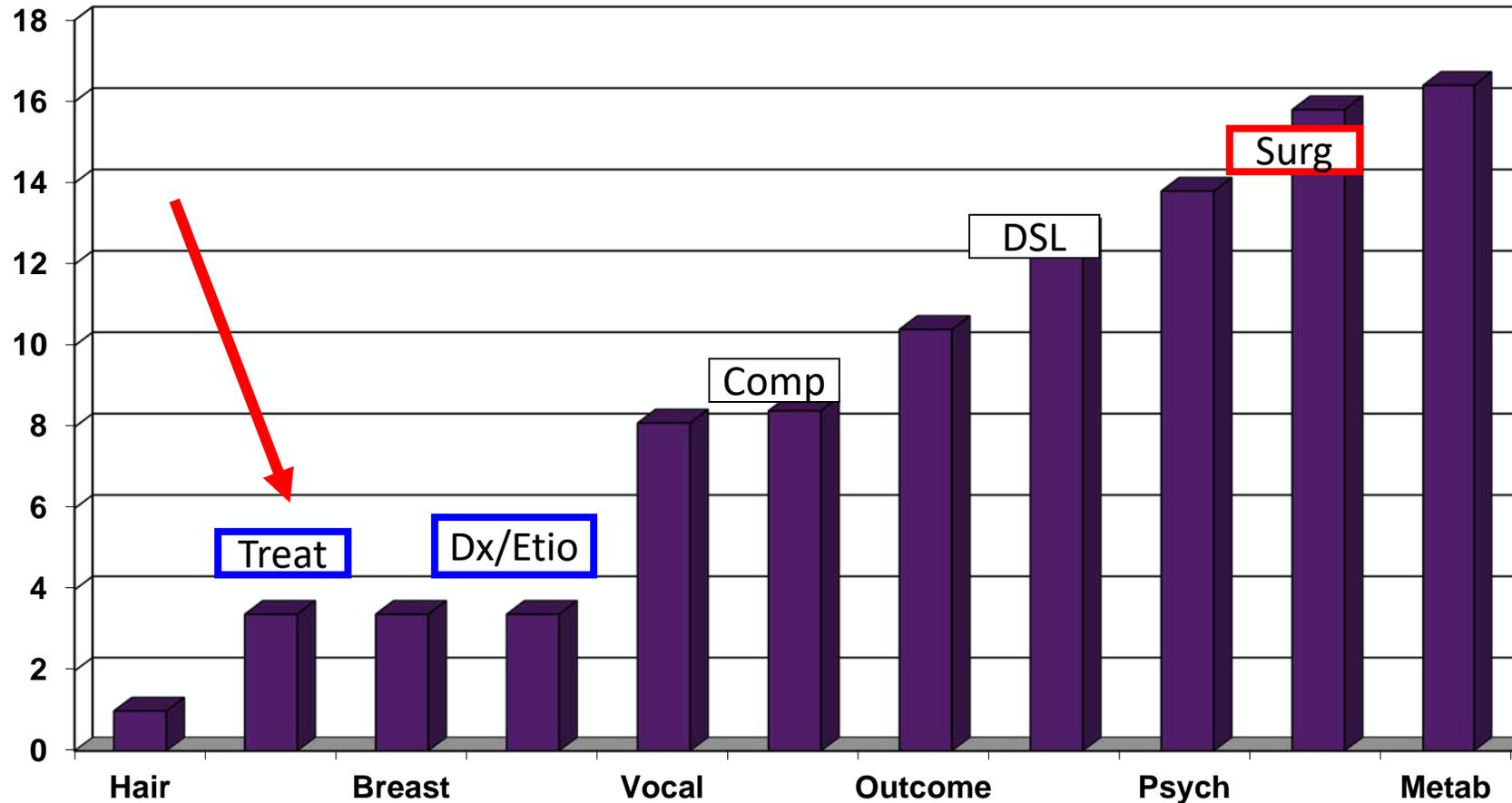


TransSEXUAL vs. TransGENDER Titles: PubMed 2008-2013



- Transgender first appeared in **1977**

Categories of Articles



Reasons For New Gender Dysphoria Guideline

1. Better understanding of gender dysphoria
2. New research data re: gender
3. Role of mental health professionals in the diagnosis of children, adolescents and adults

Reasons For New Gender Dysphoria Guideline

4. Age of pubertal suppression and sex steroid treatment
5. New protocols for adolescents and adults
6. Advances in genital surgery for trans men and trans women

Assessment

Specifically, endocrine treatment protocols for gender dysphoria (GD) /gender incongruence should include the careful assessment of:

1. Effects of prolonged delay of puberty on bone health, gonadal function and the brain in adolescents, including effects on cognitive, emotional, social, and sexual development
2. Effects on both endogenous and cross-sex hormone levels during treatment in adults
3. Requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids during treatment
4. Risks and benefits of gender affirming hormone treatment in older transgender people

Diagnostic Recommendations 2017

- Separate specific characteristics are described for those health professionals who should be qualified to treat adults with GD/gender incongruence and for those who should be qualified to treat children and adolescents with GD/gender incongruence.
- Neither pubertal blocking nor hormone treatment is recommended for prepubertal children; understanding both reversible and irreversible effects of hormones are recommended at puberty.
- Understanding the impact of puberty suppression, using GnRH analogs, and sex hormone treatment upon fertility is recommended in both adolescents and adults.

Diagnostic Recommendations 2017

- Initiating puberty of the opposite sex at age 16 or earlier should be managed by an expert multi-disciplinary team that includes a mental health professional
- Adolescents should be monitored throughout sex steroid treatment and may be referred for surgery thereafter
- Physicians treating transgender adults
 - a) by initiating and maintaining suppression of natal sex steroids and
 - b) by maintaining the desired sex steroids within the normal physiologic rangeare not limited to endocrinologists

Diagnostic Recommendations 2017

- Physicians suppressing and treating with sex steroids should monitor maintenance of clinical status, including cardiovascular status, Prolactin, BMD, breast, prostate and reproductive tract function
- Sex surgery should be collaborated between the surgeon and by both the treating physician and a consulting Mental Health Professional after 1 year of consistent and compliant treatment, social role change, good hormone effect and persistent desire for surgery
- Reproductive tract surgery should be delayed until 18 years old (or legal age of majority in his/her country) and no specific age for breast surgery is recommended

What Is New?

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VU University Medical Center, Amsterdam

Disclosures

Peggy T Cohen-Kettenis

Financial or Business/Organizational Interests:

- None

Significant Financial Interest or Leadership Position:

- None

What is New?

1. Research
2. Conceptual changes
3. Treatment

1. Research on Gender Development

Brains of trans people

- Brain phenotypes for trans males and trans females seem to exist, but not a simple cross-sex development
- There is a role of prenatal brain organization in the development of GD/gender incongruence
(Kreukels & Guillamon, 2016)

Psychosexual outcome of people with disorders of sex development (DSD) / intersex conditions

- Hormones and environment seem to influence gender development
(Berenbaum & Meyer-Bahlburg, 2015)

Clinical Approach

Because other factors than biological factors probably play a role in GD/gender incongruence

→ Not too easily assume that GD/gender incongruence in childhood will persist into adulthood because it is 'biological'

2. Conceptualization gender identity

Gender identity (gender experience) is not a binary phenomenon

- Male
- Female
- In-between
- Outside the male female continuum (gender queer, bi-gender, a-gender)

(Kuyper & Wijssen 2014; Van Caenegem et al. 2015)

2. Conceptualization diagnostic category (1)

No longer 2 categories: “transsexual” or “non-transsexual”

Instead: GD/gender incongruence can be:

- Extreme or mild
- Vary in associated distress
- Fluctuating or permanent
- More or less associated with anatomic dysphoria
- Accompanied by wish for complete or partial social transition

2. Conceptualization diagnostic category (2.1)

Mental disorder?

American Psychiatric Association has kept the diagnosis in Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

→ Yes

- Removal may block access to reimbursed care

Transgender advocates: classifying GD/gender incongruence as a diagnosis pathologizes a normal variant of human gender identity

→ No

2. Conceptualization diagnostic category (2.2)

World Health Organization will likely put the diagnosis in a chapter on Sexual and Gender Health, separate from mental health in the next version International Classification of Disease (ICD-11)

→ NO

- Diagnosis is needed for reimbursed care, but not necessarily a psychiatric diagnosis

3. Treatment Request Changes

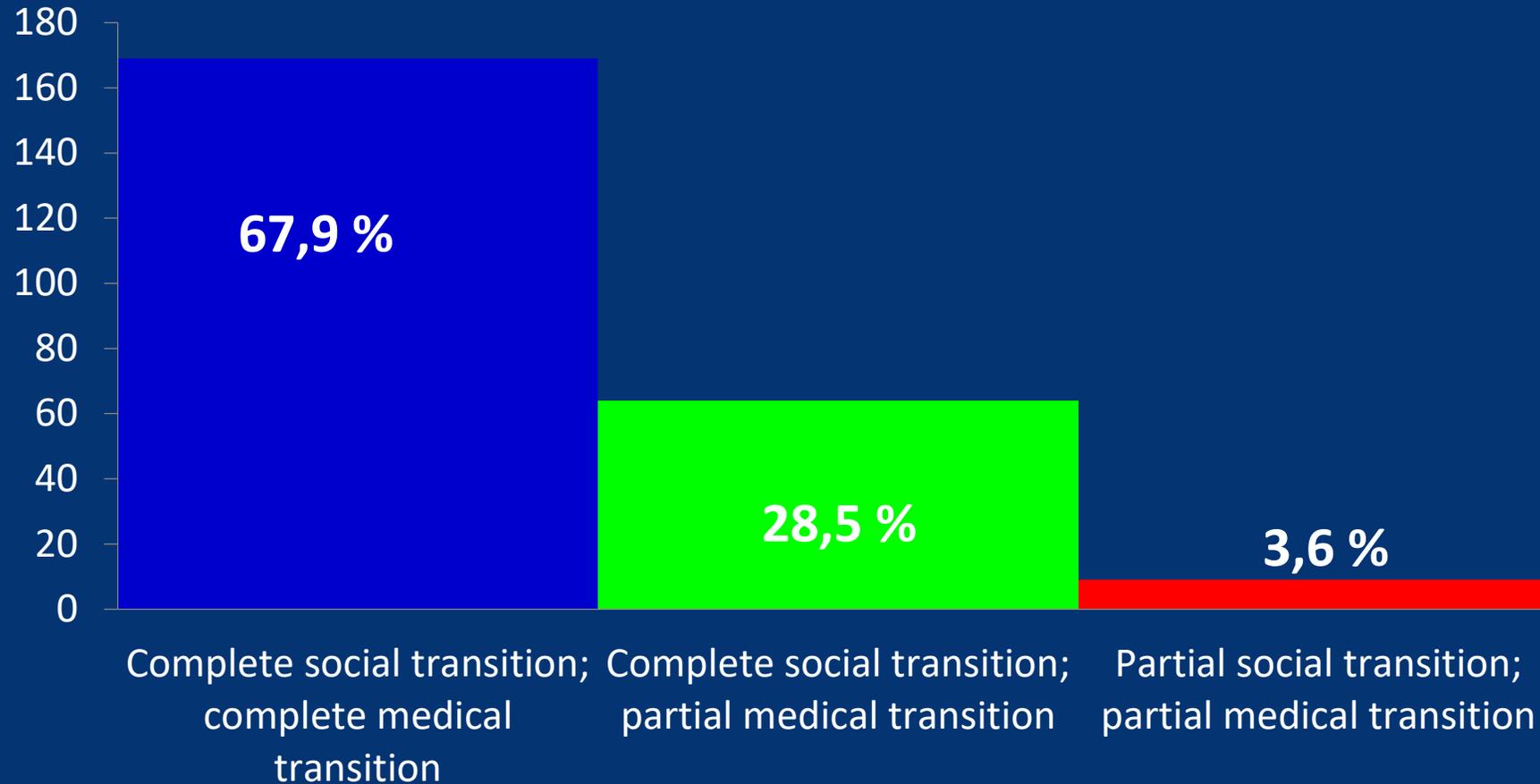
Less people requesting “classical” treatment

= First gender confirming hormones combined with social transitioning, then gender confirming surgery

Instead:

- Different order of interventions (e.g. certain forms of surgery first)
- Only certain hormones, or certain forms of surgery
(Beek et al, 2015)

Treatment requests Amsterdam gender identity clinic in 2013 (adults; N=249)



Clinical Practice Guidelines

- More room for individual variation

Quiz

Parents of a pre-pubertal child who wants to transition completely want to know what they should do until the child reaches puberty.

This is your advice:

- A. As GD/gender incongruence is biological it will not change over time, not allowing transitioning is harmful
- B. If you allow the child to transition keep in mind and explain to the child that it is likely that around puberty he/she will change his/her mind
- C. Do not allow transitioning, as this may 'push' the child prematurely into a permanent change of gender

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Children and Adolescents

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University of California San Francisco

Disclosures

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- AbbVie (consultant)

Significant Financial Interest or Leadership Position:

- Pediatric Endocrine Society (President)

GD/Gender Incongruent Youth

- New Pediatric/Adolescent recommendations
- Key learning points:
 - Outcomes of current treatment protocol
 - Gaps in knowledge
 - Priorities for research
 - Barriers to care

Prior Pediatric/Adolescent Recommendations:

- Diagnosis of GD made by mental health professional
- Medical providers ensure patients understand consequences of hormone suppression & cross-sex hormone Rx prior to Rx
- Suppression of pubertal hormones with GnRH agonist only after early puberty has been reached
- Initiate cross-sex hormone Rx at “about” age of 16 yr
- Defer surgery until at least 18 yr of age

Hembree WC et al. J Clin Endocrinol Metab 94:3132-3154, 2009

New Pediatric/ Adolescent Recommendations:

- Recognition that there may be compelling reasons to start cross-sex hormones prior to age 16 years in some GD/Gender Incongruent adolescents
 - Potential risks to bone health with prolonged hypogonadism
 - Potential risks to mental health if pubertal development is markedly out of sync with peers
- Pubertal induction schemes using transdermal estradiol or subcutaneous testosterone
- Inclusion of pubertal induction schemes for post-pubertal adolescents, resembling adult protocols
- More targeted lab surveillance during pubertal suppression and pubertal induction

Outcomes of Current Treatment Model: 6 Year Follow-Up

- N= 55 (22 MTF, 33 FTM)
- **Protocol**
 - Puberty blockers (Avg. 14.8 yr at start of Rx)
 - Cross Sex Hormones (CSH) (Avg. 16.7 yr at start of Rx)
 - “Gender Reassignment Surgery” (Avg. age 20.7 yr)
- **Mental Health Outcomes**
 - 1 yr pre-blockers, T 0 for CSH, 1 yr post-surgery
- **Results**
 - Gender Dysphoria: Resolved
 - Psychological functioning: Generally improved
 - “Well being” \geq vs. same age young adults from general population
 - No patients reported regret at any phase of protocol

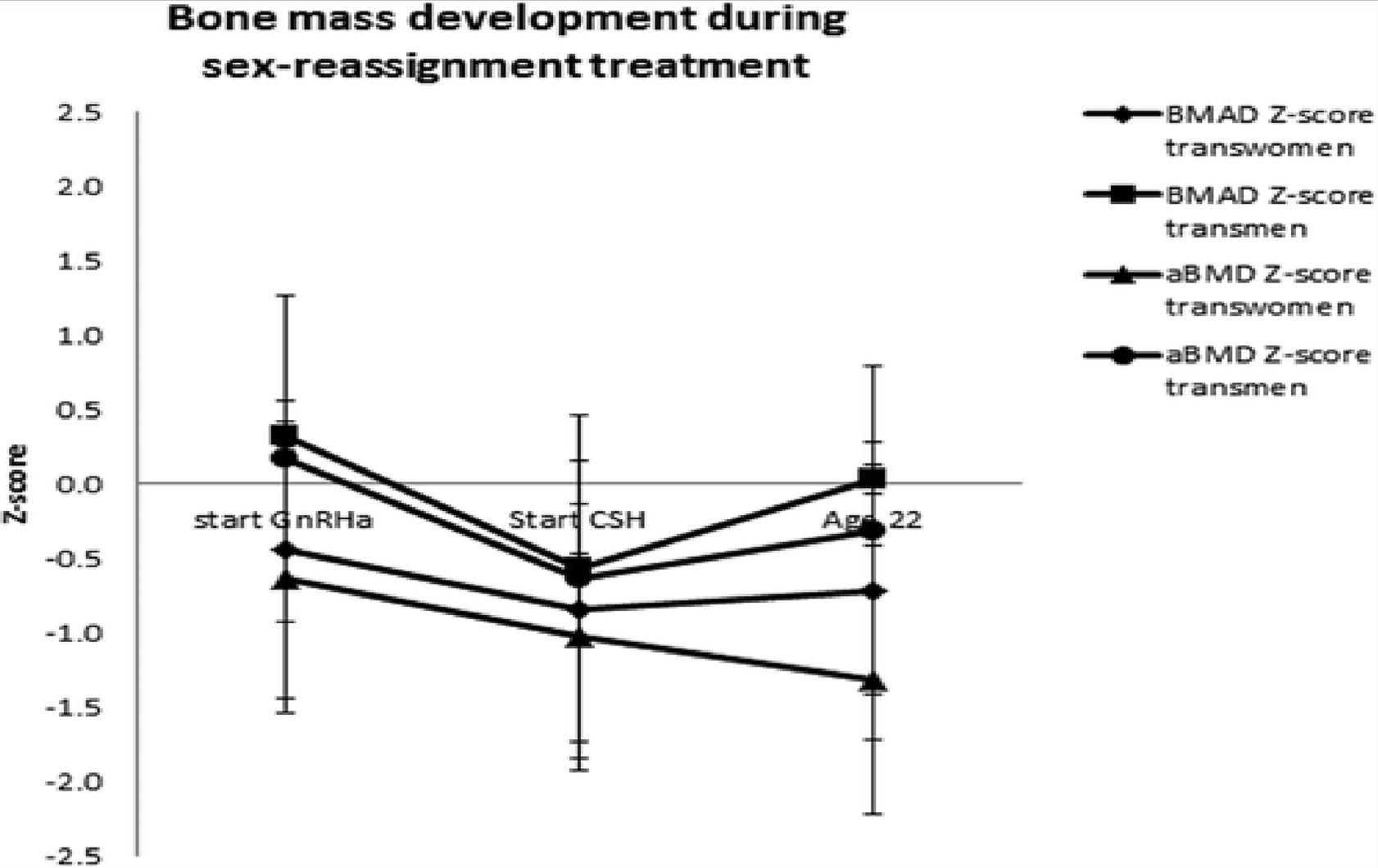
De Vries ALC et al. Pediatrics, 2014

GnRH Agonists in GD/ Gender Incongruent Youth: Potential Adverse Effects

- Bone mass, growth
 - Ameliorated with subsequent initiation of “cross-sex” hormone Rx?
- Brain
- Fertility

Current Treatment Model: 6 Year Follow-Up

Bone Mineral Density: Lumbar Spine



Klink D et al. JCEM, 2015

Current Treatment Model

Bone Mineral Density: 6 Year Follow-Up

Potential study limitations:

- Relatively small “N” (34: 15 MTF, 19 FTM)
- ? Relatively low hormone dosage during initial CSH Rx
- No data on other factors influencing bone mass:
 - Dietary calcium intake
 - Vitamin D levels
 - Weight-bearing exercise

Klink D et al. JCEM 2015

GnRH Agonists & Brain Effects in GD/Gender Incongruent Youth

Does GnRHa effect “Executive Functioning”?

- Working memory
- Reasoning
- Problem solving
- Planning and execution
- Pre-frontal activation
- Significant development during puberty

Study

- MTF (N = 18): Rx'd (8), 1.6 +/- 1 (SD) yr
- FTM (N = 22): Rx'd (12), 1.6 +/- 1 (SD) yr

Results

- No detrimental effect on Executive functioning

Staphorsius AS et al. Psychoneuroendocrinology 56:190—199, 2015

GnRH Agonists & Fertility in GD/Gender Incongruent Youth

- Blocking puberty at Tanner 2
 - Compromised oocyte maturation
 - Compromised spermatogenesis
- Parental dilemmas
- Preservation of fertility: desired option

Gaps in Knowledge & Priorities for Research

GD/Gender Incongruent Youth:

- No data with blockers in pt < 12 yr
- No data with cross-sex hormones in pt < 16 yr
- No RCTs (likely not feasible or ethical)
- Need for prospective, long-term outcomes studies of medical interventions to optimize care

GD/Gender Incongruent Youth: Barriers to Care

Limited access to Rx

- Off-label
- Expensive
- Often denied by insurance companies

Limited access to care

- Relatively few clinical programs
- Lack of training
- Prejudice/ misunderstanding

Quiz

In a transgender adolescent who has been previously blocked at early puberty with a gonadotropin releasing hormone agonist, compelling reasons to start cross-sex hormone treatment before age 16 years may include:

- A. Concerns about potential adverse effects on bone mineral density
- B. Concerns about potential adverse effects on fertility
- C. Concerns about potential adverse effects on libido

Quiz

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Monitoring and Surveillance

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Disclosures

Joshua D. Safer, MD

Financial or Business/Organizational Interests:

- None

Significant Financial Interest or Leadership Position:

- None

Summary of Updates for 2017

1. **Enhanced communication** by replacing older language.
2. **Removal of the obligation** that the transgender diagnosis be made by a mental health provider in favor of:
 - a. The suggestion that the diagnosis be made by a knowledgeable clinician and
 - b. A statement of the expertise required among treating clinicians independent of specific specialty (i.e. knowledge of transgender-specific diagnostic criteria, mental health concerns, hormone prescribing, and primary care).

Summary of Updates for 2017

3. **Recognition** that **for non-binary persons tailoring of current protocols** may be done within the context of accepted safety guidelines, using a multidisciplinary approach including mental health.
4. **Explicit suggestion** that **fertility preservation** options need to be discussed in a timely fashion.
5. **Updated gender affirming hormone regimens,** based upon recently published treatment protocols.

Recommendations 3.1- 3.4

- **Hormone treatment** of transgender individuals is straightforward - following **conventional hormone paradigms** with the **anticipated concerns** and effects that are seen when using the same hormones for other purposes.
- We recommend **diagnosis by knowledgeable clinicians (3.1)**, **monitoring as with others (3.2)** using the same hormone regimens for other purposes, treatment monitoring with conventional **laboratory testing (3.3)**, and education of transgender individuals regarding reasonable expectations of physical changes (3.4).

Recommendations 3.1- 3.4 (cont.)

- Typically, hormone treatment for **transgender men** (female to male) consists of **testosterone** to bring the serum testosterone from the female range **to the male range**. The doses required are similar to those used for treatment of hypogonadal males in general.
- Typically for **transgender women** (male to female), hormone treatment consists of an anti-androgen to lower testosterone levels (if testes are present) and estrogen supplementation.

Recommendations 3.1- 3.4 (cont.)

- The biggest concerns for testosterone therapy are an increase in **erythropoiesis** (with an increased thrombosis risk?) and a deterioration in lipid profile (with an increased CAD risk?). Androgen therapy is also associated with increased sleep apnea.

Recommendations 3.1- 3.4 (cont.)

- Usual monitoring includes serum testosterone (to determine success of therapy), hematocrit and lipid profile.
- Malignancy screening must include all body parts present regardless of whether or not they are associated with one sex or another (e.g. don't forget Pap smears and mammograms if required for transgender men with cervixes and breasts respectively).

Recommendations 3.1- 3.4 (cont.)

- The biggest concerns for estrogen therapy are an increase in risk for **thrombotic events** (DVT, PE, and CVA)
- There are insufficient data to assess the risk of therapy on triglycerides, prolactin, breast cancer risk, and other female reproductive tract carcinoma risk
- The chief bone density concern is **loss of bone if hormones are discontinued**

Recommendations 3.1- 3.4 (cont.)

- Asscheman et al. (2014) 1% incidence of VTE among 1076 transwomen (5.4 years)
- Gooren et al. (2008), no increase in VTE among 2236 transgender women on estradiol from 1975 to 200 (Ethinyl estradiol = 6 – 8% incidence)
- Wierckx et al. (2013) 5% of 214 MTF individuals developed VTE within the first three years of estrogen therapy **BUT** 10 out of 11 of these women had at least one VTE risk factor (smoking, immobilization/surgery, or thrombophilia)

Recommendations 3.1- 3.4 (cont.)

- Usual monitoring includes serum testosterone (to determine success of therapy), estrogen level (estradiol), prolactin, potassium, and triglycerides (lipid profile).
- Malignancy screening must include all body parts (including remaining prostates and newly developing breasts for transgender women)

Recommendations 4.0 - 4.3

- Hormone therapy risks for transgender individuals are not known to differ from risks to others with similar treatment and hormone profiles (4.0)
- Monitor patients every 3 months initially and then every 6-12 months (4.1)
- Monitor prolactin levels in individuals treated with estrogens (4.2)
- Monitor cardiac risk factors like lipid profile and diabetes (4.3)

Recommendations 4.4 - 4.7

- Bone density if osteoporosis risk especially when hypogonadal (4.4)
- Breast cancer surveillance (for trans women or trans men with breast tissue) per existing guidelines for all women (4.5)
- Prostate cancer surveillance (for trans women) per existing guidelines for all men (4.6)
- Hysterectomy and oophorectomy **necessity to be determined by patient and treating clinicians** (4.7)

Quiz

A 60-year-old transgender man comes in reporting stable dosing with 80 mg of subcutaneous testosterone for years but no careful follow up recently. Which laboratory test would be most important to ascertain the safety of his regimen if you could only choose one test initially?

- A. PSA
- B. Hematocrit
- C. Estradiol
- D. HDL cholesterol
- E. LDL cholesterol

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D. HDL cholesterol

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Surgery and Follow-Up Management

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Director of Fellowship Program

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Disclosures

Vin Tangpricha, MD, PhD

Financial or Business/Organizational Interests:

- *Journal of Clinical and Translational Endocrinology* (Editor)
- Cystic Fibrosis Foundation (Grantee)
- National Institutes of Health (Grantee)

Significant Financial Interest or Leadership Position:

- World Professional Association for Transgender Health (President Elect)
- American Association of Clinical Endocrinologists (Board Member).

Reaffirming 3 Previous Recommendations for Surgery

5.1 We recommend that genital gender-affirming surgery be pursued only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being.

5.2 We recommend that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3 We recommend that the clinician responsible for endocrine treatment and the primary care provider insure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborates with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

Addition of 3 More Recommendations

5.4 We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when 1) the individual has had a satisfactory social role change, 2) the individual is satisfied about the hormonal effects, and 3) the individual desires definitive surgical changes. (1|⊕○○○)

5.5 We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18-year-old or legal age of majority in his or her country. (2|⊕⊕○○).

5.6 We suggest that clinicians determine the timing of breast surgery for FTM transgender persons based upon the physical and mental health status of the individual. No specific age requirement is appropriate since breast surgery does not affect fertility. (2|⊕○○○)

Quiz

23 year old transmale college student is here for his first 3 month follow-up appointment. He was started on gender affirming hormone therapy with testosterone 3 months ago. He is now seeking chest reconstruction surgery. He wants to have a permanent change to his body to a male body.

What is the best advice that you can provide him at this time?

- A. He is not eligible right now for chest surgery because he hasn't been on hormones long enough
- B. He should wait for at least 2 years to see if the testosterone therapy modifies his breasts
- C. He will be able to lower his dose of testosterone after the surgery
- D. He should seek a second letter from his mental health provider to clear him for surgery
- E. He should seek a surgeon who has expertise in chest reconstruction surgery in transgender people

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Downgrading Of Prolactin Measurements

- From “recommend” to “suggest”
- Data from European cohorts suggest that cyproterone may be the anti-androgen causing prolactin elevations; whereas in the U.S.A, very few prolactinomas have been reported using GnRH agonists or spironolactone

Removed Recommendation To Serially Measure Liver Function Tests

- Routine measurement of LFTs have been removed from both transmasculine and transfeminine recommendations due to no evidence suggesting that hormone therapy results in adverse liver function

Bone Mineral Density Screening

- Recommend DEXA screening in those with risk factors especially after gonadectomy

Cancer Screening Recommendations

- No change in recommendations from previous guidelines. We recommend to follow screening guidelines based on tissue present.

Quiz

A 67 year old transwoman is seen in your office. She has not had any preventive health care over the past 5 years and wishes to re-establish care with you. She has been on cross sex hormones for 10 years. She is currently taking estradiol 2 mg twice a daily orally along with spironolactone 50 mg twice a daily. She has not had any gender confirming surgery. She has not had any side effects of hormone therapy.

Which of the following tests would not be appropriate at this time?

- A. Bone mineral density testing
- B. Blood clotting time
- C. Colonoscopy
- D. Serum electrolytes
- E. Mammogram

Quiz

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Summary

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Disclosures

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Guideline Task Force Chair

Financial or Business/Organizational Interests:

- None

Significant Financial Interest or Leadership Position:

- None

Conclusions

1. Endocrinologists play an important role in Gender Affirmation
2. Treatment helps develop physical characteristics of the Affirmed Gender
3. Endocrine regimens should:
 - a. Suppress endogenous sex hormone levels, and
 - b. Maintain normal sex hormone levels of person's affirmed gender

Conclusions

4. No hormone treatment for pre-pubertal persons with GD/Gender Incongruence
5. Adolescent treatment should include knowledgeable Mental Health Practitioners and fertility discussion
6. Suppress puberty at Tanner Stage G2/B2 adolescents (informed consent)
7. Gender affirming hormone at age 16 or earlier if compelling reasons

Conclusions

8. Treat adults to attain physiologic levels of gender-appropriate steroids
9. Removal of natal gonads may be required to avoid high dose steroids
10. Hormone treatment must be monitored for adverse effects and during hormone surgery

Case Study

When Ina was 6 years old, she began to be troubled about wearing dresses, being addressed as daughter, granddaughter, etc. and accepting the role of a girl.

At age 10, cutting her hair provided the idea that she actually might be a boy and saw therapists and MD's who addressed her as a boy.

Breast growth began at age 12 and occasioned medical visits with several experts in the treatment of transgender men.

Case Study

Suppression of natal sex hormones and menses began at age 14 with no adverse effects.

There was cessation of breast growth and initially monthly GnRH agonists were effective in reducing menses.

Initiation of daily topical testosterone treatment resulted in mild acne, facial and some body hair growth with no change in voice, muscle development and he grew only one inch.

Case Study

After 6 months, he began weekly injections of testosterone and continued GnRH agonist injections every 3 months.

After 6 weeks, testosterone injections were increased to 0.3 cc IM weekly and blood levels were normal male as measured on the day prior to an injection.

GnRH agonist injections were discontinued after 24 months.

Weekly testosterone injections were continued but, on occasion, he reported episodes of uterine bleeding.

Case Study Question

Which four of the following steps should be taken to prevent uterine bleeding?

1. Measure testosterone blood levels
2. Increase dose of testosterone injections
3. Decrease dose of testosterone injections
4. Replace injections with topical testosterone cream
5. Add medroxyprogesterone tablets
6. Measure estrogen and gonadotropin levels
7. Re-initiate GnRH agonist injections
8. Perform ovariectomy
9. Perform hysterectomy

- A. 2, 5, 6 & 7
- B. 1, 4, 5 & 9
- C. 5, 6, 7, & 8
- D. 1, 4, 7 & 9

Answer to Case Study

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Case Study Explanation

- In this case, gonadotropins, endogenous sex steroids (estrogen and progestin levels) and, thus, menses were suppressed by GnRH agonists and breast growth was reduced.
- Addition of treatment with testosterone not only initiates virilization but also, despite suppression of ovarian secretion, may increase estradiol levels by aromatization of testosterone.

Case Study Explanation

- Blood tests should ensure that excess aromatization of testosterone to estradiol is not a cause of uterine bleeding.
- If testosterone fails to suppress gonadotropins, thereby causing ovarian secretion of estrogens, high doses of medroxyprogesterone (20-40 mg) or GnRH agonists may also be useful.
- If blood tests indicate excess gonadotropin secretion with ovarian stimulation, ovariectomy may be considered.

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