



Topic Brief: Treatments for Gender Dysphoria in Transgender Youth

Date: 1/8/2021

Nomination Number: 0928

Purpose: This document summarizes the information addressing a nomination submitted on July 17, 2020 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: Youth who identify as transgender experience high rates of depression, anxiety, eating disorders, substance use disorders, and suicide ideation or attempts. There is a lack of current evidence-based guidance for the care of children and adolescents who identify as transgender, particularly regarding the benefits and harms of pubertal suppression, medical affirmation with hormone therapy, and surgical affirmation.

Program Decision:

The EPC Program will not develop a new systematic review because we found protocols for two systematic reviews that addresses portions of the nomination, and an insufficient number of primary studies exist to address the remainder of the nomination.

Key Findings

- We found a protocol for a systematic review that included key questions (KQs) that met the nominator's needs for KQ1 regarding pubertal suppression in transgender youth.
- For KQ 2 and 3, we found two protocols (one is the same as that for KQ1) for systematic reviews that partially address each of the two KQs, respectively. We did not find any studies addressing the parts of the KQs not addressed by these protocols.

Background

The term transgender refers to individuals whose gender identity persistently and consistently does not match their assigned sex.¹ An estimated 0.6 percent of adults² and 0.7 percent of youth ages 13 to 17 in the U.S. identify as transgender or “gender nonconforming.”³ Many transgender youth experience gender dysphoria, characterized as an impairment in peer and/or family relationships, school performance, and other aspects of life as a consequence of the discordance between their gender identity and assigned sex.¹ Transgender youth also experience high rates of depression, anxiety, eating disorders, and suicide.⁴⁻⁶

Gender affirmation is a complex interpersonal process of reflection, acceptance, social and legal recognition and medical interventions. Gender-affirming behavioral, social and medical interventions may improve psychological functioning in children and adolescents.⁶ Available interventions include the following: 1) social affirmation (e.g., expressing one's asserted gender

through hairstyle, clothing, pronouns, name, etc.); 2) legal affirmation (e.g., name and gender officially reflected on legal documents); 3) medical affirmation (e.g., using cross-sex hormones in adolescents who have initiated puberty to facilitate the development of secondary sex characteristics of the sex the individual identifies with); and/or 4) surgical affirmation (e.g., surgical interventions to masculinize or feminize features).¹

Gender-affirming health care is part of comprehensive primary care for many gender-diverse patients. There is a lack of current evidence-based guidance for the care of children and adolescents who identify as transgender, particularly regarding the benefits and harms of pubertal suppression, medical affirmation with hormone therapy, and surgical affirmation. While there are some existing guidelines and standards of care,^{1, 7, 8} most are derived from expert opinion or have not been updated recently. A comprehensive evidence review is currently not available.

Scope

1. For children and adolescents who identify as transgender and have not initiated puberty, what are the benefits and harms of pubertal suppression?
2. For adolescents who identify as transgender and have initiated puberty, what are the benefits and harms of medical affirmation with hormone therapy?
3. For adolescents who identify as transgender and have initiated puberty, what are the benefits and harms of surgical affirmation?

Table 1. Questions and PICOs

Questions	1. Pubertal suppression	2. Hormone therapy	3. Surgical affirmation
Population	Children and adolescents who identify as transgender and have not initiated puberty	Adolescents who identify as transgender and have initiated puberty	Adolescents who identify as transgender and have initiated puberty
Interventions	Pubertal suppression	Medical affirmation with hormone therapy	Surgical affirmation
Comparators	No pubertal suppression	No intervention; Social affirmation only	No intervention; social affirmation with other medical affirmation (e.g., hormone therapy); social affirmation without medical affirmation

Questions	1. Pubertal suppression	2. Hormone therapy	3. Surgical affirmation
Outcomes	<ul style="list-style-type: none"> • Depression/anxiety, suicidality, distress/dysphoria, social interaction, quality of life • Medication effects (e.g., weight gain, height, decreased secondary sex characteristics, hot flashes, headache, bone density, fertility) 	<ul style="list-style-type: none"> • Depression/anxiety, suicidality, distress/dysphoria, social interaction, quality of life • Estrogen effects (feminization, weight gain, mood swings, hot flashes, VTE, migraine, fertility, cancer risks), antiandrogen effects (feminization, hypotension, electrolyte abnormality, VTE), androgen effects (masculinization, cancer risks, hypertension, hyperlipidemia, vascular disease) 	<ul style="list-style-type: none"> • Depression/anxiety, suicidality, distress/dysphoria, social interaction, quality of life • Surgical risks (e.g., infection, bleeding, poor healing of incisions, hematoma, seroma, necrosis, nerve injury, stenosis of the vagina, injury of the urinary tract, painful intercourse)

Abbreviations: PICOS=population, intervention, comparator, outcome; VTE=venous thromboembolism.

Assessment Methods

See Appendix A.

Summary of Literature Findings

We identified a protocol for a systematic review that covered KQ1,⁹ protocols that partially covered KQ 1 and 2, and no primary literature to cover the portions of KQs 2-3 not covered by the protocols.

For KQ1, we identified a protocol for a systematic review⁹ that included the following key questions that meet the nominator’s needs:

- “For transgender adolescents, what are the long term effect of GnRH agonists compared to no treatment, in terms of surrogate outcomes, clinical outcomes, and harms?”
- “For transgender people, what are the effect of progesterones (cyproterone) compared to Medroxyprogesterone and other progesterones in terms of breast growth (adults), delay of puberty (children), and side effects?”
- “For transgender adolescents, what are the effects of suppressing puberty with GnRH agonists on quality of life?”

For KQ2, we found a protocol for a systematic review⁹ that partially covered KQ2:

- “For transgender people, what are the psychological effects (including quality of life) associated with hormone therapy.”
- “For transgender people, what are the effects of hormone therapy on metabolic syndrome?”
- “For transgender people, what are the effects of hormone therapy on fertility?”

We did not find any systematic reviews or protocols for systematic reviews for hormone effects such as cancer risks, hot flashes, or migraine, nor did we find any primary studies addressing

these remaining portions of KQ2. We did find 11 non-randomized controlled trial studies that either did not include a comparator group¹⁰⁻¹⁷ or that included a comparator group that did not match the PICOs.¹⁸⁻²¹ These studies were not included in our assessment of the feasibility of a systematic review, but are mentioned here as they are related and may be of interest.

For KQ3, we found a protocol for a systematic review that partially covered KQ3.²² Specifically, it covered top, but not bottom surgery:

- “How does age affect the benefits and risks of top surgery for transmasculine individuals and gender nonconforming individuals assigned female at birth, particularly for those under age 18?”
- “How does age affect the benefits and risks of top surgery, particularly for those under age 18 for transfeminine individuals and gender-nonconforming individuals assigned male at birth?”

We did not find any studies addressing the remainder of KQ3, namely, bottom, or genital, surgery.

Table 2. Literature identified for each KQ

Question	Systematic reviews (1/2018-1/2021)	Primary studies (1/2016-1/2021)
Question 1: Pubertal suppression	Total: 1 • PROSPERO protocol: 1	N/A
Question 2: Hormone therapy	Total: 1 • PROSPERO protocol: 1	Total: 0
Question 3: Surgical affirmation	Total: 1 • PROSPERO protocol: 1	Total: 0

Abbreviations: KQ=key question; NA=not applicable; RCT=randomized controlled trial.

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

There is a lack of current evidence-based guidance for care of children and adolescents who identify as transgender regarding the benefits and harms of pubertal suppression, medical affirmation with hormone therapy, and surgical affirmation. A systematic review is currently underway that addresses KQ1, and parts of KQs 2 and 3. There is insufficient evidence at this time to create a new systematic review that would inform the development of evidence-based guidance for the remainder of the nomination.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

References

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3. UCLA School of Law WI. Age of individuals who identify as transgender in the United States. doi: <https://williamsinstitute.law.ucla.edu/publications/age-trans-individuals-us/>.

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Author

Emily Gean

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years, January 7, 2018 - January 7, 2021, on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
 - AHRQ Evidence Reports <https://www.ahrq.gov/research/findings/evidence-based-reports/index.html>
 - EHC Program <https://effectivehealthcare.ahrq.gov/>
 - US Preventive Services Task Force <https://www.uspreventiveservicestaskforce.org/>
 - AHRQ Technology Assessment Program <https://www.ahrq.gov/research/findings/ta/index.html>
- US Department of Veterans Affairs Products publications
 - Evidence Synthesis Program <https://www.hsrd.research.va.gov/publications/esp/>
 - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program <https://www.healthquality.va.gov/>
- Cochrane Systematic Reviews <https://www.cochranelibrary.com/>
- PROSPERO Database (international prospective register of systematic reviews and protocols) <http://www.crd.york.ac.uk/prospero/>
- PubMed <https://www.ncbi.nlm.nih.gov/pubmed/>

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed from the last five years 1/7/2016 - 1/7/2021. We reviewed all identified titles and abstracts for inclusion and classified identified studies by question and study design to estimate the size and scope of a potential evidence review.

Search strategy

Ovid MEDLINE ALL 1946 to January 07, 2021

Date searched: January 8, 2021

1 Gender Dysphoria/ or Transgender Persons/ or Transsexualism/ or (F2M or M2F or "assigned female" or "assigned male" or "female-to-male" or (gender adj3 (dysphor* or minorit* or nonbinary or non-binary or nonconforming or non-conforming)) or "male-to-female" or transboy* or transfemale or trans-female or transfeminine or trans-feminine or transgender* or

trans-gender* or transgirl* or transmale or trans-male or transmasculine or trans-masculine or transsexual* or trans-sexual*).ti,kf. (20784)

2 Adolescent/ or Child/ or (adolescence or adolescent* or boy or boys or child* or girl or girls or juvenile* or paediatr* or pediatr* or prepubertal or pre-pubertal or prepubesc* or pre-pubesc* or pubesc* or pubertal or puberty or school or teen* or tween* or youth*).ti,ab,kf. or (adolescen* or child* or paediat* or pediat*).jw. (3984645)

3 Androgens/ or exp Estrogens/ or exp Gonadal Steroid Hormones/ or Hormone Replacement Therapy/ or Testosterone/ or ((gender adj3 (affirm* or confirm* or reassign*)) or androgen* or antiandrogen* or anti-androgen* or estradiol or oestradiol or estrogen* or oestrogen* or feminising or feminizing or "gonadotropin-releasing hormone" or GnRH or GnRH_a or inhibit* or HRT or (hormon* adj3 (replac* or suppress* or therap* or treat*)) or progestin* or suppress* or testosteron*).ti,ab,kf. (3230286)

4 Sex Reassignment Procedures/ or Sex Reassignment Surgery/ or (((bottom or gender or genital) adj3 surger*) or clitoroplast* or genitoplast* or hysterectom* or labiaplast* or metoidioplast* or oophorectom* or orchiectom* or phalloplast* or (sex* adj3 reassign*) or vaginectom* or vaginoplast*).ti,ab,kf. (54867)

5 or/3-4 (3275183)

6 and/1-2,5 (1189)

7 6 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti. or comment/ or editorial/ or exp review/ or meta analysis/ or consensus/ or exp guideline/) (847)

8 limit 7 to english language (791)

9 (systematic review or meta-analysis).pt. or (metaanal* or meta-anal*).ti,ab,kf. or ((systematic or evidence or integrat* or "mixed methods") adj3 (review or synthesis)).ti,ab,kf. (361026)

10 and/8-9 (6)

11 limit 10 to yr="2018 -Current" (6) Systematic Review and Meta-analysis Results

12 randomized controlled trials as topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or Controlled Clinical Trials as Topic/ or ("randomized controlled trial" or "controlled clinical trial").pt. or (blind* or placebo* or random* or trial*).ti,ab,kf. (2138071)

13 and/8,12 (37)

14 limit 13 to yr="2016 -Current" (23) Trial Results

15 exp cohort studies/ or exp epidemiologic studies/ or (clinical study or observational study).pt. or (before-after or "case control" or "case series" or (control and (group* or study)) or cohort or cohorts or ((comparative or evaluation) adj (study or studies)) or observational).ti,ab,kf. (4289515)

16 and/8,15 (286)

17 limit 16 to yr="2016-Current" (181) Observational Studies Results

18 Focus Groups/ or Grounded Theory/ or "Interviews as Topic"/ or Qualitative Research/ or "Surveys and Questionnaires"/ (585616)

19 ("critical interpretive" or "critical race" or "critical realism" or "critical realist" or ethnograph* or "grounded theory" or phenomenolog*).ti,ab,kf,kw. (51085)

20 ("case study" or "content analysis" or descriptive or "focus group" or "focus groups" or interview* or "mixed design" or "mixed methods" or qualitative or questionnaire* or survey*).ti,ab,kf,kw. (1669770)

21 (attitudes or barriers or facilitators or experiences or perceptions or perspectives or preferences or values or viewpoints or views).ti,ab,kf,kw. (1845932)

22 or/18-21 (3290543)

23 and/8,22 (335)

24 limit 23 to yr="2016-Current" (226) Qualitative Studies Results

Ovid EBM Reviews - Cochrane Central Register of Controlled Trials November 2020

Date searched: January 8, 2021

1 Gender Dysphoria/ or Transgender Persons/ or Transsexualism/ or (F2M or M2F or "assigned female" or "assigned male" or "female-to-male" or (gender adj3 (dysphor* or minorit* or nonbinary or non-binary or nonconforming or non-conforming)) or "male-to-female" or transboy* or transfemale or trans-female or transfeminine or trans-feminine or transgender* or trans-gender* or transgirl* or transmale or trans-male or transmasculine or trans-masculine or transsexual* or trans-sexual*).ti. (897)

2 Adolescent/ or Child/ or (adolescence or adolescent* or boy or boys or child* or girl or girls or juvenile* or paediatr* or pediatr* or prepubertal or pre-pubertal or prepubesc* or pre-pubesc* or pubesc* or pubertal or puberty or school or teen* or tween* or youth*).ti,ab. or (adolescen* or child* or paediat* or pediat*).jw. (271417)

3 Androgens/ or exp Estrogens/ or exp Gonadal Steroid Hormones/ or Hormone Replacement Therapy/ or Testosterone/ or ((gender adj3 (affirm* or confirm* or reassign*)) or androgen* or antiandrogen* or anti-androgen* or estradiol or oestradiol or estrogen* or oestrogen* or feminising or feminizing or "gonadotropin-releasing hormone" or GnRH or GnRHa or inhibit* or HRT or (hormon* adj3 (replac* or suppress* or therap* or treat*)) or progestin* or suppress* or testosteron*).ti,ab. (164326)

4 Sex Reassignment Procedures/ or Sex Reassignment Surgery/ or (((bottom or gender or genital) adj3 surger*) or clitoroplast* or genitoplast* or hysterectom* or labiaplast* or metoidioplast* or oophorectom* or orchiectom* or phalloplast* or (sex* adj3 reassign*) or vaginectom* or vaginoplast*).ti,ab. (8156)

5 or/3-4 (170755)

6 and/1-2,5 (16)

7 6 not ((exp animals/ not humans/) or (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti.) (16)

8 limit 7 to yr="2016 -Current" (6)

Ovid PsycInfo 1806 to January Week 1 2021

Date searched: January 8, 2021

1 Gender Dysphoria/ or Transgender/ or Transsexualism/ or (F2M or M2F or "assigned female" or "assigned male" or "female-to-male" or (gender adj3 (dysphor* or minorit* or nonbinary or non-binary or nonconforming or non-conforming)) or "male-to-female" or transboy* or transfemale or trans-female or transfeminine or trans-feminine or transgender* or trans-gender* or transgirl* or transmale or trans-male or transmasculine or trans-masculine or transsexual* or trans-sexual*).ti. (15710)

2 (adolescence or adolescent* or boy or boys or child* or girl or girls or juvenile* or paediatr* or pediatr* or prepubertal or pre-pubertal or prepubesc* or pre-pubesc* or pubesc* or pubertal or puberty or school or teen* or tween* or youth*).ti,ab. or (adolescen* or child* or paediat* or pediat* or youth*).jw. (1123314)

3 ((gender adj3 (affirm* or confirm* or reassign*)) or androgen* or antiandrogen* or anti-androgen* or estradiol or oestradiol or estrogen* or oestrogen* or feminising or feminizing or "gonadotropin-releasing hormone" or GnRH or GnRHa or inhibit* or HRT or (hormon* adj3 (replac* or suppress* or therap* or treat*)) or progestin* or suppress* or testosteron*).ti,ab. (213738)

4 (((bottom or gender or genital) adj3 surger*) or clitoroplast* or genitoplast* or hysterectom* or labiaplast* or metoidioplast* or oophorectom* or orchiectom* or phalloplast* or (sex* adj3 reassign*) or vaginectom* or vaginoplast*).ti,ab. (1929)

5 or/3-4 (215040)

6 and/1-2,5 (494)

7 6 not (animal* or canine* or crustacean* or dog or dogs or mice or monkey* or mouse or murine or primate* or rat or rats or rattus).ti. (451)

8 limit 7 to english language (393)

9 limit 8 to ("0830systematic review" or 1200 meta analysis or 1300 metasyntesis) (3)

10 limit 9 to yr="2018 -Current" (3) Systematic Review and Meta-analysis Results

11 limit 8 to "0300 clinical trial" (0)

12 limit 11 to yr="2016 -Current" (0) Trial Results

13 limit 8 to ("0400 empirical study" or "0430 followup study" or "0450 longitudinal study" or "0451 prospective study" or "0453 retrospective study" or 1800 quantitative study or 2100 treatment outcome) (201)

14 limit 13 to yr="2016 -Current" (109) Observational Study Results

15 limit 8 to 1600 qualitative study (39)

16 limit 15 to yr="2016 -Current" (32) Qualitative Study Results

ClinicalTrials.gov

Date searched: January 8, 2021

EXPERT SEARCH MODE: (F2M OR M2F OR F-2-M OR M-2-F OR EXPAND[Concept] "assigned female" OR EXPAND[Concept] "assigned male" OR EXPAND[Concept] "female-to-male" OR gender dysphoria OR gender minority OR nonbinary OR non-binary OR nonconforming OR non-conforming OR EXPAND[Concept] "male-to-female" OR transboy OR transfemale OR trans-female OR transfeminine OR trans-feminine OR transgender OR transgender OR transgirl OR transmale OR trans-male OR transmasculine OR trans-masculine OR transsexual OR trans-sexual) AND (adolescence OR adolescent OR boy OR boys OR child OR girl OR girls OR juvenile OR paediatric OR pediatric OR prepubertal OR pre-pubertal OR prepubescent OR pre-pubescent OR pubescent OR pubertal OR puberty OR school OR teen OR tween OR youth) AND (gender affirming OR gender confirming OR gender reassignment OR androgen OR antiandrogen* OR anti-androgen OR estradiol OR oestradiol OR estrogen OR oestrogen OR feminising OR feminizing OR EXPAND[Concept] "gonadotropin-releasing hormone" OR GnRH OR GnRH_a OR inhibit OR HRT OR hormone replacement OR suppression OR hormone therapy OR hormone treatment OR progestin OR testosterone OR bottom surgery OR gender surgery OR genital surgery OR clitoroplasty or genitoplasty OR hysterectomy OR labiaplast OR metoidioplasty OR oophorectomy OR orchiectomy OR phalloplast⁸ OR sex reassignment OR vaginectomy OR vaginoplasty) | Child | First posted from 01/01/2016 to 01/08/2020 (26)

clinicaltrials.gov link

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States?	Yes
1b. Is the nomination a request for an evidence report?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	An estimated 0.6% of adults ² and 0.7% of youth ages 13 to 17 ³ in the United States identify as transgender or “gender nonconforming”. While this may not be a large proportion of the population, it affects a vulnerable population.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, transgender individuals represent a vulnerable population. Transgender youth experience high rates of depression, anxiety, eating disorders, and suicide. ⁴⁻⁶
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, the cost to transition genders costs about \$20,000 over two years. ²⁴
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	No. We found one protocol for a systematic review that addresses KQ1. We found protocols that partially cover KQ 2 and 3.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. There is a lack of current evidence-based guidance for care of children and adolescents who identify as transgender, particularly regarding the benefits and harms of pubertal suppression, medical affirmation with hormone therapy, and surgical affirmation. While there are some existing guidelines and standards of care, ^{1, 7, 8} most are derived from expert opinion or have not been updated recently.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. There is a lack of current evidence-based guidance for care of children and adolescents who identify as transgender, particularly regarding the benefits and harms of pubertal suppression, medical affirmation with hormone therapy, and surgical affirmation. While there are some existing guidelines and standards of care, ^{1, 7, 8} most are derived from expert opinion or have not been updated recently.

Selection Criteria	Assessment
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: <ul style="list-style-type: none"> - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies) 	We did not find any studies addressing the remaining portions of KQ2 and 3 that were not covered by existing protocols.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=key question.