
IN THE UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

PAUL EKNES-TUCKER, et al.,

Plaintiffs-Appellees

&

UNITED STATES OF AMERICA,

Intervenor-Appellee

v.

GOVERNOR OF THE STATE OF ALABAMA, et al.,

Defendants-Appellants

ON APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF MINNESOTA

APPELLEES' SUPPLEMENTAL APPENDIX

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

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***Cosponsoring Associations:** American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

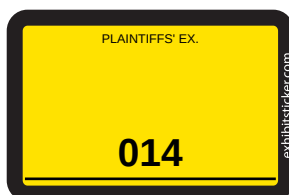
Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society-appointed task force of nine experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusion: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments—appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health



professional for adults (recommended)—should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment. (*J Clin Endocrinol Metab* 102: 3869–3903, 2017)

Summary of Recommendations

1.0 Evaluation of youth and adults

- 1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)
- 1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)
- 1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

- 1.4. We recommend against puberty blocking and gender-affirming hormone treatment in pre-pubertal children with GD/gender incongruence. (1 ⊕⊕○○)
- 1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 ⊕⊕⊕○)

2.0 Treatment of adolescents

- 2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 ⊕⊕○○)
- 2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 ⊕⊕○○)
- 2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 ⊕⊕○○)
- 2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 ⊕⊕○○).
- 2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 ⊕○○○)
- 2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 ⊕⊕○○)

3.0 Hormonal therapy for transgender adults

- 3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and

the criteria for the endocrine phase of gender transition before beginning treatment. (1 ⊕⊕⊕○)

- 3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 ⊕⊕⊕○)
- 3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 ⊕⊕○○)
- 3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 ⊕○○○)

4.0 Adverse outcome prevention and long-term care

- 4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 ⊕⊕○○)
- 4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 ⊕⊕○○)
- 4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕○○)
- 4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕○○)
- 4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 ⊕⊕○○)
- 4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 ⊕○○○)
- 4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

5.0 Surgery for sex reassignment and gender confirmation

- 5.1. We recommend that a patient pursue genital gender-affirming surgery 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. (1 ⊕⊕○○)
- 5.2. We advise 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 advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)
- 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 years 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 transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕○○○)

Changes Since the Previous Guideline

Both the current guideline and the one published in 2009 contain similar sections. Listed here are the sections contained in the current guideline and the corresponding number of recommendations: Introduction, Evaluation of Youth and Adults (5), Treatment of Adolescents (6), Hormonal Therapy for Transgender Adults (4), Adverse Outcomes Prevention and Long-term Care (7), and Surgery for Sex Reassignment and Gender Confirmation (6). The current introduction updates the diagnostic classification of "gender dysphoria/gender incongruence." It also reviews the development of "gender identity" and summarizes its natural development. The section on

clinical evaluation of both youth and adults, defines in detail the professional qualifications required of those who diagnose and treat both adolescents and adults. We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional. We recommend against puberty blocking followed by gender-affirming hormone treatment of prepubertal children. Clinicians should inform pubertal children, adolescents, and adults seeking gender-confirming treatment of their options for fertility preservation. Prior to treatment, clinicians should evaluate the presence of medical conditions that may be worsened by hormone depletion and/or treatment. A multidisciplinary team, preferably composed of medical and mental health professionals, should monitor treatments. Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence. Physicians should educate transgender persons regarding the time course of steroid-induced physical changes. Treatment should include periodic monitoring of hormone levels and metabolic parameters, as well as assessments of bone density and the impact upon prostate, gonads, and uterus. We also make recommendations for transgender persons who plan genital gender-affirming surgery.

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of individuals with GD/gender incongruence a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕○○○ denotes very low-quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the

values that the task force considered in making the recommendation. In some instances, there are remarks in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision-making, general preventive care measures, and basic principles of the treatment of transgender persons. They labeled these “Ungraded Good Practice Statement.” Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to these principles.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society’s Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline’s development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The CGS and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [e.g., stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers’ bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Review

The task force commissioned two systematic reviews to support this guideline. The first one aimed to summarize the available evidence on the effect of sex steroid use in transgender individuals on lipids and cardiovascular outcomes. The review identified 29 eligible studies at moderate risk of bias. In transgender males (female to male), sex steroid therapy was associated with a statistically significant increase in serum triglycerides and low-density lipoprotein cholesterol levels. High-density lipoprotein cholesterol levels decreased significantly across all follow-up time periods. In transgender females (male to female), serum triglycerides were significantly higher without any changes in other parameters. Few myocardial infarction, stroke, venous thromboembolism (VTE), and death events were reported. These events were more frequent in transgender females. However, the

quality of the evidence was low. The second review summarized the available evidence regarding the effect of sex steroids on bone health in transgender individuals and identified 13 studies. In transgender males, there was no statistically significant difference in the lumbar spine, femoral neck, or total hip BMD at 12 and 24 months compared with baseline values before initiating masculinizing hormone therapy. In transgender females, there was a statistically significant increase in lumbar spine BMD at 12 months and 24 months compared with baseline values before initiation of feminizing hormone therapy. There was minimal information on fracture rates. The quality of evidence was also low.

Introduction

Throughout recorded history (in the absence of an endocrine disorder) some men and women have experienced confusion and anguish resulting from rigid, forced conformity to sexual dimorphism. In modern history, there have been numerous ongoing biological, psychological, cultural, political, and sociological debates over various aspects of gender variance. The 20th century marked the emergence of a social awakening for men and women with the belief that they are “trapped” in the wrong body (3). Magnus Hirschfeld and Harry Benjamin, among others, pioneered the medical responses to those who sought relief from and a resolution to their profound discomfort. Although the term transsexual became widely known after Benjamin wrote “The Transsexual Phenomenon” (4), it was Hirschfeld who coined the term “transsexual” in 1923 to describe people who want to live a life that corresponds with their experienced gender vs their designated gender (5). Magnus Hirschfeld (6) and others (4, 7) have described other types of trans phenomena besides transsexualism. These early researchers proposed that the gender identity of these people was located somewhere along a unidimensional continuum. This continuum ranged from all male through “something in between” to all female. Yet such a classification does not take into account that people may have gender identities outside this continuum. For instance, some experience themselves as having both a male and female gender identity, whereas others completely renounce any gender classification (8, 9). There are also reports of individuals experiencing a continuous and rapid involuntary alternation between a male and female identity (10) or men who do not experience themselves as men but do not want to live as women (11, 12). In some countries, (e.g., Nepal, Bangladesh, and Australia), these nonmale or nonfemale genders are officially recognized (13). Specific treatment protocols, however, have not yet been developed for these groups.

Instead of the term transsexualism, the current classification system of the American Psychiatric Association uses the term gender dysphoria in its diagnosis of persons who are not satisfied with their designated gender (14). The current version of the World Health Organization's ICD-10 still uses the term transsexualism when diagnosing adolescents and adults. However, for the ICD-11, the World Health Organization has proposed using the term "gender incongruence" (15).

Treating persons with GD/gender incongruence (15) was previously limited to relatively ineffective elixirs or creams. However, more effective endocrinology-based treatments became possible with the availability of testosterone in 1935 and diethylstilbestrol in 1938. Reports of individuals with GD/gender incongruence who were treated with hormones and gender-affirming surgery appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association was founded in September 1979 and is now called the World Professional Association for Transgender Health (WPATH). WPATH published its first Standards of Care in 1979. These standards have since been regularly updated, providing guidance for treating persons with GD/gender incongruence (16).

Prior to 1975, few peer-reviewed articles were published concerning endocrine treatment of transgender persons. Since then, more than two thousand articles about various aspects of transgender care have appeared.

It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with GD/gender incongruence.

In the future, we need more rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols. Specifically, endocrine treatment protocols for GD/gender incongruence should include the careful assessment of the following: (1) the effects of prolonged delay of puberty in adolescents on bone health, gonadal function, and the brain (including effects on cognitive, emotional, social, and sexual development); (2) the effects of treatment in adults on sex hormone levels; (3) the requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids during treatment; and (4) the risks and benefits of gender-affirming hormone treatment in older transgender people.

To successfully establish and enact these protocols, a commitment of mental health and endocrine investigators is required to collaborate in long-term, large-scale

studies across countries that use the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools (*e.g.*, the European Network for the Investigation of Gender Incongruence) (17, 18).

Terminology and its use vary and continue to evolve. Table 1 contains the definitions of terms as they are used throughout this guideline.

Biological Determinants of Gender Identity Development

One's self-awareness as male or female changes gradually during infant life and childhood. This process of cognitive and affective learning evolves with interactions with parents, peers, and environment. A fairly accurate timetable exists outlining the steps in this process (19). Normative psychological literature, however, does not address if and when gender identity becomes crystallized and what factors contribute to the development of a gender identity that is not congruent with the gender of rearing. Results of studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomic—support the concept that gender identity and/or gender expression (20) likely reflect a complex interplay of biological, environmental, and cultural factors (21, 22).

With respect to endocrine considerations, studies have failed to find differences in circulating levels of sex steroids between transgender and nontransgender individuals (23). However, studies in individuals with a disorder/difference of sex development (DSD) have informed our understanding of the role that hormones may play in gender identity outcome, even though most persons with GD/gender incongruence do not have a DSD. For example, although most 46,XX adult individuals with virilizing congenital adrenal hyperplasia caused by mutations in *CYP21A2* reported a female gender identity, the prevalence of GD/gender incongruence was much greater in this group than in the general population without a DSD. This supports the concept that there is a role for prenatal/postnatal androgens in gender development (24–26), although some studies indicate that prenatal androgens are more likely to affect gender behavior and sexual orientation rather than gender identity *per se* (27, 28).

Researchers have made similar observations regarding the potential role of androgens in the development of gender identity in other individuals with DSD. For example, a review of two groups of 46,XY persons, each with androgen synthesis deficiencies and female raised, reported transgender male (female-to-male) gender role changes in 56% to 63% and 39% to 64% of patients, respectively (29). Also, in 46,XY female-raised individuals with cloacal

Table 1. Definitions of Terms Used in This Guideline

<i>Biological sex, biological male or female:</i> These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (e.g., a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided.
<i>Cisgender:</i> This means not transgender. An alternative way to describe individuals who are not transgender is “non-transgender people.”
<i>Gender-affirming (hormone) treatment:</i> See “gender reassignment”
<i>Gender dysphoria:</i> This is the distress and unease experienced if gender identity and designated gender are not completely congruent (see Table 2). In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced “gender identity disorder” with “gender dysphoria” and changed the criteria for diagnosis.
<i>Gender expression:</i> This refers to external manifestations of gender, expressed through one’s name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender.
<i>Gender identity/experienced gender:</i> This refers to one’s internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below), gender identity is not visible to others.
<i>Gender identity disorder:</i> This is the term used for GD/gender incongruence in previous versions of DSM (see “gender dysphoria”). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using “gender incongruence of childhood.”
<i>Gender incongruence:</i> This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity–related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment.
<i>Gender variance:</i> See “gender incongruence”
<i>Gender reassignment:</i> This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called gender-confirming or gender-affirming treatment.
<i>Gender-reassignment surgery (gender-confirming/gender-affirming surgery):</i> These terms refer only to the surgical part of gender-confirming/gender-affirming treatment.
<i>Gender role:</i> This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women.
<i>Sex designated at birth:</i> This refers to sex assigned at birth, usually based on genital anatomy.
<i>Sex:</i> This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.
<i>Sexual orientation:</i> This term describes an individual’s enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer.
<i>Transgender:</i> This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment.
<i>Transgender male (also: trans man, female-to-male, transgender male):</i> This refers to individuals assigned female at birth but who identify and live as men.
<i>Transgender woman (also: trans woman, male-to-female, transgender female):</i> This refers to individuals assigned male at birth but who identify and live as women.
<i>Transition:</i> This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.
<i>Transsexual:</i> This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.

exstrophy and penile agenesis, the occurrence of transgender male changes was significantly more prevalent than in the general population (30, 31). However, the fact that a high percentage of individuals with the same conditions did not change gender suggests that cultural factors may play a role as well.

With respect to genetics and gender identity, several studies have suggested heritability of GD/gender incongruence (32, 33). In particular, a study by Heylens *et al.* (33) demonstrated a 39.1% concordance rate for gender identity disorder (based on the DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs. Although numerous investigators have sought to identify

specific genes associated with GD/gender incongruence, such studies have been inconsistent and without strong statistical significance (34–38).

Studies focusing on brain structure suggest that the brain phenotypes of people with GD/gender incongruence differ in various ways from control males and females, but that there is not a complete sex reversal in brain structures (39).

In summary, although there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental factors, contribute to this fundamental aspect of human development.

Natural History of Children With GD/Gender Incongruence

With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called “desisters”). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence (20, 40). In adolescence, a significant number of these desisters identify as homosexual or bisexual. It may be that children who only showed some gender nonconforming characteristics have been included in the follow-up studies, because the DSM-IV text revision criteria for a diagnosis were rather broad. However, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (41, 42). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy. Together with an MHP, hormone-prescribing clinicians should examine the psychosocial impact of the potential changes on people’s lives, including mental health, friends, family, jobs, and their role in society. Transgender individuals should be encouraged to experience living in the new gender role and assess whether

this improves their quality of life. Although the focus of this guideline is gender-affirming hormone therapy, collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome.

Diagnostic assessment and mental health care

GD/gender incongruence may be accompanied with psychological or psychiatric problems (43–51). It is therefore necessary that clinicians who prescribe hormones and are involved in diagnosis and psychosocial assessment meet the following criteria: (1) are competent in using the DSM and/or the ICD for diagnostic purposes, (2) are able to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) are trained in diagnosing psychiatric conditions, (4) undertake or refer for appropriate treatment, (5) are able to do a psychosocial assessment of the patient’s understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) regularly attend relevant professional meetings.

Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex.

During assessment, the clinician obtains information from the individual seeking gender-affirming treatment. In the case

Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

- A. A marked incongruence between one’s experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
 1. 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)
 2. 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)
 3. A strong desire for the primary and/or secondary sex characteristics of the other gender
 4. A strong desire to be of the other gender (or some alternative gender different from one’s designated gender)
 5. A strong desire to be treated as the other gender (or some alternative gender different from one’s designated gender)
 6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one’s designated gender)
 - B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Specify if:
1. The condition exists with a disorder of sex development.
 2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (*e.g.*, penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

of adolescents, the clinician also obtains information from the parents or guardians regarding various aspects of the child's general and psychosexual development and current functioning. On the basis of this information, the clinician:

- decides whether the individual fulfills criteria for treatment (see Tables 2 and 3) for GD/gender incongruence (DSM-5) or transsexualism (DSM-5 and/or ICD-10);
- informs the individual about the possibilities and limitations of various kinds of treatment (hormonal/surgical and nonhormonal), and if medical treatment is desired, provides correct information to prevent unrealistically high expectations;
- assesses whether medical interventions may result in unfavorable psychological and social outcomes.

In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with positive outcomes (52–56).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (57) and an assessment of the decision-making capability of the youth. An evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic phase (58).

Social transitioning

A change in gender expression and role (which may involve living part time or full time in another gender role that is consistent with one's gender identity) may test the person's resolve, the capacity to function in the affirmed gender, and the adequacy of social, economic, and psychological supports. It assists both the individual and the clinician in their judgments about how to proceed (16). During social transitioning, the person's feelings about the social transformation (including coping with the responses of others) is a major focus of the counseling. The optimal timing for social transitioning may differ between individuals. Sometimes people wait until they

start gender-affirming hormone treatment to make social transitioning easier, but individuals increasingly start social transitioning long before they receive medically supervised, gender-affirming hormone treatment.

Criteria

Adolescents and adults seeking gender-affirming hormone treatment and surgery should satisfy certain criteria before proceeding (16). Criteria for gender-affirming hormone therapy for adults are in Table 4, and criteria for gender-affirming hormone therapy for adolescents are in Table 5. Follow-up studies in adults meeting these criteria indicate a high satisfaction rate with treatment (59). However, the quality of evidence is usually low. A few follow-up studies on adolescents who fulfilled these criteria also indicated good treatment results (60–63).

Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence

- 1.1. We advise that only trained MHPs who meet the following criteria should diagnose GD/gender incongruence in adults: (1) competence in using the DSM and/or the ICD for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)
- 1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or ICD for diagnostic

Table 3. ICD-10 Criteria for Transsexualism

Transsexualism (F64.0) has three criteria:

1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 y.
3. The disorder is not a symptom of another mental disorder or a genetic, DSD, or chromosomal abnormality.

Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (43–48, 50, 51, 64, 65). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (66), or certain forms of eunuchism (in which a person is preoccupied with or engages in castration and/or penectomy for

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
 - the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
 - gender dysphoria worsened with the onset of puberty,
 - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
 - the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,
2. And the adolescent:
 - has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
 - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment:
 - agrees with the indication for GnRH agonist treatment,
 - has confirmed that puberty has started in the adolescent (Tanner stage $\geq$ G2/B2),
 - has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
 - the persistence of gender dysphoria,
 - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
 - the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
2. And the adolescent:
 - has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
 - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
 - agrees with the indication for sex hormone treatment,
 - has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

reasons that are not gender identity related) (11). Clinicians should also be able to diagnose psychiatric conditions accurately and ensure that these conditions are treated appropriately, particularly when the conditions may complicate treatment, affect the outcome of gender-affirming treatment, or be affected by hormone use.

Values and preferences

The task force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the good practice statement.

- 1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).
- 1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 ⊕⊕○○)

Evidence

In most children diagnosed with GD/gender incongruence, it did not persist into adolescence. The percentages differed among studies, probably dependent on which version of the DSM clinicians used, the patient's age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/gender incongruent in adolescence (20). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (40). Social transition is associated with the persistence of GD/gender incongruence as a child progresses into adolescence. It may be that the presence of GD/gender incongruence in prepubertal children is the earliest sign that a child is destined to be transgender as an adolescent/adult (20). However, social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence.

This recommendation, however, does not imply that children should be discouraged from showing gender-variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the

GD/gender-incongruent children to whom this applies. At the present time, clinical experience suggests that persistence of GD/gender incongruence can only be reliably assessed after the first signs of puberty.

Values and preferences

The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence. This justifies the strong recommendation in the face of low-quality evidence.

- 1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 ⊕⊕⊕○)

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (67, 68). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding the future fertility of adolescents or adults beginning gender-affirming treatment.

Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option. This option is often not preferred, because mature sperm production is associated with later stages of puberty and with the significant development of secondary sex characteristics.

For those designated male at birth with GD/gender incongruence and who are in early puberty, sperm production and the development of the reproductive tract are insufficient for the cryopreservation of sperm. However, prolonged pubertal suppression using GnRH analogs is reversible and clinicians should inform these individuals that sperm production can be initiated following prolonged gonadotropin suppression. This can be accomplished by spontaneous gonadotropin recovery after

cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production, as stated above. Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In males treated for precocious puberty, spermarche was reported 0.7 to 3 years after cessation of GnRH analogs (69). In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6 to 12 months of gonadotropin treatment. However, sperm numbers when partners of these patients conceive are far below the “normal range” (70, 71).

In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (72, 73). Clinicians should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression.

In males with GD/gender incongruence, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis is currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In females with GD/gender incongruence, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender males, both prior to and as a result of androgen treatment (74–77), although these reports were not confirmed by others (78). Pregnancy has been reported in transgender males who have had prolonged androgen treatment and have discontinued testosterone but have not had genital surgery (79, 80). A reproductive endocrine gynecologist can counsel patients before gender-affirming hormone treatment or surgery regarding potential fertility options (81). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve, and oocyte maturation of immature tissue is being studied (82).

2.0 Treatment of Adolescents

During the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. However, for many adolescents with GD/gender incongruence, the pubertal physical changes are unbearable. As early medical intervention may prevent

psychological harm, various clinics have decided to start treating young adolescents with GD/gender incongruence with puberty-suppressing medication (a GnRH analog). As compared with starting gender-affirming treatment long after the first phases of puberty, a benefit of pubertal suppression at early puberty may be a better psychological and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche occurs ~2 years later. In boys, the first physical change is testicular growth. A testicular volume ≥ 4 mL is seen as consistent with the initiation of physical puberty. At the beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early morning with an ultrasensitive assay. From a testicular volume of 10 mL, daytime testosterone levels increase, leading to virilization (83). Note that pubic hair and/or axillary hair/odor may not reflect the onset of gonadarche; instead, it may reflect adrenarche alone.

- 2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment (Table 5), and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 $\oplus\oplus\oplus\oplus$)
- 2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty (Tanner stages G2/B2). (2 $\oplus\oplus\oplus\oplus$)

Evidence

Pubertal suppression can expand the diagnostic phase by a long period, giving the subject more time to explore options and to live in the experienced gender before making a decision to proceed with gender-affirming sex hormone treatments and/or surgery, some of which is irreversible (84, 85). Pubertal suppression is fully reversible, enabling full pubertal development in the natal gender, after cessation of treatment, if appropriate. The experience of full endogenous puberty is an undesirable condition for the GD/gender-incongruent individual and may seriously interfere with healthy psychological functioning and well-being. Treating GD/gender-incongruent adolescents entering puberty with GnRH analogs has been shown to improve psychological functioning in several domains (86).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared with initiating physical transition after puberty has been completed (60, 62). Looking like a man or woman when living as the opposite sex creates difficult

barriers with enormous life-long disadvantages. We therefore advise starting suppression in early puberty to prevent the irreversible development of undesirable secondary sex characteristics. However, adolescents with GD/gender incongruence should experience the first changes of their endogenous spontaneous puberty, because their emotional reaction to these first physical changes has diagnostic value in establishing the persistence of GD/gender incongruence (85). Thus, Tanner stage 2 is the optimal time to start pubertal suppression. However, pubertal suppression treatment in early puberty will limit the growth of the penis and scrotum, which will have a potential effect on future surgical treatments (87).

Clinicians can also use pubertal suppression in adolescents in later pubertal stages to stop menses in transgender males and prevent facial hair growth in transgender females. However, in contrast to the effects in early pubertal adolescents, physical sex characteristics (such as more advanced breast development in transgender boys and lowering of the voice and outgrowth of the jaw and brow in transgender girls) are not reversible.

Values and preferences

These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression.

Remarks

Table 6 lists the Tanner stages of breast and male genital development. Careful documentation of hallmarks of pubertal development will ensure precise timing when initiating pubertal suppression once puberty has started. Clinicians can use pubertal LH and sex steroid levels to confirm that puberty has progressed sufficiently before starting pubertal suppression (88). Reference

ranges for sex steroids by Tanner stage may vary depending on the assay used. Ultrasensitive sex steroid and gonadotropin assays will help clinicians document early pubertal changes.

Irreversible and, for GD/gender-incongruent adolescents, undesirable sex characteristics in female puberty are breasts, female body habitus, and, in some cases, relative short stature. In male puberty, they are a prominent Adam's apple; low voice; male bone configuration, such as a large jaw, big feet and hands, and tall stature; and male hair pattern on the face and extremities.

- 2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 ⊕ ⊕ ⊕ ⊕)

Evidence

Clinicians can suppress pubertal development and gonadal function most effectively via gonadotropin suppression using GnRH analogs. GnRH analogs are long-acting agonists that suppress gonadotropins by GnRH receptor desensitization after an initial increase of gonadotropins during ~10 days after the first and (to a lesser degree) the second injection (89). Antagonists immediately suppress pituitary gonadotropin secretion (90, 91). Long-acting GnRH analogs are the currently preferred treatment option. Clinicians may consider long-acting GnRH antagonists when evidence on their safety and efficacy in adolescents becomes available.

During GnRH analog treatment, slight development of secondary sex characteristics may regress, and in a later phase of pubertal development, it will stop. In girls, breast tissue will become atrophic, and menses will stop. In boys, virilization will stop, and testicular volume may decrease (92).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploration of his/her transition wish, the individual no longer desires transition, they can discontinue pubertal suppression. In subjects with

Table 6. Tanner Stages of Breast Development and Male External Genitalia

The description of Tanner stages for breast development:

1. Prepubertal
2. Breast and papilla elevated as small mound; areolar diameter increased
3. Breast and areola enlarged, no contour separation
4. Areola and papilla form secondary mound
5. Mature; nipple projects, areola part of general breast contour

For penis and testes:

1. Prepubertal, testicular volume <4 mL
2. Slight enlargement of penis; enlarged scrotum, pink, texture altered, testes 4–6 mL
3. Penis longer, testes larger (8–12 mL)
4. Penis and glans larger, including increase in breadth; testes larger (12–15 mL), scrotum dark
5. Penis adult size; testicular volume > 15 mL

Adapted from Lawrence (56).

precocious puberty, spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH analogs (93).

Recommendations 2.1 to 2.3 are supported by a prospective follow-up study from The Netherlands. This report assessed mental health outcomes in 55 transgender adolescents/young adults (22 transgender females and 33 transgender males) at three time points: (1) before the start of GnRH agonist (average age of 14.8 years at start of treatment), (2) at initiation of gender-affirming hormones (average age of 16.7 years at start of treatment), and (3) 1 year after “gender-reassignment surgery” (average age of 20.7 years) (63). Despite a decrease in depression and an improvement in general mental health functioning, GD/gender incongruence persisted through pubertal suppression, as previously reported (86). However, following sex hormone treatment and gender-reassignment surgery, GD/gender incongruence was resolved and psychological functioning steadily improved (63). Furthermore, well-being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long-term follow-up of individuals managed according to currently existing clinical practice guidelines for transgender youth, and it underscores the benefit of the multidisciplinary approach pioneered in The Netherlands; however, further studies are needed.

Side effects

The primary risks of pubertal suppression in GD/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development. Few data are available on the effect of GnRH analogs on BMD in adolescents with GD/gender incongruence. Initial data in GD/gender-incongruent subjects demonstrated no change of absolute areal BMD during 2 years of GnRH analog therapy but a decrease in BMD *z* scores (85). A recent study also suggested suboptimal bone mineral accrual during GnRH analog treatment. The study reported a decrease in areal BMD *z* scores and of bone mineral apparent density *z* scores (which takes the size of the bone into account) in 19 transgender males treated with GnRH analogs from a mean age of 15.0 years (standard deviation = 2.0 years) for a median duration of 1.5 years (0.3 to 5.2 years) and in 15 transgender females treated from 14.9 (± 1.9) years for 1.3 years (0.5 to 3.8 years), although not all changes were statistically significant (94). There was incomplete catch-up at age 22 years after sex hormone treatment from age 16.6 (± 1.4)

years for a median duration of 5.8 years (3.0 to 8.0 years) in transgender females and from age 16.4 (± 2.3) years for 5.4 years (2.8 to 7.8 years) in transgender males. Little is known about more prolonged use of GnRH analogs. Researchers reported normal BMD *z* scores at age 35 years in one individual who used GnRH analogs from age 13.7 years until age 18.6 years before initiating sex hormone treatment (65).

Additional data are available from individuals with late puberty or GnRH analog treatment of other indications. Some studies reported that men with constitutionally delayed puberty have decreased BMD in adulthood (95). However, other studies reported that these men have normal BMD (96, 97). Treating adults with GnRH analogs results in a decrease of BMD (98). In children with central precocious puberty, treatment with GnRH analogs has been found to result in a decrease of BMD during treatment by some (99) but not others (100). Studies have reported normal BMD after discontinuing therapy (69, 72, 73, 101, 102). In adolescents treated with growth hormone who are small for gestational age and have normal pubertal timing, 2-year GnRH analog treatments did not adversely affect BMD (103). Calcium supplementation may be beneficial in optimizing bone health in GnRH analog-treated individuals (104). There are no studies of vitamin D supplementation in this context, but clinicians should offer supplements to vitamin D-deficient adolescents. Physical activity, especially during growth, is important for bone mass in healthy individuals (103) and is therefore likely to be beneficial for bone health in GnRH analog-treated subjects.

GnRH analogs did not induce a change in body mass index standard deviation score in GD/gender-incongruent adolescents (94) but caused an increase in fat mass and decrease in lean body mass percentage (92). Studies in girls treated for precocious puberty also reported a stable body mass index standard deviation score during treatment (72) and body mass index and body composition comparable to controls after treatment (73).

Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRH analogs for precocious/early puberty (105, 106). Blood pressure monitoring before and during treatment is recommended.

Individuals may also experience hot flashes, fatigue, and mood alterations as a consequence of pubertal suppression. There is no consensus on treatment of these side effects in this context.

It is recommended that any use of pubertal blockers (and subsequent use of sex hormones, as detailed below) include a discussion about implications for fertility (see recommendation 1.3). Transgender adolescents may

want to preserve fertility, which may be otherwise compromised if puberty is suppressed at an early stage and the individual completes phenotypic transition with the use of sex hormones.

Limited data are available regarding the effects of GnRH analogs on brain development. A single cross-sectional study demonstrated no compromise of executive function (107), but animal data suggest there may be an effect of GnRH analogs on cognitive function (108).

Values and preferences

Our recommendation of GnRH analogs places a higher value on the superior efficacy, safety, and reversibility of the pubertal hormone suppression achieved (as compared with the alternatives) and a relatively lower value on limiting the cost of therapy. Of the available alternatives, depot and oral progestin preparations are effective. Experience with this treatment dates back prior to the emergence of GnRH analogs for treating precocious puberty in papers from the 1960s and early 1970s (109–112). These compounds are usually safe, but some side effects have been reported (113–115). Only two recent studies involved transgender youth (116, 117). One of these studies described the use of oral lynestrenol monotherapy followed by the addition of testosterone treatment in transgender boys who were at Tanner stage B4 or further at the start of treatment (117). They found lynestrenol safe, but gonadotropins were not fully suppressed. The study reported metrorrhagia in approximately half of the individuals, mainly in the first 6 months. Acne, headache, hot flashes, and fatigue were other frequent side effects. Another progestin that has been studied in the United States is medroxyprogesterone. This agent is not as effective as GnRH analogs in lowering endogenous sex hormones either and may be associated with other side effects (116). Progestin preparations may be an acceptable treatment for persons without access to GnRH analogs or with a needle phobia. If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see adult section).

Remarks

Measurements of gonadotropin and sex steroid levels give precise information about gonadal axis suppression, although there is insufficient evidence for any specific short-term monitoring scheme in children treated with GnRH analogs (88). If the gonadal axis is not completely suppressed—as evidenced by (for example) menses, erections, or progressive hair growth—the interval of GnRH analog treatment can be shortened or the dose increased. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Table 7 illustrates a suggested clinical protocol.

Anthropometric measurements and X-rays of the left hand to monitor bone age are informative for evaluating growth. To assess BMD, clinicians can perform dual-energy X-ray absorptiometry scans.

- 2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule (see Table 8) after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years (Table 5). (1 ⊕⊕○○)
- 2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 ⊕○○○)
- 2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment (Table 9). (2 ⊕⊕○○)

Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

Every 3–6 mo
Anthropometry: height, weight, sitting height, blood pressure, Tanner stages
Every 6–12 mo
Laboratory: LH, FSH, E2/T, 25OH vitamin D
Every 1–2 y
Bone density using DXA
Bone age on X-ray of the left hand (if clinically indicated)

Adapted from Hembree *et al.* (118).

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone;

Table 8. Protocol Induction of Puberty

Induction of female puberty with oral 17β -estradiol, increasing the dose every 6 mo:

5 $\mu\text{g/kg/d}$

10 $\mu\text{g/kg/d}$

15 $\mu\text{g/kg/d}$

20 $\mu\text{g/kg/d}$

Adult dose = 2–6 mg/d

In postpubertal transgender female adolescents, the dose of 17β -estradiol can be increased more rapidly:

1 mg/d for 6 mo

2 mg/d

Induction of female puberty with transdermal 17β -estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):

6.25–12.5 $\mu\text{g/24 h}$ (cut 25- μg patch into quarters, then halves)

25 $\mu\text{g/24 h}$

37.5 $\mu\text{g/24 h}$

Adult dose = 50–200 $\mu\text{g/24 h}$

For alternatives once at adult dose, see Table 11.

Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):

25 $\text{mg/m}^2/2 \text{ wk}$ (or alternatively, half this dose weekly, or double the dose every 4 wk)

50 $\text{mg/m}^2/2 \text{ wk}$

75 $\text{mg/m}^2/2 \text{ wk}$

100 $\text{mg/m}^2/2 \text{ wk}$

Adult dose = 100–200 mg every 2 wk

In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:

75 mg/2 wk for 6 mo

125 mg/2 wk

For alternatives once at adult dose, see Table 11.

Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).

Adapted from Hembree et al. (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15 to 16 years (119), and in many countries 16-year-olds are legally competent with regard to medical decision making (120). However, others believe that although some capacities are generally achieved before age 16 years, other abilities (such as good risk

assessment) do not develop until well after 18 years (121). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures, such as most surgical procedures (121).

Currently available data from transgender adolescents support treatment with sex hormones starting at age 16 years (63, 122). However, some patients may incur potential risks by waiting until age 16 years. These include the potential risk to bone health if puberty is suppressed

Table 9. Baseline and Follow-up Protocol During Induction of Puberty

Every 3–6 mo

•Anthropometry: height, weight, sitting height, blood pressure, Tanner stages

Every 6–12 mo

•In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin D

•In transgender females: prolactin, estradiol, 25OH vitamin D

Every 1–2 y

•BMD using DXA

•Bone age on X-ray of the left hand (if clinically indicated)

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).

For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.

Adapted from Hembree et al. (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.

for 6 to 7 years before initiating sex hormones (*e.g.*, if someone reached Tanner stage 2 at age 9-10 years old). Additionally, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age. However, only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents currently exist (63). Clearly, long-term studies are needed to determine the optimal age of sex hormone treatment in GD/gender-incongruent adolescents.

The MHP who has followed the adolescent during GnRH analog treatment plays an essential role in assessing whether the adolescent is eligible to start sex hormone therapy and capable of consenting to this treatment (Table 5). Support of the family/environment is essential. Prior to the start of sex hormones, clinicians should discuss the implications for fertility (see recommendation 1.5). Throughout pubertal induction, an MHP and a pediatric endocrinologist (or other clinician competent in the evaluation and induction of pubertal development) should monitor the adolescent. In addition to monitoring therapy, it is also important to pay attention to general adolescent health issues, including healthy life style choices, such as not smoking, contraception, and appropriate vaccinations (*e.g.*, human papillomavirus).

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal adolescents with GD/gender incongruence as they use in other individuals with hypogonadism, carefully monitoring for desired and undesired effects (Table 8). In transgender female adolescents, transdermal 17β -estradiol may be an alternative for oral 17β -estradiol. It is increasingly used for pubertal induction in hypogonadal females. However, the absence of low-dose estrogen patches may be a problem. As a result, individuals may need to cut patches to size themselves to achieve appropriate dosing (123). In transgender male adolescents, clinicians can give testosterone injections intramuscularly or subcutaneously (124, 125).

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an

adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 "Hormonal Therapy for Transgender Adults").

Values and preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (128).

Remarks

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed. Adult height may be a concern in transgender adolescents. In a transgender female adolescent, clinicians may consider higher doses of estrogen or a more rapid tempo of dose escalation during pubertal induction. There are no established treatments yet to augment adult height in a transgender male adolescent with open epiphyses during pubertal induction. It is not uncommon for transgender adolescents to present for clinical services after having completed or nearly completed puberty. In such cases, induction of puberty with sex hormones can be done more rapidly (see Table 8). Additionally, an adult dose of testosterone in transgender male adolescents may suffice to suppress the gonadal axis without the need to use a separate agent. At the appropriate time, the multidisciplinary team should adequately prepare the adolescent for transition to adult care.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are (1) to reduce endogenous sex hormone levels, and thus reduce

the secondary sex characteristics of the individual's designated gender, and (2) to replace endogenous sex hormone levels consistent with the individual's gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is codetermined in collaboration with both the person pursuing transition and the health care providers. The treatment team should include a medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender incongruence and the mental health concerns of transition, and a primary care provider able to provide care appropriate for transgender individuals. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being (129, 130).

- 3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 ⊕⊕⊕⊕)
- 3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment (Table 10). (1 ⊕⊕⊕⊕)
- 3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 ⊕⊕⊕⊕)

Evidence

It is the responsibility of the treating clinician to confirm that the person fulfills criteria for treatment. The treating clinician should become familiar with the terms and criteria presented in Tables 1–5 and take a thorough history from the patient in collaboration with the other members of the treatment team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, risks, and benefits of treatment are well understood; and the desire for transition persists. They also need to discuss fertility preservation options (see recommendation 1.3) (67, 68).

Transgender males

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in transgender males (Appendix A) (113, 114, 131–134). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (135). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (this is dependent on the specific assay, but is typically 320 to 1000 ng/dL) (Table 11) (136). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see section 4.0 “Adverse Outcome Prevention and Long-Term Care”) and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in transgender males results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness in those genetically predisposed, and increased sexual desire (137).

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen

Very high risk of adverse outcomes:

- Thromboembolic disease

Moderate risk of adverse outcomes:

- Macroprolactinoma
- Breast cancer
- Coronary artery disease
- Cerebrovascular disease
- Cholelithiasis
- Hypertriglyceridemia

Transgender male: testosterone

Very high risk of adverse outcomes:

- Erythrocytosis (hematocrit > 50%)

Moderate risk of adverse outcomes:

- Severe liver dysfunction (transaminases > threefold upper limit of normal)
- Coronary artery disease
- Cerebrovascular disease
- Hypertension
- Breast or uterine cancer

Table 11. Hormone Regimens in Transgender Persons

Transgender females ^a	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch	0.025–0.2 mg/d
(New patch placed every 3–5 d)	
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate ^b	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate ^c	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6% ^d	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

^aEstrogens used with or without antiandrogens or GnRH agonist.

^bNot available in the United States.

^cOne thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

^dAvoid cutaneous transfer to other individuals.

In transgender males, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, cessation of menses (usually), and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (138). Clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Transgender females

The hormone regimen for transgender females is more complex than the transgender male regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for females (139). Most published clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range (21, 113, 114, 132–134, 139, 140).

Multiple adjunctive medications are available, such as progestins with antiandrogen activity and GnRH agonists (141). Spironolactone works by directly blocking androgens during their interaction with the androgen

receptor (114, 133, 142). It may also have estrogenic activity (143). Cyproterone acetate, a progestational compound with antiandrogenic properties (113, 132, 144), is widely used in Europe. 5 α -Reductase inhibitors do not reduce testosterone levels and have adverse effects (145).

Dittrich *et al.* (141) reported that monthly doses of the GnRH agonist goserelin acetate in combination with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 60 transgender females. Leuprolide and transdermal estrogen were as effective as cyproterone and transdermal estrogen in a comparative retrospective study (146).

Patients can take estrogen as oral conjugated estrogens, oral 17 β -estradiol, or transdermal 17 β -estradiol. Among estrogen options, the increased risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically (134, 140, 141), which is why we specifically suggest that it not be used in any transgender treatment plan. Data distinguishing among other estrogen options are less well established although there is some thought that oral routes of administration are more thrombogenic due to the “first pass effect” than are transdermal and parenteral routes, and that the risk of thromboembolic events is dose-dependent. Injectable estrogen and sublingual

estrogen may benefit from avoiding the first pass effect, but they can result in more rapid peaks with greater overall periodicity and thus are more difficult to monitor (147, 148). However, there are no data demonstrating that increased periodicity is harmful otherwise.

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogen use. Clinicians should measure serum estradiol and serum testosterone and maintain them at the level for premenopausal females (100 to 200 pg/mL and <50 ng/dL, respectively). The transdermal preparations and injectable estradiol cypionate or valerate preparations may confer an advantage in older transgender females who may be at higher risk for thromboembolic disease (149).

Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (150).

Not all individuals with GD/gender incongruence seek treatment as described (e.g., male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (151). We need prospective studies to better understand treatment options for these persons.

- 3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 ⊕○○○)

Evidence

Transgender males

Physical changes that are expected to occur during the first 1 to 6 months of testosterone therapy include

cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice (152, 153), clitoromegaly, and male pattern hair loss (in some cases) (114, 144, 154, 155) (Table 12).

Transgender females

Physical changes that may occur in transgender females in the first 3 to 12 months of estrogen and anti-androgen therapy include decreased sexual desire, decreased spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, increased breast tissue growth, and redistribution of fat mass (114, 139, 149, 154, 155, 161) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (114, 139, 149, 155). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in transgender females has been studied (150), precise information about other changes induced by sex hormones is lacking (141). There is a great deal of variability among individuals, as evidenced during pubertal development. We all know that a major concern for transgender females is breast development. If we work with estrogens, the result will be often not what the transgender female expects.

Alternatively, there are transgender females who report an anecdotal improved breast development, mood, or sexual desire with the use of progestogens. However, there have been no well-designed studies of the role of progestogens in feminizing hormone regimens, so the question is still open.

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	— ^a
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	— ^b
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Assche-man *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

^aPrevention and treatment as recommended for biological men.

^bMenorrhagia requires diagnosis and treatment by a gynecologist.

Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y ^a
Scalp hair	Variable	— ^b
Voice changes	None	— ^c

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

^aComplete removal of male sexual hair requires electrolysis or laser treatment or both.

^bFamilial scalp hair loss may occur if estrogens are stopped.

^cTreatment by speech pathologists for voice training is most effective.

development in transgender females is extremely sparse and based on the low quality of evidence. Current evidence does not indicate that progestogens enhance breast development in transgender females, nor does evidence prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions (162).

Values and preferences

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.*, breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone-induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender males and females confers many of the same risks associated with sex hormone replacement therapy in nontransgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (131, 139).

- 4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every

3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 ⊕⊕○○)

Evidence

Pretreatment screening and appropriate regular medical monitoring are recommended for both transgender males and females during the endocrine transition and periodically thereafter (26, 155). Clinicians should monitor weight and blood pressure, conduct physical exams, and assess routine health questions, such as tobacco use, symptoms of depression, and risk of adverse events such as deep vein thrombosis/pulmonary embolism and other adverse effects of sex steroids.

Transgender males

Table 14 contains a standard monitoring plan for transgender males on testosterone therapy (154, 159). Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (135).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (163, 164). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (144, 165, 166).

Transgender females

Table 15 contains a standard monitoring plan for transgender females on estrogens, gonadotropin suppression, or antiandrogens (160). Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitor serum estradiol levels using laboratories participating in external quality control, as measurements of estradiol in blood can be very challenging (167).

VTE may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (161). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (149). The incidence decreased when clinicians stopped administering ethinyl estradiol (161). Thus, the use of synthetic estrogens and conjugated estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1 of 60 of transgender females treated with a GnRH analog and oral

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:^a
 - a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
 - b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
 - c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

^aAdapted from Lapauw *et al.* (154) and Ott *et al.* (159).

estradiol (141). The patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase gene. In an Austrian gender clinic, administering gender-affirming hormones to 162 transgender females and 89 transgender males was not associated with VTE, despite an 8.0% and 5.6% incidence of thrombophilia (159). A more recent multinational study reported only 10 cases of VTE from a cohort of 1073 subjects (168). Thrombophilia screening of transgender persons initiating hormone treatment should be restricted to those with a personal or family history of VTE (159). Monitoring D-dimer levels during treatment is not recommended (169).

- 4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 ⊕⊕○○)

Evidence

Estrogen therapy can increase the growth of pituitary lactotroph cells. There have been several reports of prolactinomas occurring after long-term, high-dose

estrogen therapy (170–173). Up to 20% of transgender females treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (156). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or discontinuation of cyproterone acetate (157, 174, 175).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and every 2 years thereafter. Given that only a few case studies reported prolactinomas, and prolactinomas were not reported in large cohorts of estrogen-treated persons, the risk is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in transgender females, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels (174).

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
 - a. Serum testosterone levels should be <50 ng/dL.
 - b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

- 4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 |⊕⊕○○)

Evidence

Transgender males

Administering testosterone to transgender males results in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol values (176–179). Studies of the effect of testosterone on insulin sensitivity have mixed results (178, 180). A randomized, open-label uncontrolled safety study of transgender males treated with testosterone undecanoate demonstrated no insulin resistance after 1 year (181, 182). Numerous studies have demonstrated the effects of sex hormone treatment on the cardiovascular system (160, 179, 183, 184). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185). A systematic review of the literature found that data were insufficient (due to very low-quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176). Clinicians should manage cardiovascular risk factors as they emerge according to established guidelines (186).

Transgender females

A prospective study of transgender females found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (178). However, increased weight, blood pressure, and markers of insulin resistance attenuated these favorable lipid changes. In a meta-analysis, only serum triglycerides were higher at ≥ 24 months without changes in other parameters (187). The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).

Thus, there is limited evidence to determine whether estrogen is protective or detrimental on lipid and glucose metabolism in transgender females (176). With aging, there is usually an increase of body weight. Therefore, as with nontransgender individuals, clinicians should

monitor and manage glucose and lipid metabolism and blood pressure regularly according to established guidelines (186).

- 4.4. We recommend that clinicians obtain BMD measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 |⊕⊕○○)

Evidence

Transgender males

Baseline bone mineral measurements in transgender males are generally in the expected range for their pre-treatment gender (188). However, adequate dosing of testosterone is important to maintain bone mass in transgender males (189, 190). In one study (190), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels in the normal range may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol, both systemically and locally in the bone.

Transgender females

A baseline study of BMD reported T scores less than -2.5 in 16% of transgender females (191). In aging males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (192, 193) and is more important for peak bone mass (194). Estrogen preserves BMD in transgender females who continue on estrogen and antiandrogen therapies (188, 190, 191, 195, 196).

Fracture data in transgender males and females are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss. There have been no studies to determine whether clinicians should use the sex assigned at birth or affirmed gender for assessing osteoporosis (e.g., when using the FRAX tool). Although some researchers use the sex assigned at birth (with the assumption that bone mass has usually peaked for transgender people who initiate hormones in early adulthood), this should be assessed on a case-by-case basis until there are more data available. This assumption will be further complicated by the increasing prevalence of transgender people who undergo hormonal transition at a pubertal age or soon after puberty. Sex for comparison within risk assessment tools may be based on the age at which hormones were initiated and the length of exposure to hormones. In some cases, it may be

reasonable to assess risk using both the male and female calculators and using an intermediate value. Because all subjects underwent normal pubertal development, with known effects on bone size, reference values for birth sex were used for all participants (154).

- 4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for those designated female at birth. (2 ⊕⊕○○)
- 4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 ⊕○○○)

Evidence

Studies have reported a few cases of breast cancer in transgender females (197–200). A Dutch study of 1800 transgender females followed for a mean of 15 years (range of 1–30 years) found one case of breast cancer. The Women's Health Initiative study reported that females taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with females taking placebo (137).

In transgender males, a large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven breast cancers (194). The authors reported that this was not above the expected rate of breast cancers in cisgender females in this cohort. Furthermore, they did report one breast cancer that developed in a transgender male patient after mastectomy, supporting the fact that breast cancer can occur even after mastectomy. Indeed, there have been case reports of breast cancer developing in subareolar tissue in transgender males, which occurred after mastectomy (201, 202).

Women with primary hypogonadism (Turner syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (203, 204). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20 to 30 years). We need long-term studies to determine the actual risk, as well as the role of screening mammograms. Regular examinations and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen deprivation therapy (205). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (206). Although van Kesteren *et al.* (207) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostates of

transgender females, studies have reported cases of benign prostatic hyperplasia in transgender females treated with estrogens for 20 to 25 years (208, 209). Studies have also reported a few cases of prostate carcinoma in transgender females (210–214).

Transgender females may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for transgender females who transitioned after age 20 years to have annual screening digital rectal examinations after age 50 years and prostate-specific antigen tests consistent with U.S. Preventive Services Task Force Guidelines (215).

- 4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

Evidence

Although aromatization of testosterone to estradiol in transgender males has been suggested as a risk factor for endometrial cancer (216), no cases have been reported. When transgender males undergo hysterectomy, the uterus is small and there is endometrial atrophy (217, 218). Studies have reported cases of ovarian cancer (219, 220). Although there is limited evidence for increased risk of reproductive tract cancers in transgender males, health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer (221).

Values

Given the discomfort that transgender males experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. Additionally, in certain countries, the approval required to change the sex in a birth certificate for transgender males may be dependent on having a complete hysterectomy. Clinicians should help patients research nonmedical administrative criteria and

provide counseling. If individuals decide not to undergo hysterectomy, screening for cervical cancer is the same as all other females.

5.0 Surgery for Sex Reassignment and Gender Confirmation

For many transgender adults, genital gender-affirming surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. The type of surgery falls into two main categories: (1) those that directly affect fertility and (2) those that do not. Those that change fertility (previously called sex reassignment surgery) include genital surgery to remove the penis and gonads in the male and removal of the uterus and gonads in the female. The surgeries that effect fertility are often governed by the legal system of the state or country in which they are performed. Other gender-conforming surgeries that do not directly affect fertility are not so tightly governed.

Gender-affirming surgical techniques have improved markedly during the past 10 years. Reconstructive genital surgery that preserves neurologic sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (187). Additionally, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (130, 144) (Table 16).

Surgery that affects fertility is irreversible. The World Professional Association for Transgender Health Standards of Care (222) emphasizes that the “threshold of 18 should not be seen as an indication in itself for active intervention.” If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then the individual should not be referred for surgery (223, 224).

Gender-affirming genital surgeries for transgender females that affect fertility include gonadectomy, penectomy, and creation of a neovagina (225, 226). Surgeons often invert the skin of the penis to form the wall of the vagina, and several literatures reviews have

reported on outcomes (227). Sometimes there is inadequate tissue to form a full neovagina, so clinicians have revisited using intestine and found it to be successful (87, 228, 229). Some newer vaginoplasty techniques may involve autologous oral epithelial cells (230, 231).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also creating a sensate pedicled-spot adding a G spot to the neovagina to increase sensation (232). Most recently, plastic surgeons have developed techniques to fashion labia minora. To further complete the feminization, uterine transplants have been proposed and even attempted (233).

Neovaginal prolapse, rectovaginal fistula, delayed healing, vaginal stenosis, and other complications do sometimes occur (234, 235). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsivity and other aspects of sexual function are usually preserved following genital gender-affirming surgery (236, 237).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of transgender males (152, 238). No studies have compared the effectiveness of speech therapy, laryngeal surgery, or combined treatment.

Breast surgery is a good example of gender-confirming surgery that does not affect fertility. In all females, breast size exhibits a very broad spectrum. For transgender females to make the best informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, because the breasts continue to grow during that time (141, 155).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (e.g., cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

laser treatments. Other feminizing surgeries, such as that to feminize the face, are now becoming more popular (239–241).

In transgender males, clinicians usually delay gender-affirming genital surgeries until after a few years of androgen therapy. Those surgeries that affect fertility in this group include oophorectomy, vaginectomy, and complete hysterectomy. Surgeons can safely perform them vaginally with laparoscopy. These are sometimes done in conjunction with the creation of a neopenis. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (242, 243). Radial forearm flap seems to be the most satisfactory procedure (228, 244). Other flaps also exist (245). Surgeons can make neopenile erections possible by reinnervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (246, 247), but results are inconsistent (248). Surgeons can also stiffen the penis by imbedding some mechanical device (*e.g.*, a rod or some inflatable apparatus) (249, 250). Because of these limitations, the creation of a neopenis has often been less than satisfactory. Recently, penis transplants are being proposed (233).

In fact, most transgender males do not have any external genital surgery because of the lack of access, high cost, and significant potential complications. Some choose a metaoidioplasty that brings forward the clitoris, thereby allowing them to void in a standing position without wetting themselves (251, 252). Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (253).

The most important masculinizing surgery for the transgender male is mastectomy, and it does not affect fertility. Breast size only partially regresses with androgen therapy (155). In adults, discussions about mastectomy usually take place after androgen therapy has started. Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy 2 years after they begin androgen therapy and before age 18 years. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (254, 255). These often involve chest contouring (256). Mastectomy is often necessary for living comfortably in the new gender (256).

- 5.1. We recommend that a patient pursue genital gender-affirming surgery 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. (1 ⊕⊕○○)

- 5.2. We advise 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 advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)
- 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 years 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 transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕○○○)

Evidence

Owing to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. However, one systematic review including a large numbers of studies reported satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (257). For transgender males, the outcomes are less certain. However, the problems are now better understood (258). Several postoperative studies report significant long-term psychological and psychiatric pathology (259–261). One study showed satisfaction with breasts, genitals, and femininity increased significantly and showed the importance of surgical treatment as a key therapeutic option for transgender females (262). Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of

causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263). Reversal surgery in regretful male-to-female transsexuals after sexual reassignment surgery represents a complex, multistage procedure with satisfactory outcomes. Further insight into the characteristics of persons who regret their decision postoperatively would facilitate better future selection of applicants eligible for sexual reassignment surgery. We need more studies with appropriate controls that examine long-term quality of life, psychosocial outcomes, and psychiatric outcomes to determine the long-term benefits of surgical treatment.

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies criteria for gender-affirming surgery (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (176). For this reason, the surgeon and the hormone-prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery. One study suggests that preoperative factors (such as compliance) are less important for patient satisfaction than are the physical postoperative results (56). However, other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not achieve treatment goals (264) and experience higher rates of postoperative infections and other complications (265, 266). It is also important that the person requesting surgery feels comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (223).

An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.

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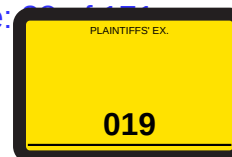
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Biased Science: The Texas and Alabama Measures Criminalizing Medical Treatment for Transgender Children and Adolescents Rely on Inaccurate and Misleading Scientific Claims

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Introduction and Summary

On February 18, 2022, Texas Attorney General Ken Paxton issued an interpretation of Texas state law (the “AG Opinion”), taking the position that certain medical procedures constitute child abuse as defined in the Texas Family Code.¹ Texas Governor Greg Abbott cited the AG Opinion as authority for his February 22, 2022 directive requiring the Texas Department of Family and Protective Services to “conduct a prompt and thorough investigation of any reported instances of these abusive procedures” (the “Governor’s Directive”).²

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¹ Tex. Op. Att’y. Gen. No. KP-0401 (Feb. 18, 2022) (hereinafter, “AG Opinion”).

² Letter from Greg Abbott, Governor of Texas, to Jaime Masters, Commissioner, Texas Department of Family and Protective Services, Feb. 22, 2022, at <https://gov.texas.gov/uploads/files/press/O-MastersJaime202202221358.pdf>

On April 7, 2022, Governor Kay Ivey of Alabama signed S.B. 184 (the “Alabama Law”), which imposes felony penalties on anyone providing certain medical care to any child, adolescent, or young adult under age 19.³

We are a group of six scientists and one law professor. Among the scientists, three of us are M.D.s., three are PhD’s, and all treat transgender children and adolescents in daily clinical practice. We all hold academic appointments at major medical schools, including the University of Texas Southwestern and Yale University. In this report, we examine in depth the scientific claims made in the AG Opinion and the text of the Alabama Law about medical care for transgender children and adolescents. Note that, although we reject the AG’s assertion that gender-affirming care constitutes child abuse and we oppose the Alabama Law’s criminalization of such care, we do not address, in this report, the legal validity of either.⁴ In accordance with our expertise, our focus is on the science.

After examining the AG Opinion and the findings of “fact” in the Alabama Law in detail, we conclude that their medical claims are not grounded in reputable science and are full of errors of omission and inclusion. These errors, taken together, thoroughly discredit the AG Opinion’s claim that standard medical care for transgender children and adolescents constitutes child abuse. The Alabama Law contains similar assertions of scientific fact, and these too are riddled with errors, calling into question the scientific foundations of the law.

In this report, we focus closely on the AG Opinion, because it contains a full explanation of its reasoning, while the Alabama law presents a list of purported scientific findings without argument or citation. We note, throughout, when the purported findings in the Alabama law echo the claims made in the AG Opinion.

The Texas Attorney General either misunderstands or deliberately misstates medical protocols and scientific evidence. The AG Opinion and the Alabama Law make exaggerated and unsupported claims about the course of treatment for gender dysphoria, specifically claiming that standard medical care for pediatric patients includes surgery on genitals and reproductive organs. In fact, the authoritative protocols for medical care for transgender children and adolescents, which define what we term “gender-affirming care,” specifically state that individuals must be over the age of majority before they can undergo such surgery. The AG Opinion and the Alabama Law also ignore the mainstream scientific evidence showing the significant benefits of gender-affirming care and exaggerate potential risks.

These are not close calls or areas of reasonable disagreement. The AG Opinion and the Alabama Law’s findings ignore established medical authorities and repeat discredited, outdated, and poor-quality information. The AG Opinion also mischaracterizes reputable sources and repeatedly cites a fringe group whose listed advisors have limited (or no) scientific and medical credentials and include well-known anti-trans activists.

³ Vulnerable Child Compassion and Protection Act, 2022 Ala. Laws 289 (hereinafter, “Alabama Law”).

⁴ For legal analysis, see Plaintiffs’ Original Petition and Application for Temporary Restraining Order, Temporary Injunction, Permanent Injunction, and Request for Declaratory Relief, Doe v. Abbott, March 1, 2022, at <https://www.aclu.org/legal-document/doe-v-abbott-petition>.

The AG Opinion falsely implies that puberty blockers and hormones are administered to prepubertal children, when, in fact, the standard medical protocols recommend drug treatments only for adolescents (and not prepubertal children). For purposes of this report, we use the term “adolescent” to refer to a child under the age of majority in whom pubertal development has begun.

The AG Opinion also omits mention of the extensive safeguards established by the standard protocols to ensure that medication is needed and that adolescents and their parents give informed assent and consent, respectively, to treatment when it is determined to be essential care. There is no rush to treatment: the course of gender-affirming care is tailored to each individual, and standard protocols mandate a process of consultation involving an interdisciplinary team including mental health professionals, medical providers, and parents.

By omitting the evidence demonstrating the substantial benefits of treatment for gender dysphoria, and by focusing on invented and exaggerated harms, the AG Opinion and the Alabama Law portray a warped picture of the scientific evidence. Contrary to their claims, a solid body of reputable evidence shows that gender-affirming care can be lifesaving and significantly improves mental health and reduces suicide attempts. The standard medical protocols were crafted by bodies of international experts based on a solid scientific foundation and have been in use for decades. Thus, treating gender dysphoria is considered not only ethical but also the clinically and medically recommended standard of care. Indeed, it would be considered unethical to *withhold* medical care from patients with gender dysphoria, just as it would be unethical to withhold potentially lifesaving care for patients with any other serious medical condition.

The repeated errors and omissions in the AG Opinion are so consistent and so extensive that it is difficult to believe that the opinion represents a good-faith effort to draw legal conclusions based on the best scientific evidence. It seems apparent that the AG Opinion is, rather, motivated by bias and crafted to achieve a preordained goal: to deny gender-affirming care to transgender youth. The same is true of the scientific claims made in the Alabama Law.

Many reputable scientific and professional organizations have issued statements opposing the Texas action,⁵ but to our knowledge, none have conducted the in-depth, point-by-point review that we provide here.

⁵ See APA President Condemns Texas Governor’s Directive to Report Parents of Transgender Minors [Internet]. Washington, D.C.: American Psychological Association; 2022 Feb 24 [cited 2022 Apr 15]. Available from: <https://www.apa.org/news/press/releases/2022/02/report-parents-transgender-children>; American Academy of Pediatrics, AAP, Texas Pediatric Society Oppose Actions in Texas Threatening Health of Transgender Youth [Internet]. Itasca (IL): American Academy of Pediatrics; 2022 Feb 24 [cited 2022 Apr 15]. Available from: <https://www.aap.org/en/news-room/news-releases/aap/2022/aap-texas-pediatric-society-oppose-actions-in-texas-threatening-health-of-transgender-youth/>; AACAP Statement Opposing Actions in Texas Threatening the Health, Mental Health and Well-Being of Transgender and Gender Diverse Youth and Their Families [Internet]. Washington, D.C.: American Academy of Child & Adolescent Psychiatry; 2022 March 1 [cited 2022 Apr 22]. Available from:

https://www.aacap.org/AACAP/zLatest_News/AACAP_Statement_Opposing_Actions_in_Texas.aspx.

See also Letter from James L. Madara, CEO and Executive Vice President of the American Medical Association, to Bill McBride, Executive Director of the National Governors Association, April 26, 2021 (opposing legislation in

Throughout this report, we use the highest-quality scientific evidence available. In this context, large-scale, randomized controlled trials would be inappropriate for ethical reasons: when medical care has been shown (by other methods) to reduce gender dysphoria and improve mental health, as is the case for gender-affirming care for individuals with gender dysphoria, it would be unethical to deny that care to a control group of patients. This is true in many areas of medicine. In such cases, physicians instead rely on studies using other scientific methods, and they judge the relative quality of evidence based on several factors, including whether the study is peer-reviewed, published in a high-impact journal, up to date, and conducted by reputable investigators.

In this report, we cite studies that are peer-reviewed, up to date, conducted by respected investigators, and published in high-impact journals that are widely read. This represents the highest-quality evidence available to physicians making treatment decisions in this context. By contrast, the AG Opinion relies on very poor-quality evidence. Only two of its sources are peer-reviewed scientific studies. Of these, one is badly out-of-date, and the other is cited for a proposition that is irrelevant to the treatment of transgender children and adolescents.⁶

To summarize, we find that:

1. The AG Opinion and the Alabama Law falsely claim that current medical standards authorize the surgical sterilization of transgender children and adolescents. In fact, present medical standards state that individuals must be the age of majority or older before undergoing surgery on genitals or reproductive organs.

Current medical protocols do not allow for either surgery or drug therapy for prepubertal children and specifically state that genital surgery should not be carried out before patients reach the legal age of majority. The standards of care do permit the careful use of drug therapies for adolescents (but not prepubertal children) and caution that drug therapies should be undertaken only after a careful, staged process of psychological and medical counseling. The AG Opinion's and Alabama Law's lists of "sex change procedures" and the claims that doctors are routinely sterilizing children and teenagers do not reflect current medical practice.

Arkansas and other states that would deny gender-affirming care), at <https://www.ama-assn.org/press-center/press-releases/ama-states-stop-interfering-health-care-transgender-children>; Clarke M, Farnan A, Barba A, Giovanni K, Brymer M, Julian J. Gender-Affirming Care Is Trauma-Informed Care [Internet]. Los Angeles (CA) and Durham (NC): National Child Traumatic Stress Network; 2022 [cited 2022 Apr 15]. Available from: <https://www.nctsn.org/sites/default/files/resources/fact-sheet/gender-affirming-care-is-trauma-informed-care.pdf>.

⁶ One study is Dhejne C, Lichtenstein P, Boman M, Johansson AL, Langstrom N, Landen M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011 Feb 22;6(2):e16885. We discuss in Section 2 why Dhejne et al. is out of date and unsupportive of the AG's claims. The AG Opinion also cites one study for the proposition that "hysterectomy, oophorectomy, and orchiectomy result in permanent sterility." The cited study is Cheng PJ, Pastuszak AW, Myers JB, Goodwin IA, Hotaling JM. Fertility concerns of the transgender patient. *Transl Androl Urol*. 2019 Jun;8(3):209-218. As we explain in Section 1, current medical protocols do not authorize surgery on genitals or reproductive organs for anyone under the age of majority, and so the reference is irrelevant to the treatment of minors.

2. The AG Opinion and the Alabama Law ignore the substantial benefits of medical care for transgender children and adolescents, care which has consistently been shown to reduce gender dysphoria and improve mental health. The best scientific evidence shows that gender dysphoria is real, that untreated gender dysphoria leads predictably to serious, negative medical consequences, and that gender-affirming care significantly improves mental health outcomes, including reducing rates of suicide.

The AG Opinion and the Alabama Law omit any discussion of the demonstrated benefits of gender-affirming care as recognized by established medical science. The AG Opinion and the Alabama Law also greatly exaggerate the percentage of adolescents whose diagnosed gender dysphoria dissipates without gender-affirming care. And the AG Opinion repeats discredited evidence claiming that there is a wave of so-called “rapid-onset” gender dysphoria among U.S. adolescents.

3. The AG Opinion and the Alabama Law greatly exaggerate the risks of gender-affirming drug therapy.

The AG Opinion exhibits a poor understanding of medicine and consistently misstates medical protocols and scientific evidence. Contrary to the AG Opinion’s statements, gender-affirming drug therapy (including puberty blockers and hormonal treatments) is safe and effective and has been approved by the major medical authorities. Puberty blockers are fully reversible; when discontinued, puberty begins, and fertility develops normally.

Gender-affirming hormone treatments can reduce fertility to some degree while ongoing, but the evidence suggests that these effects are reversible when hormone therapy is discontinued. Standard medical protocols manage these risks in the way any medical risks should be managed: by weighing the benefits of treatment against potential harms and by a careful and individualized process of consultation and consent. Indeed, the informed consent procedures for gender-affirming drug treatment are at least as rigorous as the consent required for any other drug treatment.

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Section 1. The AG Opinion and the Alabama Law falsely claim that current medical standards authorize the surgical sterilization of transgender children and adolescents. In fact, present medical standards state that individuals must be the age of majority or older before undergoing surgery on genitals or reproductive organs.

The AG Opinion asserts that the medical treatments for transgender children include a list of surgical procedures including “sterilization through castration, vasectomy, hysterectomy, oophorectomy, metoidioplasty, orchiectomy, penectomy, phalloplasty, and vaginoplasty.”⁷ The AG Opinion also claims that physicians dispense “drugs to children that induce transient or permanent infertility,” including “(1) puberty-suppression or puberty-blocking drugs, (2) supraphysiologic doses of testosterone to females; and (3) supraphysiologic doses of estrogen to males.”⁸ The AG Opinion asserts that “[t]he novel trend of providing these elective sex changes to minors often has the effect of permanently sterilizing those minor children.”⁹ The Alabama Law contains similar statements.¹⁰

These statements are incorrect. Current medical protocols state that genital surgery should not be carried out before patients reach the legal age of majority. To make the distinction clear, we refer to the AG Opinion’s list of procedures as the “AG Opinion claims.” We refer to the standard medical protocols issued by the World Professional Association for Transgender Health (“WPATH”) and the Endocrine Society as “gender-affirming care.”¹¹

The AG Opinion fails to engage with the WPATH and Endocrine Society guidelines (or any other recognized set of medical guidelines), even though these are well-known, widely viewed as authoritative, and readily available to the public.¹² These standards are explicitly

⁷ AG Opinion, p. 1. The AG Opinion also includes “(2) mastectomies; and (3) removing from children otherwise healthy or non-diseased body part or tissue.” These procedures do not affect fertility, which is the opinion’s stated concern, and they are common among cisgender adolescents (e.g., rhinoplasty and breast reduction). We do not address these procedures in this report.

⁸ AG Opinion, p. 1.

⁹ AG Opinion, pp. 2-3.

¹⁰ Alabama Law, Section 2(6).

¹¹ See Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfafflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, 7th version [Internet]. East Dundee (IL): World Professional Association for Transgender Health; 2012 [cited 2022 Apr 17]. Available from: <https://www.wpath.org/publications/soc> (hereinafter, “WPATH (2012)”); Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T’Sjoen GG. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Sept 13;102(11):3869-3903 (hereinafter, “Endocrine Society (2017)”).

¹² The AG Opinion quotes the WPATH standards once, but the opinion mischaracterizes the source material and persists in its repeated claims that gender-affirming care involves genital surgery on children. At page 4, the AG Opinion quotes WPATH (2012) to the effect that genital surgery should not be carried out before patients reach the age of majority. See AG Opinion, p. 4. The AG Opinion misleadingly uses the WPATH quotation as evidence that there is no benefit from gender-affirming care; in fact, WPATH (2012), pp. 10-21, acknowledges the benefits of psychotherapy and, in the case of adolescents, puberty blockers and hormone therapy. Apart from the isolated and misleading citation to WPATH (2012) at p. 4, the AG Opinion does not otherwise discuss the WPATH standards or correct its repeated assertion that children and adolescents are undergoing “sex change” procedures.

followed by major gender clinics in the United States.¹³ We address the AG Opinion's misstatements in turn.

a. The medical standards of care for transgender children specifically state that individuals must be the age of majority or older before undergoing surgery on genitals or reproductive organs.

Gender dysphoria is a recognized medical condition¹⁴ that merits medical treatment, and the evidence shows that treatment improves mental health outcomes, including reducing rates of suicidal ideation and suicide attempts. (See Section 2 of this report.)

Individuals with gender dysphoria seek care at a wide variety of ages, which depends on sociocultural and environmental factors, including parental support, socioeconomic status, and access to care. In the early phases of treatment, gender-affirming care consists of using the individual's preferred pronouns, psychosocial support, and education about the next stages of transition if desired. Medical professionals draw an important distinction between hormonal treatment and gender-affirming surgery. Hormonal transition is an established practice in older adolescents experiencing gender dysphoria, but current standards for gender-affirming care set the age of majority as the threshold for considering surgery on genitals and reproductive organs.

Two of the leading guidelines for the medical treatment of transgender children and adolescents are those published by WPATH and by the Endocrine Society. WPATH is a leading international organization of scientists, which has issued standards of care for transgender adults and children since 1979.¹⁵ Several revisions have been made as scientific evidence drives changes in standards. The current version, WPATH Standards of Care, version 7, is viewed as authoritative in the medical community and is widely consulted by physicians and other clinicians. The WPATH standards explicitly state that genital surgery should not be carried out until the patient reaches the age of majority. Further, WPATH advises that "the age threshold should be seen as a minimum criterion and not an indication in and of itself for active intervention."¹⁶

The Endocrine Society is the leading international organization of endocrinologists, i.e., physicians specializing in the study and treatment of the human endocrine system, including hormonal treatment.¹⁷ In 2017, the Endocrine Society issued clinical practice guidelines for the

¹³ See Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. *Pediatrics* 2020 Apr;145(4):e20193006. doi: 10.1542/peds.2019-3006 (stating that Endocrine Society guidelines are followed). The same is true of the Greenwich Center for Gender & Sexuality. The Yale Pediatric Gender Clinic generally follows WPATH standards.

¹⁴ American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*, Fifth edition. 2013.

¹⁵ The current version is WPATH (2012). According to WPATH, the first six versions were published in 1979, 1980, 1981, 1990, 1998, and 2001.

¹⁶ WPATH (2012), at p. 21: "Genital surgery should not be carried out until (i) patients reach the legal age of majority to give consent for medical procedures in a given country, and (ii) patients have lived continuously for at least 12 months in the gender role that is congruent with their gender identity. The age threshold should be seen as a minimum criterion and not an indication in and of itself for active intervention."

¹⁷ Who We Are [Internet]. Washington, D.C.: The Endocrine Society; c2022 [cited 2022 Apr 15]. Available from: <https://www.endocrine.org/about-us>.

treatment of gender dysphoria.¹⁸ Like WPATH, the Endocrine Society does not authorize surgery on the genitals or reproductive organs of transgender children or adolescents.¹⁹

Both WPATH and Endocrine Society guidelines are based on reviews of the best available science conducted by panels of experts across medical disciplines. These guidelines are updated periodically to ensure that they reflect a current understanding of scientific knowledge and clinical practice. The statements in this report refer to current WPATH and Endocrine Society standards, i.e., those in force as of the date of publication of this report.

b. The standards of care do not recommend drug treatments (puberty blockers or hormones) for prepubertal children.

The AG Opinion wrongly conflates treatments available to adolescents with those offered to children.²⁰ In fact, current medical protocols for gender-affirming care do not recommend either surgery or drug treatments (puberty blockers and hormones) for prepubertal children.

The WPATH standards state clearly that physical interventions, including drug therapy, are recommended only for adolescents and only after an in-depth process of mental health and medical counseling, described below. The WPATH standards state that social transition, which is entirely reversible, may be considered by the parents of prepubertal children.²¹ (Social transition consists of, e.g., wearing clothes and using a name that are consistent with the child's gender identity.) The Endocrine Society also "recommend[s] against puberty blocking and gender-affirming hormone treatment in prepubertal children."²² (There is, of course, no need for such medication in children who have not reached puberty.)

c. Present standards of care recommend drug treatments for adolescents (youth who have developed pubertal changes) only for those with puberty-induced worsening gender dysphoria and only after a careful protocol that begins with psychological and medical counseling to ensure valid consent.

The AG Opinion claims that "[c]hildren and adolescents are promised relief and asked to 'consent' to life-altering, irreversible treatment—and to do so in the midst of reported psychological distress, when they cannot weigh long-term risks the way adults do."²³ The Alabama Law contains a similar statement.²⁴

This statement misdescribes both medical practice and the consent procedures used for the treatment of adolescents. Legally, a parent or guardian must consent to the medical treatment of a minor, and so the AG Opinion is incorrect in implying that medical treatment depends on a

¹⁸ Endocrine Society (2017).

¹⁹ Id. (Guideline 5.5).

²⁰ AG Opinion, p. 2 (claiming that there is a "novel trend of providing these elective sex changes to minors," with "sex changes" previously defined to include surgery and drug therapies).

²¹ WPATH (2012), p. 17.

²² Endocrine Society (2017) (Guideline 1.4).

²³ AG Opinion, p. 4.

²⁴ Alabama Law, Section 2(15).

child or teenager's consent alone.²⁵ As noted above, medical protocols do not recommend drug therapy for prepubertal children, and so consent by young children is never an issue. For adolescents, the standard medical protocols provide for gender-affirming drug therapy only when medically necessary and after a comprehensive process that includes specialist medical consultation and assessment, parent consent and youth assent, and mental health evaluation.

A key feature of both the WPATH Standards of Care and the Endocrine Society Clinical Practice Guidelines is the central role of mental health professionals in assessing gender dysphoria and appropriate modes of medical treatment. The Endocrine Society notes, for example, that, "because of the psychological vulnerability of many individuals with [gender dysphoria], it is important that mental health care is available before, during, and sometimes also after transitioning."²⁶ Both WPATH and the Endocrine Society provide extensive guidance on how to provide psychosocial support to youth experiencing gender dysphoria, as well as a definition of what constitutes a properly trained mental health professional.

Contrary to the AG Opinion's implication, there is no medical rush to prescribe drug treatments to transgender adolescents. The current WPATH and Endocrine Society standards recommend a staged process for physical interventions, one that takes into account the presentation of gender dysphoria in each individual, along with their medical history and psychological functioning. Social transition, puberty blockers, and hormonal treatment may be used in stages, but not all adolescents with gender dysphoria undergo each treatment.²⁷ As always in medicine, the priority is to treat the patient as an individual and to address their physical and mental health needs holistically. WPATH, for example, expressly states that, "[b]efore any physical interventions are considered for adolescents, extensive exploration of psychological, family, and social issues should be undertaken The duration of this exploration may vary considerably depending on the complexity of the situation."²⁸

WPATH and Endocrine Society standards recommend puberty-suppressing medications (GnRH agonist treatment), only for adolescents and only with guardrails to ensure that medication is medically necessary and that adolescents and their parents give informed consent to treatment. These safeguards are worth summarizing in some detail, because they contradict the AG Opinion's claim that gender-affirming care, including drug therapy, is being casually administered.²⁹

For puberty-suppressing medications, the standards require the participation of a qualified mental health practitioner, who confirms that the adolescent has demonstrated a long-lasting and intense pattern of gender dysphoria, that gender dysphoria worsened with the onset of

²⁵ While the law usually grants parents the final decision, bioethicists have found that adolescents can be meaningful participants in the consent process. Clark BA, Virani A. "This Wasn't a Split-Second Decision": An Empirical Ethical Analysis of Transgender Youth Capacity, Rights, and Authority to Consent to Hormone Therapy. *J Bioeth Inq.* 2021 Mar;18(1):151-64; Vrouenraets LJ, de Vries ALC, de Vries MC, van der Miesen AIR, Hein IM. Assessing Medical Decision-Making Competence in Transgender Youth. *Pediatrics* 2021 Dec 1;148(6):e2020049643.

²⁶ Endocrine Society (2017).

²⁷ WPATH (2012), p. 18; Endocrine Society (2017) (Guidelines 2.1 and 2.2).

²⁸ WPATH (2012), p. 16.

²⁹ We quote the Endocrine Society phrasing, but the two protocols are substantively the same.

puberty, and that any coexisting psychological, medical, or social problems that could interfere with treatment have been addressed, so that the adolescent's situation and functioning are stable enough to start treatment. The guidelines also require informed assent by adolescents and (if under the age of majority) informed consent by their parents, and they require the involvement of a pediatric endocrinologist (or another physician versed in gender-affirming treatment) to ensure that puberty-blocking medication is warranted, that puberty has begun in the adolescent patient, and that there are no medical contraindications to puberty-blocking medication.³⁰

For those adolescents for whom progression to hormone therapy is medically indicated, WPATH and the Endocrine Society require additional counseling regarding the possible fertility effects of hormone therapy. In addition to parental consent, the guidelines require that a mental health practitioner confirm that the adolescent has "sufficient mental capacity (which most adolescents have by age 16 years)" to evaluate the benefits and risks of treatment.³¹

Section 2. The AG Opinion and the Alabama Law ignore the substantial benefits of medical care for transgender children and adolescents, care which has consistently been shown to reduce gender dysphoria and improve mental health. The best scientific evidence shows that gender dysphoria is real, that untreated gender dysphoria leads predictably to serious, negative medical consequences, and that gender-affirming care significantly improves mental health outcomes, including reducing rates of suicide.

The AG Opinion omits any discussion of the documented benefits of gender-affirming care and vastly overstates potential risks by relying on misrepresented or unreliable studies. The AG Opinion also misstates scientific evidence on the percentage of children and adolescents whose gender dysphoria resolves without treatment (sometimes termed "desistance"), and the opinion repeats discredited evidence on a purported novel trend of so-called rapid-onset gender dysphoria. The Alabama Law contains similar errors.³²

The AG Opinion falsely states that "The medical evidence does not demonstrate that children and adolescents benefit from engaging in these irreversible sterilization procedures."³³ Contrary to the AG Opinion's statements, scientific studies have demonstrated that gender dysphoria is a well-documented condition for which medical care is essential treatment. The established scientific evidence shows that treatment improves mental health outcomes, including reducing rates of suicidal ideation and suicide attempts.

In this Section, we review the scientific evidence on gender dysphoria and the benefits of gender-affirming treatment, and we correct the AG Opinion's and Alabama Law's erroneous claims.

a. Gender dysphoria is real, and untreated gender dysphoria is harmful.

The American Psychiatric Association explains that

³⁰ Endocrine Society (2017) (Table 5), citing WPATH (2012), p. 16.

³¹ Endocrine Society (2017) (Table 5).

³² Alabama Law, Section 2 and Section 2(4).

³³ AG Opinion, at 3.

[T]he term “transgender” refers to a person whose sex assigned at birth (i.e., the sex assigned by a physician at birth, usually based on external genitalia) does not match their gender identity (i.e., one’s psychological sense of their gender). Some people who are transgender will experience “gender dysphoria,” which refers to psychological distress that results from an incongruence between one’s sex assigned at birth and one’s gender identity. Though gender dysphoria often begins in childhood, some people may not experience it until after puberty or much later.³⁴

In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, the standard reference for the diagnosis of mental health conditions. The DSM-5 recognizes gender dysphoria and sets forth criteria for diagnosis. These criteria include “a marked incongruence between one’s experienced/expressed gender and primary and/or secondary sex characteristics” and “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).” To meet diagnostic criteria, an individual must exhibit “clinically significant distress or impairment in social, occupational, or other important areas of functioning.”³⁵

In other words, individuals who live in a manner that is physically and socially incongruent to their gender identity can experience gender dysphoria – a clinically significant psychological distress that can lead to depressed mood.³⁶ Suicidal ideation and attempts have been found to be significantly higher among transgender adolescents who cannot obtain or do not receive gender-affirming care than among their cisgender peers. The harm of not providing gender-affirming care is well documented: 40% of trans individuals who do not receive hormones will attempt or complete suicide in their lifetime.³⁷ Untreated gender dysphoria can also lead to disordered eating. Patients may engage in unsafe eating behaviors (e.g., food restriction or purging) as a body-affirming tool and an effort to align their bodies with their gender identity. These behaviors can impair physical health and development.³⁸

³⁴ What is Gender Dysphoria? [Internet]. Washington, D.C.: American Psychiatric Association; 2020 Nov [cited 2022 Apr 15]. Available from: <https://www.psychiatry.org/patients-families/gender-dysphoria/what-is-gender-dysphoria>.

³⁵ American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, D.C.: American Psychiatric Association; 2013.

³⁶ Sorbara JC, Chiniara LN, Thompson S, Palmert MR. Mental health and timing of gender-affirming care. *Pediatrics* 2020 Oct 1;146(4):e20193600 (hereinafter, “Sorbara et al. 2020”).

³⁷ Herman JL, Brown TNT, Haas AP. Suicide Thoughts and Attempts Among Transgender Adults [Internet]. Los Angeles (CA): The Williams Institute, UCLA School of Law; 2019 Sept [cited 2022 Apr 1]. Available from: <https://williamsinstitute.law.ucla.edu/publications/suicidality-transgender-adults/>. So-called “conversion” therapy (an extreme form of denying gender-affirming care, which attempts to change a person’s gender identity to match the sex assigned at birth) has been shown to create psychological distress and prompt suicide. Turban JL, Beckwith N, Reisner SL, Keuroghlian AS. Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults. *JAMA Psychiatry* 2019 Sept 11;77(1):68-76.

³⁸ Coelho JS, Suen J, Clark BA, Marshall SK, Geller J, Lam PY. Eating Disorder Diagnoses and Symptom Presentation in Transgender Youth: a Scoping Review. *Curr Psychiatry Rep*. 2019 Oct 15;21(11):107; Kamody RC, Yonkers K, Pluhar EI, Olezeski CL. Disordered Eating Among Trans-Masculine Youth: Considerations Through a Developmental Lens. *LGBT Health*. 2020 May/Jun;7(4):170-73; Legroux I, Cortet B. Factors influencing bone loss in anorexia nervosa: assessment and therapeutic options. *RMD Open*. 2019 Nov 13;5(2):e001009.

For all these reasons, the American Academy of Pediatrics, the American Psychological Association, and the American Academy of Child and Adolescent Psychiatry – the three major professional associations of pediatricians, psychologists, and child and adolescent psychiatrists – have endorsed gender-affirming care and condemned efforts to deny medical care to transgender people, as have the Texas Medical Society and the Alabama Psychological Association.³⁹ These organizations have also condemned so-called “conversion therapy” as ineffective, unethical, and dangerous.⁴⁰

The scientific consensus is clear: denying gender-affirming care harms transgender people and puts their lives at risk.⁴¹

b. Gender-affirming care has measurable and significant benefits.

The AG Opinion incorrectly states that “There is no evidence that long-term mental health outcomes are improved or that rates of suicide are reduced by hormonal or surgical intervention.”⁴² The AG’s statement that gender-affirming care is not beneficial is contradicted by a significant body of recent scientific evidence.⁴³

³⁹ Rafferty J, Committee on Psychosocial Aspects of Child and Family Health; Committee on Adolescence; Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness, Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. Pediatrics. 2018 Oct;142(4):e20182162; American Psychological Association. Guidelines for psychological practice with transgender and gender nonconforming people. American Psychologist 2015 Dec;70(9):832-64 (hereinafter, “American Psychological Association (2015)”; AAP Continues to Support Care of Transgender Youth as More States Push Restrictions [Internet]. Itasca (IL): American Academy of Pediatrics; 2022 Jan 6 [cited 2022 Mar 31]. Available from: <https://publications.aap.org/aapnews/news/19021/AAP-continues-to-support-care-of-transgender>; Criminalizing Gender Affirmative Care with Minors [Internet]. Washington, D.C.: American Psychological Association; [cited 2022 Mar 30]. Available from: <https://www.apa.org/pi/lgbt/resources/policy/issues/gender-affirmative-care>; AACAP Statement Opposing Actions in Texas Threatening the Health, Mental Health and Well-Being of Transgender and Gender Diverse Youth and Their Families, Washington, D.C.: American Academy of Child & Adolescent Psychiatry; 2022 March 1 [cited 2022 Apr 22=]. Available from: https://www.aacap.org/AACAP/zLatest_News/AACAP_Statement_Opposing_Actions_in_Texas.aspx; Statement of the Alabama Psychological Association (aPA) Supporting Gender-Affirming Care for Transgender Youth and Urging Opposition to Alabama SB184/HB266 [internet]. Alabama Psychological Association 2022. Available at https://cdn.ymaws.com/www.alapsych.org/resource/resmgr/2022/sb184-hb266_apa_statement_3-.pdf; Sorrel AL, TMA Supports Evidence-Based Gender-Affirming Care in Lawsuit [internet]. Texas Medical Association. March 14, 2022. Available from <https://www.texmed.org/TexasMedicineDetail.aspx?id=59040>.

⁴⁰ APA Resolution on Gender Identity Change Efforts [Internet]. Washington, D.C.: American Psychological Association; 2021 Feb [cited 2022 Mar 31]. Available from: <https://www.apa.org/about/policy/resolution-gender-identity-change-efforts.pdf>.

⁴¹ Abreu RL, Sostre JP, Gonzalez KA, Lockett GM, Matsuno E. “I am afraid for those kids who might find death preferable”: Parental figures’ reactions and coping strategies to bans on gender-affirming care for transgender and gender diverse youth. Psychology of Sexual Orientation and Gender Diversity [Internet]. 2021 Jul 29 [cited 2022 Mar 31]; advance online publication. Available from: <https://psycnet.apa.org/record/2021-67997-001>; Hughes LD, Kidd KM, Gamarel KE, Operario D, Dowshen N. (2021). “These Laws Will Be Devastating”: Provider Perspectives on Legislation Banning Gender-Affirming Care for Transgender Adolescents. Journal of Adolescent Health 2021 Dec;69(6):976-82; Kidd KM, Sequeira GM, Paglisotti T, Katz-Wise SL, Kazmerski TM, Hillier A, Miller E, Dowshen N. “This could mean death for my child”: Parent perspectives on laws banning gender-affirming care for transgender adolescents. Journal of Adolescent Health 2021 Jun;68(6):1082-88.

⁴² AG Opinion, p. 4.

⁴³ De Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. The Journal of Sexual Medicine 2011 Aug;8(8):2276-83; De Vries

As explained in Section 1 of this report, social transition is an important first step for adolescents (and is the only medically accepted form of gender-affirming care for prepubertal children). The scientific evidence shows that social transition, including using a child or adolescent's chosen name, reduces depression and suicide risk.⁴⁴

A solid body of reliable research has shown that the potential next steps in gender-affirming care for adolescents with gender dysphoria – puberty-blocking medications and hormone therapy – have major mental-health benefits, including higher levels of general well-being and significantly decreased levels of suicidality.⁴⁵ Puberty blockers have been shown to

AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics* 2014 Oct;134(4):696-704; Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. *The Journal of Sexual Medicine* 2015 Nov;12(11):2206-14 (hereinafter, "Costa et al. 2015"); Allen LR, Watson LB, Egan AM, Moser CN. Well-being and suicidality among transgender youth after gender-affirming hormones. *Clinical Practice in Pediatric Psychology* 2019 Sept;7(3):302-11 (hereinafter, "Allen et al 2019"); Kaltiala R, Heino E, Tyolajarvi M, Suomalainen L. Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. *Nordic Journal of Psychiatry* 2020 Apr;74(3):213-19; de Lara DL, Rodriguez OP, Flores IC, Masa JLP, Campos-Munoz L, Hernandez MC, Amador JTR. Psychosocial assessment in transgender adolescents. *Anales de Pediatria (English Edition)* 2020 Jul;93(1):41-48; van der Miesen AI, Steensma TD, de Vries AL, Bos H, Popma A. Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared with Cisgender General Population Peers. *Journal of Adolescent Health* 2020 Jun;66(6):699-704; Achille C, Taggart T, Eaton NR, Osipoff J, Tafuri K, Lane A, Wilson TA. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. *International Journal of Pediatric Endocrinology* 2020;2020:8; Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. *Pediatrics* 2020 Apr;145(4):e20193006; Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics* 2020 Feb;145(2):e20191725; Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, Skageberg EM, Khadr S, Viner RM. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. *PLoS One* 2021 Feb 2;16(2):e0243894; Grannis C, Leibowitz SF, Gahn S, Nahata L, Morningstar M, Mattson WI, Chen D, Strang JF, Nelson EE. Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys. *Psychoneuroendocrinology* 2021 Oct;132:105358; Hisle-Gorman E, Schvey NA, Adirim TA, Rayne AK, Susi A, Roberts TA, Klein DA. Mental Healthcare Utilization of Transgender Youth Before and After Affirming Treatment. *The Journal of Sexual Medicine* 2021 Aug;18(8):1444-54; Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy with Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *Journal of Adolescent Health* 2022 Apr;70(4):643-49 (hereinafter, "Green et al. 2022"); Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. *PLoS One* 2022 Jan 12;17(1):e0261039 (hereinafter, "Turban et al. 2022"); Tordoff DM, Wanta JW, Collin A, Stephney C, Inwards-Breland DJ, Ahrens K. Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. *JAMA Network Open* 2022 Feb 1;5(2):e220978 (hereinafter, "Tordoff et al. (2022)").

⁴⁴ Russell ST, Pollitt AM, Li G, Grossman AH. Chosen name use is linked to reduced depressive symptoms, suicidal ideation, and suicidal behavior among transgender youth. *Journal of Adolescent Health* 2018 Oct;63(4):503-05; Durwood L, McLaughlin KA, Olson KR. Mental health and self-worth in socially transitioned transgender youth. *Journal of the American Academy of Child & Adolescent Psychiatry* 2017 Feb;56(2):116-23.

⁴⁵ Allen et al. 2019, cited in note 43; Green et al. (2022), cited in note 43; Connolly MD, Zervos MJ, Barone II CJ, Johnson CC, Joseph CL. The Mental Health of Transgender Youth: Advances in Understanding. *Journal of Adolescent Health* 2016 Nov;59(5):489-95; Turban et al. 2022, cited in note 43; Costa et al. (2015), cited in note 43; See also Witcomb GL, Bouman WP, Claes L, Brewin N, Crawford JR, Arcelus J. Levels of depression in transgender people and its predictors: Results of a large matched control study with transgender people accessing clinical services. *Journal of Affective Disorders* 2018 Aug 1; 235:308-15.

decrease suicidality in adulthood and to improve affect and psychosocial functioning as well as social life.⁴⁶ Hormone therapy has been shown to reduce suicidality in transgender adolescents when compared to peers with gender dysphoria who did not receive it.⁴⁷ Notably, none of the studies has found a worsening of these mental health measures among recipients of gender-affirming care.

Among children and adolescents, patients who present for gender-affirming care at later pubertal stages are more likely to require psychoactive medications and are more likely to have considered or attempted suicide than patients who received gender-affirming care at earlier stages of pubertal development.⁴⁸

As evidence for the proposition that “[t]here is no evidence that long-term mental health outcomes are improved or that rates of suicide are reduced by hormonal or surgical intervention,” the AG Opinion cites a 2011 Swedish study by Dhejne et al. that, the AG Opinion claims, “monitored transitioned individuals for 30 years [and] found high rates of post-transition suicide and significantly elevated all-cause mortality, including increased death rates from cardiovascular disease and cancer, although causality could not be established.”⁴⁹ In fact, the 2011 study by Dhejne is badly out-of-date and does not support the AG Opinion’s claim.

The Dhejne study compared post-gender-affirmation transgender individuals with cisgender individuals from the general population, as opposed to transgender individuals who did not receive gender-affirming care. Therefore, as the study’s author explicitly cautions in the body of the text, *it is impossible to conclude from this data* that gender-affirming procedures were a causative factor in suicidality among transgender individuals.⁵⁰ Rather, the study shows only that transgender adults were more likely to experience suicidal ideation/attempts and risky behavior when compared to the general population in Sweden between 1973 and 2003. Further, the Dhejne study is not generalizable to a modern American population or to adolescents. During the study period, Swedish law required that individuals seeking gender-affirming surgery be

⁴⁶ Rew L, Young CC, Monge M, Bogucka R. Review: Puberty blockers for transgender and gender diverse youth – a critical review of the literature. *Child and Adolescent Mental Health* 2021 Feb;26(1):3-14; de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med.* 2011 Aug;8(8):2276-83. Epub 2010 Jul 14 (hereinafter, “de Vries et al. (2011)”).

⁴⁷ Tordoff et al (2022), cited in note 43; Sorbara et. al. (2020), cited in note 36.

⁴⁸ Sorbara JC et. al. (2020), cited in note 36. Studies of adults confirm that gender-affirming treatment has been associated with marked improvement in mental health outcomes in transgender patients. See Almazan AN, Keuroghlian AS. Association Between Gender-Affirming Surgeries and Mental Health Outcomes. *JAMA Surgery* 2021 Jul 1;156(7):611-18; Marano AA, Louis MR, Coon D. Gender-Affirming Surgeries and Improved Psychosocial Health Outcomes. *JAMA Surgery* 2021 Jul 1;156(7):685-87; Swan J, Phillips TM, Sanders T, Mullens AB, Debattista J and Bromdal A. Mental health and quality of life outcomes of gender-affirming surgery: A systematic literature review, *Journal of Gay & Lesbian Mental Health*, 2022.

⁴⁹ AG Opinion, at 4, citing Dhejne C, Lichtenstein P, Boman M, Johansson AL, Langstrom N, Landen M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011 Feb 22;6(2):e16885 (hereinafter, “Dhejne (2011)”).

⁵⁰ “It is therefore important to note that the current study is only informative with respect to [transgender] persons’ health after sex reassignment; *no inferences can be drawn as to the effectiveness of sex reassignment as a treatment for transsexualism*. In other words, the results should not be interpreted such as sex reassignment per se increases morbidity and mortality. Things might have been even worse without sex reassignment.” Dhejne (2011) at 7 (emphasis added).

sterilized. The presence of this law alone might account for the higher risk of suicide attempts and risky behavior in the transgender population compared to the cisgender population at the time.⁵¹

The AG Opinion also mischaracterizes an important governmental decision, claiming incorrectly that the Centers for Medicare and Medicaid Services (“CMS”) found that gender-affirming care has no benefits. The AG Opinion claims that “there is no scientific consensus that [medical care] even serve[s] to benefit minor children dealing with gender dysphoria,” and that “[t]he lack of evidence in this field is why the CMS rejected a nationwide coverage mandate for adult gender transition surgeries during the Obama Administration.”⁵² Although the CMS did issue a 2016 Decision Memo denying blanket, automatic coverage for gender-affirming surgery, the decision specifically *authorizes* Medicare and Medicaid providers to cover such surgery on a case-by-case basis.⁵³ Thus, contrary to AG Opinion’s claim, the CMS decision memo expressly *permits* state and local decision-makers to authorize coverage for gender-affirming surgery.⁵⁴ The federal directive simply declines to authorize automatic coverage in every case. And, in fact, the 2016 CMS decision marks an expansion of the permissibility of gender-affirming treatment: the Decision Memo followed the 2014 revocation of the CMS’s 1989 decision to deny nationwide coverage.⁵⁵

Further, the CMS did not reach any negative conclusion on the benefits of gender-affirming care for children and adolescents. The CMS reviewed only studies on the outcomes of surgery (not hormone treatment) for an adult population that is overwhelmingly elderly (over age 65) and has a high prevalence of preexisting medical conditions that can make surgery risky, regardless of its purpose.⁵⁶

⁵¹ Nelson R. Transgender People in Sweden No Longer Face Forced Sterilization. Time [Internet]. 2013 Jan 14 [cited 2022 Apr 1]; Available from: <https://newsfeed/time.com/2013/01/14/transgender-people-in-sweden-no-longer-face-forced-sterilization/>. The presence of this law alone might account for the higher risk of suicide attempts and risky behavior in the transgender population at the time.

⁵² AG Opinion, at 3-4, citing Jensen TS, Chin J, Rollins J, Koller E, Gousis L. Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N). Baltimore (MD): Centers for Medicare and Medicaid Services; 2016 Aug 30 [cited 2022 Feb 18]. Available from: <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=282>.

⁵³ Id.

⁵⁴ Id. (“We acknowledge that [gender reassignment surgery] may be a reasonable and necessary service for certain beneficiaries with gender dysphoria. The current scientific information is not complete for CMS to make a [national coverage decision] that identifies the precise patient population for whom the service would be reasonable and necessary.”)

⁵⁵ Id.

⁵⁶ The CMS Decision Memo notes that “the Medicare population is different from the general population in age (65 years and older) and/or disability as defined by the Social Security Administration. Due to the biology of aging, older adults may respond to health care treatments differently than younger adults. These differences can be due to, for example, multiple health conditions or co-morbidities, longer duration needed for healing, metabolic variances, and impact of reduced mobility. All of these factors can impact health outcomes. The disabled Medicare population, who are younger than age 65, is different from the general population and typical study populations due to the presence of the causes of disability such as psychiatric disorders, musculoskeletal health issues, and cardiovascular issues.” Id.

c. The AG Opinion repeats discredited and unreliable evidence on “desistance” and “rapid-onset gender dysphoria.”

The AG Opinion greatly exaggerates the extent to which adolescent gender dysphoria abates without treatment, and it repeats discredited claims that there is a novel wave of rapid-onset dysphoria among today’s teens.

“Desistance.” The AG Opinion asserts that “[c]hildhood-onset gender dysphoria has been shown to have a high rate of natural resolution, with 61-98% of children reidentifying with their biological sex during puberty.”⁵⁷ The Alabama law makes a parallel statement.⁵⁸ The assertion is incorrect.

As authority for the claimed 61-98% figure, the AG Opinion does not cite reputable scientific evidence. Instead, it cites a biased source – the website of the so-called Society for Evidence-Based Gender Medicine (“SEGM”). SEGM is not a recognized scientific organization, and in Appendix A we document the bias that infuses its medical claims. The SEGM website badly mischaracterizes the underlying source that it cites for the 61-98% figure.

The study SEGM cites is Steensma et al. (2013).⁵⁹ But the Steensma study was not designed to (and the lead author has acknowledged) does not provide a basis for calculating what percentage of prepubertal children diagnosed with gender dysphoria persist with that diagnosis into adolescence. Rather, the Steensma study was designed only to study the characteristics of those who persisted.⁶⁰ Among other limitations, in Steensma (2013), former patients who opted to not participate in the study (either refused to participate or did not respond to an offer to participate) were categorized as “desisters,” i.e., patients whose gender dysphoria resolved without transition or treatment. Patients can fail to respond to a study request for many reasons, including having moved away, receiving treatment elsewhere, or being uninterested in participating in a study. Thus, SEGM misuses the Steensma data by counting nonresponding patients as having “desisted” in experiencing gender dysphoria.⁶¹ Indeed, in published correspondence, Steensma emphasizes that the 2013 study should *not* be used to calculate the percentages of “persisters” and “desisters.”⁶² The misrepresentation of Steensma on the SEGM website constitutes a major violation of the scientific method and the accepted conventions of research.

⁵⁷ AG Opinion, at 4.

⁵⁸ Alabama Law, Section 2(4).

⁵⁹ Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistance and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2013 Jun;52(6):582-90.

⁶⁰ Steensma TD, Cohen-Kettenis PT. A critical commentary on follow-up studies and “desistance” theories about transgender and gender non-conforming children. *Int J Transgend*. 2018 May; 19(2):225-30.

⁶¹ See American Psychological Association (2015), p. 842 (noting that several studies categorized youth who did not return to the clinic after initial assessment as “desisters” who no longer identified with a gender different than sex assigned at birth; “As a result, this research runs a strong risk of inflating estimates of the number of youth who do not persist with a TGNC identity”).

⁶² *Id.*

Actual scientific evidence on the course of gender dysphoria emphasizes the importance of distinguishing between prepubertal children and adolescents. The evidence suggests that the course of dysphoria is more diverse for prepubertal children, and so it is critical to recognize them as a distinct population from adolescents. By referring to “children,” the AG Opinion creates the misimpression that most or all children *and* teens diagnosed with dysphoria will cease identifying with the gender not assigned at birth. This is false.

The evidence suggests that the vast majority of adolescents who are diagnosed with gender dysphoria will persist in their gender identity and will benefit from gender-affirming medical care.⁶³ In a Dutch study, among 70 adolescents diagnosed with gender dysphoria and treated with puberty-suppressing hormones, 100% opted to continue with gender-affirming treatment.⁶⁴ A recent U.S. study found a consistent pattern. Following a large cohort of U.S. young people who reported some evidence of gender dysphoria but had not yet been formally diagnosed, the study found that adolescents were far more likely than prepubertal children to go on to a formal diagnosis of gender dysphoria and to receive gender-affirming treatment.⁶⁵

The course of gender dysphoria is different in pre-pubertal children. For this group, the percentage of those whose dysphoria resolves without treatment is higher than for adolescents but likely lower than the AG Opinion’s claimed 61-98% figure. When prepubertal children experience gender dysphoria, some will find that their dysphoria resolves before adolescence. That is, many of these children will not, as adolescents, identify as transgender or proceed with gender-affirming medical care. Importantly, as we have emphasized, standard medical protocols do not treat prepubertal children with drug therapy or genital surgery, and so there is zero risk that a prepubertal child with dysphoria will have received physical interventions.

Further, the AG Opinion’s claim of 98% “desistance” is overstated even for prepubertal children. The Endocrine Society reports that, “[c]ombining all outcome studies to date, the [gender dysphoria]/gender incongruence of a minority of prepubertal children appears to persist

⁶³ American Psychological Association (2015), p. 843; WPATH (2012), p. 11; Endocrine Society (2017). See also Turban JL, DeVries ALC, Zucker K. Gender Incongruence & Gender Dysphoria. In Martin A, Bloch MH, Volkmar FR (editors): *Lewis’s Child and Adolescent Psychiatry: A Comprehensive Textbook*, Fifth Edition. Philadelphia: Wolters Kluwer 2018, pp. 20-21 (“we must recognize that [the existing studies of persistence] have been quite limited in power and generalizability and should not be misused to create barriers for TGD youth seeking gender-affirming care. The most relevant conclusions from these studies are that insistent cross-gender identification in adolescence most often correlates with persistent TGD identities in adulthood”).

⁶⁴ de Vries et al. 2011, cited in note 43 (“None of the gender dysphoric adolescents in this study renounced their wish for [gender reassignment] during puberty suppression. This finding supports earlier studies showing that young adolescents who had been carefully diagnosed show persisting gender dysphoria into late adolescence or young adulthood”).

⁶⁵ Wagner S, Panagiotakopoulos L, Nash R, Bradlyn A, Getahun D, Lash TL, Roblin D, Silverberg MJ, Tangpricha V, Vupputuri S, Goodman M. Progression of Gender Dysphoria in Children and Adolescents: A Longitudinal Study. *Pediatrics*. 2021 Jul;148(1):e2020027722. doi: 10.1542/peds.2020-027722. Epub 2021 Jun 7. PMID: 34099504; PMCID: PMC8276590. Wagner et. al (2021) studied this cohort for only (on average) 3.5 years; by the end of the study period, roughly 35% of teens but only about 15-18% of prepubertal children received a formal diagnosis of gender dysphoria. Note that these data do *not* establish that only 35% of teens *with gender dysphoria* persist in their diagnosis. This was not a population already diagnosed with dysphoria, and so the persistence rate cannot be calculated. Rather, Wagner et al. (2021) shows that, among a population with some evidence of dysphoria, adolescents are far more likely than young children to continue to a formal diagnosis.

in adolescence.”⁶⁶ A reasonable summary of the literature would be that around 50% of prepubertal children diagnosed with gender dysphoria (using older, less stringent diagnostic criteria) will not persist in identifying as transgender into adolescence and adulthood.⁶⁷

Recent evidence suggests that the spontaneous resolution of true gender dysphoria among prepubertal children is likely even lower. Earlier studies likely overstate the spontaneous resolution of gender dysphoria among children diagnosed before puberty, because their data incorporated broader diagnostic criteria.⁶⁸ That is, the studies likely included prepubertal children with gender variant behavior (e.g., boys with feminine interests or “tomboy” girls) alongside children who would meet today’s diagnostic criteria for gender dysphoria – a deeply felt and lasting transgender identity with clinically significant distress and impaired functioning.⁶⁹ Consistent with this hypothesis is the recent finding that “the intensity of early dysphoria appears to be an important predictor” of the persistence of dysphoria into adolescence.⁷⁰ The evidence thus implies that, had the earlier studies focused on prepubertal children with intense gender dysphoria, the rates of spontaneous resolution of dysphoria would be lower.

To summarize, then, the key to the question of whether gender dysphoria persists over time is whether the patient is diagnosed with gender dysphoria in adolescence. (This might be a new diagnosis or it might be a persistent diagnosis from childhood.) Put plainly: *adolescents with gender dysphoria rarely find that their dysphoria resolves without treatment.*

“*Rapid-onset*” gender dysphoria. The AG Opinion also asserts that there has been a recent spike in gender dysphoria diagnosis and gender-affirming treatment among U.S. adolescents.⁷¹ The AG insists that this is a “novel cohort” of youth and implies that their gender dysphoria is transient.⁷²

As evidence, the AG Opinion again fails to consult reputable science and instead cites the SEGM website, which features a graph showing an increase from 2010 to 2020 in referrals of British adolescents to a specialized gender clinic.⁷³ The graph is calibrated to look as if the

⁶⁶ Endocrine Society (2017). See Wallien MS, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. *J Am Acad Child Adolesc Psychiatry*. 2008 Dec;47(12):1413-23. doi: 10.1097/CHI.0b013e31818956b9. PMID: 18981931.

⁶⁷ American Psychological Association (2015), pp. 841-2 (“existing research suggests that between 12% and 50% of children diagnosed with gender dysphoria may persist in their identification with a gender different than sex assigned at birth into late adolescence and young adulthood”).

⁶⁸ See Temple Newhook J, Pyne J, Winters K, Feder S, Holmes C, Tosh J, Sinnott ML, Jamieson A, and Pickett S, A critical commentary on follow-up studies and “desistance” theories about transgender and gender-nonconforming children, *International Journal of Transgenderism*, vol. 19(2), pp. 212-224 (2018) doi: 10.1080/15532739.2018.1456390.

⁶⁹ Endocrine Society (2017).

⁷⁰ Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistance and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2013 Jun;52(6):582-90 (finding that “children with persistent GID are characterized by more extreme gender dysphoria in childhood than children with desisting gender dysphoria”).

⁷¹ AG Opinion, at 3 (stating that “the spike in [surgical and drug] procedures is a relatively recent development”).

⁷² AG Opinion, at 4.

⁷³ The AG Opinion cites to the website of the Society for Evidence-Based Gender Medicine (SEGM). SEGM’s homepage provides an uncredited and unverifiable graph, which claims to depict referrals to an undefined term,

increase is very large, but in fact, the absolute numbers are small. The information depicted cannot be verified, because SEGM provides no citation. But taking the data at face value, in 2020 about 2600 children and teens sought treatment at the U.K. gender clinic. That is a very small percentage of Britain's child population. Further, the data appear to show only the number of children and adolescents referred for consultation; only a subset of these will ultimately be diagnosed with gender dysphoria and will continue with medical treatment.⁷⁴ The claimed "spike" in referrals certainly reflects the reduction in social stigma over the past decade and the expansion of care options.

By contrast, reliable recent data shows that, among high-school students, the percentage who identify as transgender is under 2% (1.8%).⁷⁵ These data come from the Centers for Disease Control's Youth Risk Behavior Surveillance System, which is the largest repository of data on self-reported behaviors in the United States. Because not all transgender people seek medical treatment, the percentage seeking medical care would be smaller.

The AG Opinion also repeats a discredited claim that a novel wave of "adolescent-onset gender dysphoria" is sweeping the U.S.⁷⁶ This statement echoes (without citing or quoting) a poor-quality study by Lisa Littman.⁷⁷ Littman's 2018 article contended that a novel pathology, "rapid-onset gender dysphoria" was leading teenagers to claim a transgender identity because of peer influence. WPATH, among other authorities, has taken a skeptical view of Littman's claim,⁷⁸ and the study has been criticized for serious methodological errors, including the use of parent reports instead of clinical data and the recruitment of its sample of parents from anti-transgender websites.⁷⁹ The journal of publication required an extensive correction of the

"GIDS." SEGM [Internet]. c2020 [cited 2022 Apr 1]. Available from: <https://segm.org/>. Although GIDS is not defined on the SEGM site, it appears to refer to the Gender Identity Development Service, a specialized UK gender clinic for children and adolescents. GIDS [Internet]. c2022 [cited 2022 Apr 1]. Available from: <https://gids.nhs.uk/about-us#main-content>.

⁷⁴ A referral means that a medical provider (or, possibly, the patient) has suggested an appointment with GIDS. A referral does not equate to the receipt of gender-affirming care. See GIDS [internet]. Available from <https://gids.nhs.uk/about-us#main-content>.

⁷⁵ Johns MM, Lowry R, Andrzejewski J, Barrios LC, Demissie Z, McManus T, Rasberry CN, Robin L, Underwood JM. Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students – 19 States and Large Urban School Districts, 2017. *MMWR Morb Mortal Wkly Rep*. 2019 Jan 25;68(3):67-71.

⁷⁶ AG Opinion, at 4.

⁷⁷ Littman L. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. *PLoS One*. 2018 Aug 16;13(8):1-44; Littman L. Correction: Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. *PLoS One*. 2019 Mar 19;14(3):1-7.

⁷⁸ WPATH Global Board of Directors. WPATH Position on "Rapid-Onset Gender Dysphoria" [Internet]. 2018 Sep 4 [cited 2022 Apr 1]. Available from: https://www.wpath.org/media/cms/Documents/Public%20Policies/2018/9_Sept/WPATH%20Position%20on%20Rapid-Onset%20Gender%20Dysphoria_9-4-2018.pdf (stating that ROGD "constitutes nothing more than an acronym created to describe a proposed clinical phenomenon that may or may not warrant further peer-reviewed scientific investigation").

⁷⁹ Restar AJ. Methodological Critique of Littman's (2018) Parental-Respondents Accounts of "Rapid-Onset Gender Dysphoria". *Arch Sex Behav*. 2020 Jan;49(1):61-66. doi: 10.1007/s10508-019-1453-2 (hereinafter, "Restar 2020"); Temple Newhook, J, Pyne, J, Winters, K, Feder, S, Holmes, C, Tosh, J, and Pickett, S. A critical commentary on follow-up studies and "desistance" theories about transgender and gender-nonconforming children. *International Journal of Transgenderism*, 19(2), 212-224. (2018).

original Littman article because of its misstatements.⁸⁰ Such a correction in reputable, peer-reviewed academic journals is taken only when a panel of experts, in retrospect, came to recognize the methodological flaws of the original study and concluded that it would be unscientific to allow the originally published findings to stand.

Littman's hypothesis that rapid-onset gender dysphoria exists as a distinct condition has not been supported by studies of clinical data.⁸¹ Neither the American Psychiatric Association nor any other reputable professional organization has recognized rapid-onset gender dysphoria as a distinct clinical condition or diagnosis.⁸²

Section 3. The AG Opinion and the Alabama Law greatly exaggerate the risks of gender-affirming drug therapy.

The AG Opinion claims that "sex change procedures," including surgery and drug therapies "often ha[ve] the effect of permanently sterilizing those minor children."⁸³ The Alabama Law makes similar claims.⁸⁴ Section 1 of this report has established that the AG Opinion's claim with respect to surgery is false: current medical protocols state that individuals must be the age of majority or older before undergoing surgery on genitals or reproductive organs. In this Section, we focus on the AG Opinion's (and Alabama Law's) claims regarding the medical effects of drug treatment for transgender adolescents.

a. The AG Opinion and the Alabama Law greatly overstate the risks of puberty-blocking medication and incorrectly state that it results in sterilization.

The Texas Attorney General claims that "[t]here is insufficient medical evidence available to demonstrate that discontinuing [puberty-blocking] medication resumes a normal puberty process."⁸⁵ The Alabama Law contains similar statements.⁸⁶ The claim is false: puberty-blocking medication has been shown to be safe, effective, and fully reversible.

As noted in Section 1 of this report, puberty-blocking medication (gonadotropin-releasing hormone agonists, or GnRHa's) can be part of a staged approach to gender-affirming care for

⁸⁰ Littman L. Correction: Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. PLoS One. 2019 Mar 19;14(3):1-7 (altering the original article to, inter alia, clarify that the article collected no data from adolescents or clinicians and generates only a hypothesis for further exploration).

⁸¹ Bauer GR, Lawson ML, Metzger DL; Trans Youth CAN! Research Team. Do Clinical Data from Transgender Adolescents Support the Phenomenon of "Rapid Onset Gender Dysphoria"? J Pediatr. 2022 Apr; 243:224-227. See also Arnoldussen M, Steensma TD, Popma A, van der Miesen AIR, Twisk JWR, de Vries ALC. Re-evaluation of the Dutch approach: are recently referred transgender youth different compared to earlier referrals? Eur Child Adolesc Psychiatry. 2020 Jun;29(6):803-811. Erratum in: Eur Child Adolesc Psychiatry. 2020 Dec 16 (concluding that there has been no marked change in the characteristics of the population of adolescents referred for gender dysphoria from 2000 to 2016; the authors hypothesize that the increase in number of referrals reflects the increasing social acceptability of seeking treatment).

⁸² Restar (2018), cited in note 79.

⁸³ AG Opinion, at 2-3. The AG Opinion repeats its claim about sterilization. Id. at 5 ("The surgical and chemical procedures you ask about can and do cause sterilization.")

⁸⁴ Alabama Law, Sections 2(9), 2(11), 2(12), 2(13) and 2(14).

⁸⁵ AG Opinion, at 5.

⁸⁶ Alabama Law, Sections 2(7), (11), (12) and (13).

adolescents. By stalling pubertal maturation, the medication relieves adolescents of the intense gender dysphoria that can accompany pubertal development along the pathway of their assigned sex. During this pause, the adolescent is given time to confirm their gender identity and to consider the need for appropriate gender-affirming hormone therapy without having had their body mature along pubertal path incongruent with their gender identity. Adolescents who continue to identify as transgender will be able to proceed with gender-affirming hormone therapy when they, their parents, and their providers determine that treatment is medically appropriate. Puberty blockers not only alleviate gender dysphoria in adolescence but have beneficial lifelong effects on dysphoria and can minimize the need for subsequent treatments, including surgery in adulthood. In the unlikely event that a teen realizes that they identify as cisgender, they can discontinue the blocker and spontaneous pubertal maturation will resume.

The scientific evidence clearly shows that treatment with puberty blockers is fully reversible. GnRHa therapy has been used since the 1980's in children with precocious puberty, and a solid body of evidence documents that pubertal progression stops with drug therapy and that spontaneous pubertal development occurs after discontinuation of the medication.⁸⁷

Recent studies suggest that puberty-blocking medication has negligible or small effects on bone development in adolescents, and any negative effects are temporary and reversible. The most recent studies show that puberty-blocking drug therapy either has no effect on bone mineral density (BMD), a proxy measure of bone strength, or is associated with a very small decrease.⁸⁸

⁸⁷ Manasco PK, Pescovitz OH, Feuillan PP, Hench KD, Barnes KM, Jones J, Hill SC, Loriaux DL, Cutler Jr GB. Resumption of puberty after long term luteinizing hormone-releasing hormone agonist treatment of central precocious puberty. *J Clin Endocrinol Metab.* 1988 Aug 1;67(2):368-72; Heger S, Muller M, Ranke M, Schwarz H, Waldhauser F, Partsch C, Sippell WG. Long-term GnRH agonist treatment for female central precocious puberty does not impair reproductive function. *Mol Cell Endocrinol.* 2006 Jul 25;254-255:217-220; Feuillan PP, Jones JV, Barnes K, Oerter-Klein K, Cutler Jr GB. Reproductive Axis after Discontinuation of Gonadotropin-Releasing Hormone Analog Treatment of Girls with Precocious Puberty: Long Term Follow-Up Comparing Girls with Hypothalamic Hamartoma to Those with Idiopathic Precocious Puberty. *J Clin Endocrinol Metab.* 1999 Jan;84(1):44-49; Bertelloni S, Baroncelli GI, Ferdeghini M, Menchini-Fabris F, Saggese G. Final height, gonadal function and bone mineral density of adolescent males with central precocious puberty after therapy with gonadotropin-releasing hormone analogues. *Eur J Pediatr.* 2000 May;159(5):369-74 (hereinafter, "Bertelloni et al (2000)"); Bertelloni S, Mul D. Treatment of central precocious puberty by GnRH analogs: long-term outcome in men. *Asian J Androl.* 2008 Jul;10(4):525-34; Luo X, Liang Y, Hou L, Wu W, Ying Y, Ye F. Long-term efficacy and safety of gonadotropin-releasing hormone analog treatment in children with idiopathic central precocious puberty: A systematic review and meta-analysis. *Clin Endocrinol.* 2021 May; 94(5):786-96.

⁸⁸ Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. *J Clin Endocrinol Metab.* 2015 Feb;100(2):E270-75 (hereinafter, "Klink et al. 2015"); Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. *J Clin Endocrinol Metab.* 2020 Dec 1;105(12): e4252-e4263 (hereinafter, Schagen et al. 2020"); Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. *Eur J Endocrinol.* 2006;155:S131-S137. Studies of children treated for precocious puberty found that BMD was normal at final height attainment. Alessandri SB, Pereira F de A, Villela RA, Antonini SRR, Elias PCL, Martinelli Jr CE, de Castro M, Moreira AC, de Paula FJA. Bone mineral density and body composition in girls with idiopathic central precocious puberty before and after treatment with a gonadotropin-releasing hormone agonist. *Clinics (Sao Paulo).* 2012;67(6):591-96; Antoniazzi F, Zamboni G, Bertoldo F, Lauriola S, Mengarda F, Pietrobelli A, Tato L. Bone mass at final height in precocious puberty after gonadotropin-releasing hormone agonist with and without calcium supplementation. *J Clin Endocrinol Metab.* 2003 Mar;88(3):1096-1101 (hereinafter,

Calcium supplementation has been shown to protect patients from bone loss.⁸⁹ Critically, any reduction in BMD is recovered when adolescents cease taking puberty-blocking medication, whether or not they continue to gender-affirming hormone therapy.⁹⁰

Tellingly, the AG Opinion does not cite scientific evidence for its claim regarding “insufficient medical evidence.”⁹¹ Instead, it cites two legal cases, neither of which contains sound scientific evidence on this subject.⁹² One of the cited cases is irrelevant, because it involves legal claims about surgery, not puberty blockers.⁹³ The other cited case, *Bell v. Tavistock and Portman NHS Foundation Trust* (2020), was reversed on appeal in the U.K. in 2021 because the decision relied on biased and inexperienced scientific testimony.⁹⁴

The AG Opinion also attacks puberty blockers by claiming that their use “is not approved by the federal Food and Drug Administration and is considered an ‘off-label’ use of the medications.”⁹⁵ The Alabama Law makes a similar claim.⁹⁶ The implication is that off-label use of medication is harmful, but this claim is unfounded.

“Antoniazzi et al. (2003)”); Heger S, Partsch CJ, Sippell WG. Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. *J Clin Endocrinol Metab.* 1999 Dec;84(12):4583-90; Neely EK, Bachrach LK, Hintz RL, Habiby RL, Slemenda CW, Feezle L, Pescovitz OH. Bone mineral density during treatment of central precocious puberty. *J Pediatr.* 1995 Nov;127(5):819-22.

⁸⁹ Antoniazzi et al. (2003), cited in note 88.

⁹⁰ Klink et al. (2015), cited in note 88; Schagen et al. (2020), cited in note 88. Bertelloni et al. (2000), cited in note 87; Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. *J Clin Endocrinol Metab.* 2008 Jan;93(1):190-195; Magiakou MA, Manousaki D, Papadaki M, Hadjidakis D, Levidou G, Vakaki M, Papaefstathiou A, Lalioti N, Kanaka-Gantenbein C, Piaditis G, Chrousos GP, Dacou-Voutetakis C. The efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. *J Clin Endocrinol Metab.* 2010 Jan;95(1):109-17; Bertelloni S, Baroncelli GI, Sorrentino MC, Perri G, Saggese G. Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *Eur J Pediatr.* 1998 May;157(5):363-67.

⁹¹ AG Opinion, at 5.

⁹² The AG Opinion’s citation is “see generally *Hennessy-Waller v. Snyder*, 529 F. Supp. 3d 1031, 1042 (D. Ariz. 2021), citing *Bell v. Tavistock and Portman NHS Foundation Trust*, 2020 EWHC 3274, para. 134 (Dec. 1, 2020) (referring to Bell’s conclusion that a clinic’s practice of prescribing puberty-suppressing medication to individuals under age 18 with gender dysphoria and determining such treatment was experimental).” Id. at 5-6.

⁹³ *Hennessy-Waller* is a decision that denies a motion for preliminary injunction against an insurance company for failure to cover gender-affirming surgery. The decision involves surgery, not puberty blockers, and it is not a fully-adjudicated factual determination about either surgery or puberty blockers. *Hennessy-Waller v. Snyder*, 529 F. Supp. 3d 1031 (D. Ariz. 2021).

⁹⁴ *Bell v. The Tavistock and Portman NHS Foundation Trust* [2021] EWCA (Civ) 1363 [38] (Eng.) (noting that the claimant’s (plaintiff’s) expert evidence was faulty: “None of it complied with the rules regarding expert evidence and a good deal of it is argumentative and adversarial.”). For a scientific review of the evidence in the lower court decision, see de Vries ALC, Richards C, Tishelman AC, Motmans J, Hannema SE, Green J, Rosenthal SM. *Bell v. Tavistock and Portman NHS Foundation Trust* [2020] EWHC 3274: Weighing current knowledge and uncertainties in decisions about gender-related treatment for transgender adolescents. *Int J Transgend Health.* 2021 Apr 5;22(3):217-24.

⁹⁵ AG Opinion, at 5.

⁹⁶ Alabama Law, Section 2(7).

“Off label” means only that the FDA has not specifically approved a particular medication for a particular use. The off-label use of medications for children is quite common and often necessary, because an “overwhelming number of drugs” have no FDA-approved instructions for use in pediatric patients.⁹⁷ This is in part because pharmaceutical companies often lack financial incentives to support research required for FDA approval for specific use in children.⁹⁸ Indeed, the American Academy of Pediatrics specifically approves the off-label use of drugs:

The purpose of off-label use is to benefit the individual patient. Practitioners use their professional judgment to determine these uses. As such, *the term “off-label” does not imply an improper, illegal, contraindicated, or investigational use.* Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient.⁹⁹

Many common medications, including hormones, are used off-label in adults and minors. In fact, pediatricians prescribe off-label drugs in 20% of patient visits.¹⁰⁰ Estrogen and testosterone are often used off-label to treat adolescents with intersex conditions. Common hormonal medications used off-label include norethindrone, a progesterone analogue used off-label for the treatment of heavy menstrual bleeding in those with polycystic ovarian syndrome, bleeding disorder, and anovulatory bleeding of early puberty. It is also used to treat endometriosis, which is a painful inflammatory condition. Many forms of combined hormonal contraception, as well as a testosterone-blocking medication (spironolactone), are used off-label to treat acne. Other examples include clonidine, a blood pressure medication used off-label for the treatment of ADHD, migraine headaches, disorders of behavioral regulation, and insomnia; and propranolol, a blood pressure medication used off-label for the treatment of performance anxiety.

b. The AG Opinion and the Alabama Law exaggerate the fertility risks of gender-affirming hormonal treatment.

⁹⁷ The quote is from the American Academy of Pediatrics Committee on Drugs. See Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, Van Den Anker JN; American Academy of Pediatrics Committee on Drugs. Off-label use of drugs in children. *Pediatrics*. 2014 Mar;133(3):563-7 (hereinafter, “AAP Committee on Drugs (2014)”); see also Allen HC, Garbe MC, Lees J, Aziz N, Chaaban H, Miller JL, Johnson P, DeLeon S. Off-Label Medication use in Children, More Common than We Think: A Systematic Review of the Literature. *J Okla State Med Assoc*. 2018 Oct;111(8):776-783.

⁹⁸ AAP Committee on Drugs (2014), cited in note 97.

⁹⁹ AAP Committee on Drugs (2014), cited in note 97 (emphasis added). See also Schrier L, Hadjipanayis A, Stiris T, Ross-Russell RI, Valiulis A, Turner MA, Zhao W, De Cock P, de Wildt SN, Allegaert K, van den Anker J. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology. *Eur J Pediatr*. 2020 May;179(5):839-847.

¹⁰⁰ Hoon D, Taylor MT, Kapadia P, Gerhard T, Strom BL, Horton DB. Trends in Off-Label Drug Use in Ambulatory Settings: 2006-2015. *Pediatrics*. 2019 Oct;144(4):1-10 (emphasis added).

The AG Opinion claims that gender-affirming hormone treatments cause infertility.¹⁰¹ The Alabama Law contains a similar statement.¹⁰² These are unwarranted exaggerations, which ignore the substantial evidence of reversibility of the fertility effects of hormone therapy.

Treatment with gender-affirming sex hormones impacts fertility while drug therapy is ongoing, but the effect is anticipated to be reversible if medication is discontinued. Importantly, hormone therapy is always individualized, and some transgender and non-binary teens remain on puberty blockers up to the age of majority without proceeding to hormone treatment.

For transgender men (persons assigned female sex at birth who retain ovaries), testosterone treatment can affect ovarian function, inhibiting menses in the majority of those on therapy. The evidence shows that most transgender men who had regular menses before starting testosterone therapy are reported to resume menses if testosterone is discontinued.¹⁰³ Some transgender men may retain fertility during hormone treatment: spontaneous pregnancies have occurred in testosterone-treated transgender men, some while still amenorrheic.¹⁰⁴ Further, a number of transgender men have discontinued testosterone therapy prior to undergoing assisted reproductive technology and have carried pregnancies to term with delivery of normal infants.¹⁰⁵

The effects of gender-affirming estrogen treatment on testicular histology vary among individuals. Reduced spermatogenesis is common while patients remain on estrogen, but fully normal spermatogenic activity has been documented.¹⁰⁶ Importantly, return of spermatogenesis occurred quickly in patients who discontinued hormone treatment.¹⁰⁷ Patients who were treated with puberty blockers (GnRHa's) starting at the onset of pubertal development and estrogen at

¹⁰¹ AG Opinion, at 3.

¹⁰² Alabama Law, Section 2(13).

¹⁰³ Endocrine Society (2017). Light AD, Obedin-Maliver J, Sevelius JM, Kerns JL. Transgender men who experienced pregnancy after female-to-male gender transitioning. *Obstet Gynecol.* 2014;124(6):1120–1127 (hereinafter, “Light et al. 2014”); Pelusi C, Costantino A, Martelli V, et al. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med.* 2014;11(12):3002–3011.; Smith KP, Madison CM, Milne NM. Gonadal suppressive and cross-sex hormone therapy for gender dysphoria in adolescents and adults. *Pharmacotherapy.* 2014;34(12):1282–1297.

¹⁰⁴ Light et al. (2014), cited in note 103; Light A, Wang LF, Zeymo A, Gomez-Lobo V. Family planning and contraception use in transgender men. *Contraception.* 2018 Oct;98(4):266-69.

¹⁰⁵ Leung A, Sakkas D, Pang S, Thornton K, Resetkova N. Assisted reproductive technology outcomes in female-to-male transgender patients compared with cisgender patients: a new frontier in reproductive medicine. *Fertil Steril.* 2019 Nov;112(5):858-65; Wallace SA, Blough KL, Kondapalli LA. Fertility preservation in the transgender patient: expanding oncofertility care beyond cancer. *Gynecol Endocrinol.* 2014;30(12):868-71; Maxwell S, Noyes N, Keefe D, Berkeley AS, Goldman KN. Pregnancy outcomes after fertility preservation in transgender men. *Obstet Gynecol.* 2017 Jun;129(6):1031-34.; Gale J, Magee B, Forsyth-Greig A, Visram H, Jackson A. Oocyte cryopreservation in a transgender man on long-term testosterone therapy: a case report. *F S Rep.* 2021 Feb 20;2(2):249-51.

¹⁰⁶ Schneider F, Kliesch S, Schlatt S, Neuhaus N. Andrology of male -to-female transsexuals: influence of cross-sex hormone therapy on testicular function. *Andrology.* 2017 Sept;5(5):873-80.

¹⁰⁷ Schneider F, Neuhaus N, Wistuba J, Zitzmann M, Heß J, Mahler D, van Ahlen H, Schlatt S, Kliesch S. Testicular functions and clinical characterization of patients with gender dysphoria (GD) undergoing sex reassignment surgery (SRS). *J Sex Med.* 2015 Nov;12(11):2190-2200.

16 years of age were shown to have normal-appearing, immature sperm-producing cells in the testes, suggesting those individuals retained fertility potential.¹⁰⁸

As with any other medical decision, parents and providers carefully weigh the risks of treating the individual adolescent against the risks of not treating them, including the mental health impact and potential suicide risk of not beginning gender-affirming care.

As the standard protocols summarized in Section 1 of this report demonstrate, there is no push by physicians to proceed to hormone therapy. On the contrary, the decision to proceed with drug therapy and the choice of therapy are determined after assessing each adolescent's medical history as well as their past and ongoing mental health concerns. The standard of care specifically states that any existing mental health issues must be stable prior to moving forward with gender-affirming medical interventions. When counseling transgender adolescents who are considering gender-affirming drug therapy, physicians can also offer sperm or oocyte (egg) cryopreservation.

In addition to its claims about fertility, the AG Opinion offers a list of asserted medical harms without citation to any existing medical authority. The cited source is a healthcare website, and the underlying document has been removed from the site and is not otherwise available on the Internet.¹⁰⁹ The opinion offers no scientific foundation for its claims but seems to conflate long-outdated practice with the current standard of care.¹¹⁰

A more accurate perspective begins with an understanding of the role of hormones in the body. Hormones play a role in determining the medical profile of cisgender people. Generally speaking, cisgender women have relatively higher levels of estrogen and lower levels of testosterone, and cisgender men have the reverse. Each hormonal profile carries with it medical benefits and risks. Cisgender women, for example, have lower rates of cardiovascular disease than cisgender men but higher risks of venous thromboembolism. When a transgender individual receives gender-affirming hormone treatment, they take doses of exogenous sex hormones that approximate the physiologic state of their identified gender. Put simply, a transgender female is supplied an amount of estrogen similar to the estrogen that a cisgender woman's ovaries typically produce. Similarly, a transgender male receives a dose of testosterone that approximates what a cisgender male's testicles typically produce. Protocols provide explicit dosage guidelines to approximate the physiology of the patient's identified gender rather than to develop desired physical characteristics.

The medical result is that transgender individuals move toward the typical medical profile of their identified gender. And so transgender women, like cisgender women, have lower risks of

¹⁰⁸ de Nie I, Mulder CL, Meißner A, Schut Y, Holleman EM, van der Sluis WB, Hannema SE, den Heijer M, Huirne J, van Pelt AMM, van Mello NM. Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in transgender women. *Hum Reprod.* 2022 Jan 28;37(1):297-308.

¹⁰⁹ The AG Opinion cites to Timothy Cavanaugh, M.D., Cross-Sex Hormone Therapy, FENWAY HEALTH (2015), <https://www.lgbtqihealtheducation.org/wp-content/uploads/Cross-Sex-Hormone-Therapy1.pdf>. A search conducted in March 2022 found that the link was broken and the document could not be found on the Fenway Health website or elsewhere on the Internet.

¹¹⁰ The iatrogenic (drug-induced) risks of hepatotoxicity, meningioma, and prolactinoma are now zero, because the medication associated with those risks (cyproterone) is no longer in use in the United States. WPATH (2012), p. 48.

cardiovascular disease than cisgender men.¹¹¹ Transgender women, like cisgender women, have a slightly higher risk of venous thromboembolism than cisgender men. In fact, transgender women have a *lower* risk of venous thromboembolism than cisgender women, and the overall risk is extremely low (less than 1%) for all transgender individuals, both women and men.¹¹² The risk of venous thromboembolism in transgender women and non-pregnant cisgender women is less than the risk in pregnancy, which is the highest estrogenic physiologic state known.

It is also critical to note that the medical impact of gender-affirming treatment is generally the same in transgender people as in cisgender people who take the same hormone medications. For example, physicians commonly prescribe hormonal contraceptives containing ethinyl estradiol (a synthetic estrogen) to adolescents for reasons including birth control, management of irregular or painful menstrual periods, and acne. In other words, similar doses of exogenous sex hormones are commonly administered to cisgender individuals for a host of reasons and are well tolerated.

¹¹¹ Connelly PJ, Marie Freel E, Perry C, Ewan J, Touyz RM, Currie G, Delles C. Gender-Affirming Hormone Therapy, Vascular Health and Cardiovascular Disease in Transgender Adults. *Hypertension*. 2019 Dec;74(6):1266-1274. doi: 10.1161/HYPERTENSIONAHA.119.13080. Epub 2019 Oct 28. Erratum in: *Hypertension*. 2020 Apr;75(4):e10. PMID: 31656099; PMCID: PMC6887638.

¹¹² Oral estradiol, the preferred estrogen formulation that is given to transgender women in the United States, carries a VTE risk of <1%. T'Sjoen G, Arcelus J, Gooren L, Klink DT, Tangpricha V. Endocrinology of Transgender Medicine. *Endocr Rev*. 2019 Feb 1;40(1):97-117. In transgender men, the overall risk of VTE ranges from 0% to 0.34%. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, Davidge-Pitts CJ, Nippoldt TB, Prokop LJ, Murad MH. Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab*. 2017 Nov 1;102(11):3914-23.

Appendix A: Additional Information on Biased Sources of Information in the AG Opinion

Here, we address two sources of information mischaracterized by the AG Opinion as authorities on, respectively, science and medical ethics.

a. The Society for Evidence-Based Gender Medicine

The AG Opinion twice cites the Society for Evidence-Based Gender Medicine (“SEGM”). SEGM claims to be “an international group of over 100 clinicians and researchers concerned about the lack of quality evidence for the use of hormonal and surgical interventions as first-line treatment for young people with gender dysphoria.”¹¹³

Despite SEGM’s statement, the group appears to be nothing more than a website; it does not appear to hold meetings, screen its members, or publish a journal. The original content on the website includes statements unsupported by any citations. When the content does provide citations, they are often unreliable or misleading. The SEGM website includes a list of citations to more than 100 articles as evidence for the medical risks of gender-affirming care, but we reviewed each article and found the vast majority to be of low quality. The site’s content omits mention of the standards of care published by mainstream scientific organizations, and it falsely claims that the standard protocols permit gender-affirming surgery before the age of majority. The long list of citations omits mainstream scientific articles that do not support the SEGM agenda, and the list includes a large number of letters to the editor, which are not peer-reviewed or fact-checked,¹¹⁴ as well as other sources of little scientific value, including opinion pieces and case studies.

Although the SEGM site claims “over 100 clinicians and researchers” as members, it lists as “clinical and academic advisors” a group of only 14 people, many of whom have limited (or no) scientific qualifications related to the study of medical treatment for transgender people. Of the 14, only eight claim academic credentials above the master’s degree level (and, of these, two of the PhD’s are in sociology and evolutionary biology). None have academic appointments in pediatric medicine or child psychology; none have published original empirical research on the medical treatment of transgender people in a peer-reviewed publication; and none currently treat patients in a recognized gender clinic.¹¹⁵

A contextual examination reveals that SEGM is an ideological organization without apparent ties to mainstream scientific or professional organizations. Its 14 core members are a small group of repeat players in anti-trans activities – a fact that the SEGM website does not disclose. These 14 often write letters to the editor of mainstream scientific publications; these letters appear in the list of publications on the website (even though letters to the editor typically are not peer-reviewed or fact-checked). (Our review shows that the group of 14 has a total of 39 relevant publications and that 75% of these are letters to the editor.)

¹¹³ All SEGM.org website citations reflect visits to the site in March 2022.

¹¹⁴ Of the 123 listed papers (some are listed more than once), 49 (or 40%) are letters to the editor or opinion pieces.

¹¹⁵ These findings are based on the biographical data posted on the SEGM.org website, supplemented with searches of Google (to determine academic appointments and listed publications) and the database PubMed (to determine medical publication records).

The core members of SEGM frequently serve together on the boards of other organizations that oppose gender-affirming treatment and, like SEGM, feature biased and unscientific content. These include Genspect, Gender Identity Challenge (GENID), Gender Health Query, Rethink Identity Medicine Ethics, Sex Matters, Gender Exploratory Therapy Team, Gender Dysphoria Working Group, and the Institute for Comprehensive Gender Dysphoria Research.

b. Purported bioethics experts

The AG Opinion cites two purported ethics experts for the proposition that “it is particularly unethical to radically intervene in the normal physical development of a child to ‘affirm’ a ‘gender identity’ that is at odds with bodily sex.”¹¹⁶

This is an unreliable citation for two reasons. First, the cited item is not published in a peer-reviewed or mainstream legal or ethics journal. It appears, instead, in *Public Discourse*, an online journal on the website of an organization with no clear academic or professional affiliation.¹¹⁷ Second, the two authors have strong ties to anti-trans activism. The first author, Ryan T. Anderson, is the president of a right-wing, Catholic-identified think tank.¹¹⁸ (Anderson is also the founder of the publishing journal, *Public Discourse*, further undermining the credibility of the citation.) The second author, Robert George, is a professor at Princeton who has long been engaged in anti-trans political activism. George is the founder of The American Principles Project, which states: “We want to impose a political cost on the Left’s anti-family extremism. If they want to attack parental rights [or] confuse young children about their gender...they are going to be punished at the polls.”¹¹⁹

By contrast, academic experts in bioethics consider gender-affirming treatment to be ethical.¹²⁰ They emphasize “the importance of balanced decision making when counseling and

¹¹⁶ AG Opinion, at 4 (citing Anderson RT, George RP. Physical Interventions on the Bodies of Children to “Affirm” their “Gender Identity” Violate Sound Medical Ethics and Should Be Prohibited [Internet]. *Public Discourse: The Journal of the Witherspoon Institute*; 2019 Dec 8 [cited 2022 Mar]. Available from: <https://www.thepublicdiscourse.com/2019/12/58839/>).

¹¹⁷ “*Public Discourse* is the online journal of the Witherspoon Institute, a 501(c)3 research center located in Princeton, New Jersey”. Our Mission. *Public Discourse: The Journal of the Witherspoon Institute*; c2022 [cited 2022 Mar]. Available from: <https://www.thepublicdiscourse.com/our-mission/>.

¹¹⁸ “Founded in 1976, the Ethics and Public Policy Center” works “to apply the riches of the Judeo-Christian tradition to contemporary questions of law, culture, and politics, in pursuit of America’s continued civic and cultural renewal.” About. *Ethics & Public Policy Center*; c2022 [cited 2022 Mar]. Available from: <https://eppc.org/about/>. The EPPC’s programs include “Catholic Studies” and the “Catholic Women’s Forum. Programs. *Ethics & Public Policy Center*; c2022 [cited 2022 Mar]. Available from: <https://eppc.org/program/>. Anderson is listed as the president. Ryan T. Anderson. *Ethics & Public Policy Center*; c2022 [cited 2022 Mar]. Available from: https://eppc.org/author/ryan_anderson/.

¹¹⁹ About. *American Principles Project*; c2020 [cited 2022 Mar]. Available from: <https://americanprinciplesproject.org/about/>. On another page, the website states that the American Principles Project was founded in 2009 by George and “veteran political strategist Frank Cannon.” History. *American Principles Project*; c2020 [cited 2022 Mar]. Available from: <https://americanprinciplesproject.org/about/history-story/>.

¹²⁰ For examples, see Kimberly LL, Folkers KM, Friesen P, Sultan D, Quinn GP, Bateman-House A, Parent B, Konnoth C, Janssen A, Shah LD, Bluebond-Langner R, Salas-Humara C. Ethical Issues in Gender-Affirming Care for Youth. *Pediatrics*. 2018 Dec;142(6):e20181537; Bizic MR, Jevtovic M, Pusica S, Stojanovic B, Duisin D,

treating adolescents with nonconforming gender identities,”¹²¹ and they have evaluated decision-making procedures that can ensure that adolescents and their parents give fully-informed consent to treatment.¹²² These considerations align with the consent processes prescribed by standard medical protocols, which we discuss in Section 1.

Vujovic S, Rakic V, Djordjevic ML. Gender Dysphoria: Bioethical Aspects of Medical Treatment. *BioMed Res Int*. 2018 Jun 13;2018:9652305; Strang JF, Powers MD, Knauss M, Sibarium E, Leibowitz SF, Kenworthy L, Sadikova E, Wyss S, Willing L, Caplan R, Pervez N, Nowak J, Gohari D, Gomez-Lobo V, Call D, Anthony LG. “They Thought It Was an Obsession”: Trajectories and Perspectives of Autistic Transgender and Gender-Diverse Adolescents. *J Autism Dev Disord*. 2018 Dec;48(12):4039-55.

¹²¹ Steensma TD, Wensing-Kruger SA, Klink DT. How Should Physicians Help Gender-Transitioning Adolescents Consider Potential Iatrogenic Harms of Hormone Therapy? *AMA J Ethics*. 2017 Aug 1;19(8):762-70.

¹²² Vrouwenraets LJ, Hartman LA, Hein IM, de Vries ALC, de Vries MC, Molewijk BAC. Dealing with Moral Challenges in Treatment of Transgender Children and Adolescents: Evaluating the Role of Moral Case Deliberation. *Arch Sex Behav*. 2020 Oct;49(7):2619-34.

POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System
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DEDICATED TO THE HEALTH OF ALL CHILDREN™

Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents

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As a traditionally underserved population that faces numerous health disparities, youth who identify as transgender and gender diverse (TGD) and their families are increasingly presenting to pediatric providers for education, care, and referrals. The need for more formal training, standardized treatment, and research on safety and medical outcomes often leaves providers feeling ill equipped to support and care for patients that identify as TGD and families. In this policy statement, we review relevant concepts and challenges and provide suggestions for pediatric providers that are focused on promoting the health and positive development of youth that identify as TGD while eliminating discrimination and stigma.

abstract

FREE

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Dr Rafferty conceptualized the statement, drafted the initial manuscript, reviewed and revised the manuscript, approved the final manuscript as submitted, and agrees to be accountable for all aspects of the work.

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INTRODUCTION

In its dedication to the health of all children, the American Academy of Pediatrics (AAP) strives to improve health care access and eliminate disparities for children and teenagers who identify as lesbian, gay, bisexual, transgender, or questioning (LGBTQ) of their sexual or gender identity.^{1,2} Despite some advances in public awareness and legal protections, youth who identify as LGBTQ continue to face disparities that stem from multiple sources, including inequitable laws and policies, societal discrimination, and a lack of access to quality health care, including mental health care. Such challenges are often more intense for youth who do not conform to social expectations and norms regarding gender. Pediatric providers are increasingly encountering such youth and their families, who seek medical advice and interventions, yet they may lack the formal training to care for youth that identify as transgender and gender diverse (TGD) and their families.³

This policy statement is focused specifically on children and youth that identify as TGD rather than the larger LGBTQ population, providing brief, relevant background on the basis of current available research

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TABLE 1 Relevant Terms and Definitions Related to Gender Care

Term	Definition
Sex	An assignment that is made at birth, usually male or female, typically on the basis of external genital anatomy but sometimes on the basis of internal gonads, chromosomes, or hormone levels
Gender identity	A person's deep internal sense of being female, male, a combination of both, somewhere in between, or neither; resulting from a multifaceted interaction of biological traits, environmental factors, self-understanding, and cultural expectations
Gender expression	The external way a person expresses their gender, such as with clothing, hair, mannerisms, activities, or social roles
Gender perception	The way others interpret a person's gender expression
Gender diverse	A term that is used to describe people with gender behaviors, appearances, or identities that are incongruent with those culturally assigned to their birth sex; gender-diverse individuals may refer to themselves with many different terms, such as transgender, nonbinary, genderqueer; ⁷ gender fluid, gender creative, gender independent, or noncisgender. "Gender diverse" is used to acknowledge and include the vast diversity of gender identities that exists. It replaces the former term, "gender nonconforming," which has a negative and exclusionary connotation.
Transgender	A subset of gender-diverse youth whose gender identity does not match their assigned sex and generally remains persistent, consistent, and insistent over time; the term "transgender" also encompasses many other labels individuals may use to refer to themselves.
Cisgender	A term that is used to describe a person who identifies and expresses a gender that is consistent with the culturally defined norms of the sex they were assigned at birth
Agender	A term that is used to describe a person who does not identify as having a particular gender
Affirmed gender	When a person's true gender identity, or concern about their gender identity, is communicated to and validated from others as authentic
MTF; affirmed female; trans female	Terms that are used to describe individuals who were assigned male sex at birth but who have a gender identity and/or expression that is asserted to be more feminine
FTM; affirmed male; trans male	Terms that are used to describe individuals who were assigned female sex at birth but who have a gender identity and/or expression that is asserted to be more masculine
Gender dysphoria	A clinical symptom that is characterized by a sense of alienation to some or all of the physical characteristics or social roles of one's assigned gender; also, gender dysphoria is the psychiatric diagnosis in the <i>DSM-5</i> , which has focus on the distress that stems from the incongruence between one's expressed or experienced (affirmed) gender and the gender assigned at birth.
Gender identity disorder	A psychiatric diagnosis defined previously in the <i>DSM-IV</i> (changed to "gender dysphoria" in the <i>DSM-5</i>); the primary criteria include a strong, persistent cross-sex identification and significant distress and social impairment. This diagnosis is no longer appropriate for use and may lead to stigma, but the term may be found in older research.
Sexual orientation	A person's sexual identity in relation to the gender(s) to which they are attracted; sexual orientation and gender identity develop separately.

This list is not intended to be all inclusive. The pronouns "they" and "their" are used intentionally to be inclusive rather than the binary pronouns "he" and "she" and "his" and "her." Adapted from Bonifacio HJ, Rosenthal SM. Gender variance and dysphoria in children and adolescents. *Pediatr Clin North Am*. 2015;62(4):1001–1016. Adapted from Vance SR Jr, Ehrensaft D, Rosenthal SM. Psychological and medical care of gender nonconforming youth. *Pediatrics*. 2014;134(6):1184–1192. *DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; FTM, female to male; MTF, male to female.

and expert opinion from clinical and research leaders, which will serve as the basis for recommendations. It is not a comprehensive review of clinical approaches and nuances to pediatric care for children and youth that identify as TGD. Professional understanding of youth that identify as TGD is a rapidly evolving clinical field in which research on appropriate clinical management is limited by insufficient funding.^{3,4}

DEFINITIONS

To clarify recommendations and discussions in this policy statement, some definitions are provided. However, brief descriptions of human behavior or identities may not capture nuance in this evolving field.

"Sex," or "natal gender," is a label, generally "male" or "female," that is typically assigned at birth on the basis of genetic and anatomic characteristics, such as genital anatomy, chromosomes, and sex hormone levels. Meanwhile, "gender identity" is one's internal sense of who one is, which results from a multifaceted interaction of biological traits, developmental influences, and environmental conditions. It may be male, female, somewhere in between, a combination of both, or neither (ie, not conforming to a binary conceptualization of gender). Self-recognition of gender identity develops over time, much the same way as a child's physical body does. For some people, gender identity can be fluid, shifting in different contexts. "Gender expression"

refers to the wide array of ways people display their gender through clothing, hair styles, mannerisms, or social roles. Exploring different ways of expressing gender is common for children and may challenge social expectations. The way others interpret this expression is referred to as "gender perception" (Table 1).^{5,6}

These labels may or may not be congruent. The term "cisgender" is used if someone identifies and expresses a gender that is consistent with the culturally defined norms of the sex that was assigned at birth. "Gender diverse" is an umbrella term to describe an ever-evolving array of labels that people may apply when their gender identity, expression, or even perception does not conform

to the norms and stereotypes others expect of their assigned sex. “Transgender” is usually reserved for a subset of such youth whose gender identity does not match their assigned sex and generally remains persistent, consistent, and insistent over time. These terms are not diagnoses; rather, they are personal and often dynamic ways of describing one’s own gender experience.

Gender identity is not synonymous with “sexual orientation,” which refers to a person’s identity in relation to the gender(s) to which they are sexually and romantically attracted. Gender identity and sexual orientation are distinct but interrelated constructs.⁸ Therefore, being transgender does not imply a sexual orientation, and people who identify as transgender still identify as straight, gay, bisexual, etc, on the basis of their attractions. (For more information, *The Gender Book*, found at www.thegenderbook.com, is a resource with illustrations that are used to highlight these core terms and concepts.)

EPIDEMIOLOGY

In population-based surveys, questions related to gender identity are rarely asked, which makes it difficult to assess the size and characteristics of the population that is TGD. In the 2014 Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention, only 19 states elected to include optional questions on gender identity. Extrapolation from these data suggests that the US prevalence of adults who identify as transgender or “gender nonconforming” is 0.6% (1.4 million), ranging from 0.3% in North Dakota to 0.8% in Hawaii.⁹ On the basis of these data, it has been estimated that 0.7% of youth ages 13 to 17 years (~150 000) identify as transgender.¹⁰ This number is much higher than previous estimates, which were

extrapolated from individual states or specialty clinics, and is likely an underestimate given the stigma regarding those who openly identify as transgender and the difficulty in defining “transgender” in a way that is inclusive of all gender-diverse identities.¹¹

There have been no large-scale prevalence studies among children and adolescents, and there is no evidence that adult statistics reflect young children or adolescents. In the 2014 Behavioral Risk Factor Surveillance System, those 18 to 24 years of age were more likely than older age groups to identify as transgender (0.7%).⁹ Children report being aware of gender incongruence at young ages. Children who later identify as TGD report first having recognized their gender as “different” at an average age of 8.5 years; however, they did not disclose such feelings until an average of 10 years later.¹²

MENTAL HEALTH IMPLICATIONS

Adolescents and adults who identify as transgender have high rates of depression, anxiety, eating disorders, self-harm, and suicide.^{13–20} Evidence suggests that an identity of TGD has an increased prevalence among individuals with autism spectrum disorder, but this association is not yet well understood.^{21,22} In 1 retrospective cohort study, 56% of youth who identified as transgender reported previous suicidal ideation, and 31% reported a previous suicide attempt, compared with 20% and 11% among matched youth who identified as cisgender, respectively.¹³ Some youth who identify as TGD also experience gender dysphoria, which is a specific diagnosis given to those who experience impairment in peer and/or family relationships, school performance, or other aspects of their life as a consequence of the

incongruence between their assigned sex and their gender identity.²³

There is no evidence that risk for mental illness is inherently attributable to one’s identity of TGD. Rather, it is believed to be multifactorial, stemming from an internal conflict between one’s appearance and identity, limited availability of mental health services, low access to health care providers with expertise in caring for youth who identify as TGD, discrimination, stigma, and social rejection.²⁴ This was affirmed by the American Psychological Association in 2008²⁵ (with practice guidelines released in 2015⁸) and the American Psychiatric Association, which made the following statement in 2012:

Being transgender or gender variant implies no impairment in judgment, stability, reliability, or general social or vocational capabilities; however, these individuals often experience discrimination due to a lack of civil rights protections for their gender identity or expression.... [Such] discrimination and lack of equal civil rights is damaging to the mental health of transgender and gender variant individuals.²⁶

Youth who identify as TGD often confront stigma and discrimination, which contribute to feelings of rejection and isolation that can adversely affect physical and emotional well-being. For example, many youth believe that they must hide their gender identity and expression to avoid bullying, harassment, or victimization. Youth who identify as TGD experience disproportionately high rates of homelessness, physical violence (at home and in the community), substance abuse, and high-risk sexual behaviors.^{5,6,12,27–31} Among the 3 million HIV testing events that were reported in 2015, the highest percentages of new infections were among women who identified as transgender³² and were also at particular risk for not knowing their HIV status.³⁰

GENDER-AFFIRMATIVE CARE

In a gender-affirmative care model (GACM), pediatric providers offer developmentally appropriate care that is oriented toward understanding and appreciating the youth's gender experience. A strong, nonjudgmental partnership with youth and their families can facilitate exploration of complicated emotions and gender-diverse expressions while allowing questions and concerns to be raised in a supportive environment.⁵ In a GACM, the following messages are conveyed:

- transgender identities and diverse gender expressions do not constitute a mental disorder;
- variations in gender identity and expression are normal aspects of human diversity, and binary definitions of gender do not always reflect emerging gender identities;
- gender identity evolves as an interplay of biology, development, socialization, and culture; and
- if a mental health issue exists, it most often stems from stigma and negative experiences rather than being intrinsic to the child.^{27,33}

The GACM is best facilitated through the integration of medical, mental health, and social services, including specific resources and supports for parents and families.²⁴ Providers work together to destigmatize gender variance, promote the child's self-worth, facilitate access to care, educate families, and advocate for safer community spaces where children are free to develop and explore their gender.⁵ A specialized gender-affirmative therapist, when available, may be an asset in helping children and their families build skills for dealing with gender-based stigma, address symptoms of anxiety or depression, and reinforce the child's overall resiliency.^{34,35} There is a limited but growing body

of evidence that suggests that using an integrated affirmative model results in young people having fewer mental health concerns whether they ultimately identify as transgender.^{24,36,37}

In contrast, "conversion" or "reparative" treatment models are used to prevent children and adolescents from identifying as transgender or to dissuade them from exhibiting gender-diverse expressions. The Substance Abuse and Mental Health Services Administration has concluded that any therapeutic intervention with the goal of changing a youth's gender expression or identity is inappropriate.³³ Reparative approaches have been proven to be not only unsuccessful³⁸ but also deleterious and are considered outside the mainstream of traditional medical practice.^{29,39–42} The AAP described reparative approaches as "unfair and deceptive."⁴³ At the time of this writing,* conversion therapy was banned by executive regulation in New York and by legislative statutes in 9 other states as well as the District of Columbia.⁴⁴

Pediatric providers have an essential role in assessing gender concerns and providing evidence-based information to assist youth and families in medical decision-making. Not doing so can prolong or exacerbate gender dysphoria and contribute to abuse and stigmatization.³⁵ If a pediatric provider does not feel prepared to address gender concerns when they occur, then referral to a pediatric or mental health provider with more expertise is appropriate. There is little research on communication and efficacy with transfers in care for youth who identify as TGD,

particularly from pediatric to adult providers.

DEVELOPMENTAL CONSIDERATIONS

Acknowledging that the capacity for emerging abstract thinking in childhood is important to conceptualize and reflect on identity, gender-affirmation guidelines are being focused on individually tailored interventions on the basis of the physical and cognitive development of youth who identify as TGD.⁴⁵ Accordingly, research substantiates that children who are prepubertal and assert an identity of TGD know their gender as clearly and as consistently as their developmentally equivalent peers who identify as cisgender and benefit from the same level of social acceptance.⁴⁶ This developmental approach to gender affirmation is in contrast to the outdated approach in which a child's gender-diverse assertions are held as "possibly true" until an arbitrary age (often after pubertal onset) when they can be considered valid, an approach that authors of the literature have termed "watchful waiting." This outdated approach does not serve the child because critical support is withheld. Watchful waiting is based on binary notions of gender in which gender diversity and fluidity is pathologized; in watchful waiting, it is also assumed that notions of gender identity become fixed at a certain age. The approach is also influenced by a group of early studies with validity concerns, methodologic flaws, and limited follow-up on children who identified as TGD and, by adolescence, did not seek further treatment ("desisters").^{45,47} More robust and current research suggests that, rather than focusing on who a child will become, valuing them for who they are, even at a young age, fosters secure attachment and resilience, not only for the child but also for the whole family.^{5,45,48,49}

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@aap.org.

MEDICAL MANAGEMENT

Pediatric primary care providers are in a unique position to routinely inquire about gender development in children and adolescents as part of recommended well-child visits⁵⁰ and to be a reliable source of validation, support, and reassurance. They are often the first provider to be aware that a child may not identify as cisgender or that there may be distress related to a gender-diverse identity. The best way to approach gender with patients is to inquire directly and nonjudgmentally about their experience and feelings before applying any labels.^{27,51}

Many medical interventions can be offered to youth who identify as TGD and their families. The decision of whether and when to initiate gender-affirmative treatment is personal and involves careful consideration of risks, benefits, and other factors unique to each patient and family. Many protocols suggest that clinical assessment of youth who identify as TGD is ideally conducted on an ongoing basis in the setting of a collaborative, multidisciplinary approach, which, in addition to the patient and family, may include the pediatric provider, a mental health provider (preferably with expertise in caring for youth who identify as TGD), social and legal supports, and a pediatric endocrinologist or adolescent-medicine gender specialist, if available.^{6,28} There is no prescribed path, sequence, or end point. Providers can make every effort to be aware of the influence of their own biases. The medical options also vary depending on pubertal and developmental progression.

Clinical Setting

In the past year, 1 in 4 adults who identified as transgender avoided a necessary doctor's visit because of fear of being mistreated.³¹ All clinical office staff have a role in affirming a patient's gender identity. Making flyers available or displaying posters

related to LGBTQ health issues, including information for children who identify as TGD and families, reveals inclusivity and awareness. Generally, patients who identify as TGD feel most comfortable when they have access to a gender-neutral restroom. Diversity training that encompasses sensitivity when caring for youth who identify as TGD and their families can be helpful in educating clinical and administrative staff. A patient-asserted name and pronouns are used by staff and are ideally reflected in the electronic medical record without creating duplicate charts.^{52,53} The US Centers for Medicare and Medicaid Services and the National Coordinator for Health Information Technology require all electronic health record systems certified under the Meaningful Use incentive program to have the capacity to confidentially collect information on gender identity.^{54,55} Explaining and maintaining confidentiality procedures promotes openness and trust, particularly with youth who identify as LGBTQ.¹ Maintaining a safe clinical space can provide at least 1 consistent, protective refuge for patients and families, allowing authentic gender expression and exploration that builds resiliency.

Pubertal Suppression

Gonadotrophin-releasing hormones have been used to delay puberty since the 1980s for central precocious puberty.⁵⁶ These reversible treatments can also be used in adolescents who experience gender dysphoria to prevent development of secondary sex characteristics and provide time up until 16 years of age for the individual and the family to explore gender identity, access psychosocial supports, develop coping skills, and further define appropriate treatment goals. If pubertal suppression treatment is

suspended, then endogenous puberty will resume.^{20,57,58}

Often, pubertal suppression creates an opportunity to reduce distress that may occur with the development of secondary sexual characteristics and allow for gender-affirming care, including mental health support for the adolescent and the family. It reduces the need for later surgery because physical changes that are otherwise irreversible (protrusion of the Adam's apple, male pattern baldness, voice change, breast growth, etc) are prevented. The available data reveal that pubertal suppression in children who identify as TGD generally leads to improved psychological functioning in adolescence and young adulthood.^{20,57–59}

Pubertal suppression is not without risks. Delaying puberty beyond one's peers can also be stressful and can lead to lower self-esteem and increased risk taking.⁶⁰ Some experts believe that genital underdevelopment may limit some potential reconstructive options.⁶¹ Research on long-term risks, particularly in terms of bone metabolism⁶² and fertility,⁶³ is currently limited and provides varied results.^{57,64,65} Families often look to pediatric providers for help in considering whether pubertal suppression is indicated in the context of their child's overall well-being as gender diverse.

Gender Affirmation

As youth who identify as TGD reflect on and evaluate their gender identity, various interventions may be considered to better align their gender expression with their underlying identity. This process of reflection, acceptance, and, for some, intervention is known as "gender affirmation." It was formerly referred to as "transitioning," but many view the process as an affirmation and acceptance of who they have always been rather than a transition

TABLE 2 The Process of Gender Affirmation May Include ≥ 1 of the Following Components

Component	Definition	General Age Range ^a	Reversibility ^a
Social affirmation	Adopting gender-affirming hairstyles, clothing, name, gender pronouns, and restrooms and other facilities	Any	Reversible
Puberty blockers	Gonadotropin-releasing hormone analogues, such as leuprolide and histrelin	During puberty (Tanner stage 2–5) ^b	Reversible ^c
Cross-sex hormone therapy	Testosterone (for those who were assigned female at birth and are masculinizing); estrogen plus androgen inhibitor (for those who were assigned male at birth and are feminizing)	Early adolescence onward	Partially reversible (skin texture, muscle mass, and fat deposition); irreversible once developed (testosterone: Adam’s apple protrusion, voice changes, and male pattern baldness; estrogen: breast development); unknown reversibility (effect on fertility)
Gender-affirming surgeries	“Top” surgery (to create a male-typical chest shape or enhance breasts); “bottom” surgery (surgery on genitals or reproductive organs); facial feminization and other procedures	Typically adults (adolescents on case-by-case basis ^d)	Not reversible
Legal affirmation	Changing gender and name recorded on birth certificate, school records, and other documents	Any	Reversible

^a Note that the provided age range and reversibility is based on the little data that are currently available.

^b There is limited benefit to starting gonadotropin-releasing hormone after Tanner stage 5 for pubertal suppression. However, when cross-sex hormones are initiated with a gradually increasing schedule, the initial levels are often not high enough to suppress endogenous sex hormone secretion. Therefore, gonadotropin-releasing hormone may be continued in accordance with the Endocrine Society Guidelines.⁶⁸

^c The effect of sustained puberty suppression on fertility is unknown. Pubertal suppression can be, and often is indicated to be, followed by cross-sex hormone treatment. However, when cross-sex hormones are initiated without endogenous hormones, then fertility may be decreased.⁶⁸

^d Eligibility criteria for gender-affirmative surgical interventions among adolescents are not clearly defined between established protocols and practice. When applicable, eligibility is usually determined on a case-by-case basis with the adolescent and the family along with input from medical, mental health, and surgical providers.^{68–71}

from 1 gender identity to another. Accordingly, some people who have gone through the process prefer to call themselves “affirmed females, males, etc” (or just “females, males, etc”), rather than using the prefix “trans-.” Gender affirmation is also used to acknowledge that some individuals who identify as TGD may feel affirmed in their gender without pursuing medical or surgical interventions.^{7,66}

Supportive involvement of parents and family is associated with better mental and physical health outcomes.⁶⁷ Gender affirmation among adolescents with gender dysphoria often reduces the emphasis on gender in their lives, allowing them to attend to other developmental tasks, such as academic success, relationship building, and future-oriented planning.⁶⁴ Most protocols for gender-affirming interventions incorporate World Professional Association of Transgender

Health³⁵ and Endocrine Society⁶⁸ recommendations and include ≥ 1 of the following elements (Table 2):

1. Social Affirmation: This is a reversible intervention in which children and adolescents express partially or completely in their asserted gender identity by adapting hairstyle, clothing, pronouns, name, etc. Children who identify as transgender and socially affirm and are supported in their asserted gender show no increase in depression and only minimal (clinically insignificant) increases in anxiety compared with age-matched averages.⁴⁸ Social affirmation can be complicated given the wide range of social interactions children have (eg, extended families, peers, school, community, etc). There is little guidance on the best approach (eg, all at once, gradual, creating new social networks, or affirming within existing networks, etc). Pediatric providers

can best support families by anticipating and discussing such complexity proactively, either in their own practice or through enlisting a qualified mental health provider.

2. Legal Affirmation: Elements of a social affirmation, such as a name and gender marker, become official on legal documents, such as birth certificates, passports, identification cards, school documents, etc. The processes for making these changes depend on state laws and may require specific documentation from pediatric providers.
3. Medical Affirmation: This is the process of using cross-sex hormones to allow adolescents who have initiated puberty to develop secondary sex characteristics of the opposite biological sex. Some changes are partially reversible if hormones are stopped, but others become

irreversible once they are fully developed (Table 2).

4. **Surgical Affirmation:** Surgical approaches may be used to feminize or masculinize features, such as hair distribution, chest, or genitalia, and may include removal of internal organs, such as ovaries or the uterus (affecting fertility). These changes are irreversible. Although current protocols typically reserve surgical interventions for adults,^{35,68} they are occasionally pursued during adolescence on a case-by-case basis, considering the necessity and benefit to the adolescent's overall health and often including multidisciplinary input from medical, mental health, and surgical providers as well as from the adolescent and family.^{69–71}

For some youth who identify as TGD whose natal gender is female, menstruation, breakthrough bleeding, and dysmenorrhea can lead to significant distress before or during gender affirmation. The American College of Obstetrics and Gynecology suggests that, although limited data are available to outline management, menstruation can be managed without exogenous estrogens by using a progesterone-only pill, a medroxyprogesterone acetate shot, or a progesterone-containing intrauterine or implantable device.⁷² If estrogen can be tolerated, oral contraceptives that contain both progesterone and estrogen are more effective at suppressing menses.⁷³ The Endocrine Society guidelines also suggest that gonadotrophin-releasing hormones can be used for menstrual suppression before the anticipated initiation of testosterone or in combination with testosterone for breakthrough bleeding (enables phenotypic masculinization at a lower dose than if testosterone is used alone).⁶⁸ Masculinizing hormones in natal female patients may lead to a cessation of menses,

but unplanned pregnancies have been reported, which emphasizes the need for ongoing contraceptive counseling with youth who identify as TGD.⁷²

HEALTH DISPARITIES

In addition to societal challenges, youth who identify as TGD face several barriers within the health care system, especially regarding access to care. In 2015, a focus group of youth who identified as transgender in Seattle, Washington, revealed 4 problematic areas related to health care:

1. safety issues, including the lack of safe clinical environments and fear of discrimination by providers;
2. poor access to physical health services, including testing for sexually transmitted infections;
3. inadequate resources to address mental health concerns; and
4. lack of continuity with providers.⁷⁴

This study reveals the obstacles many youth who identify as TGD face in accessing essential services, including the limited supply of appropriately trained medical and psychological providers, fertility options, and insurance coverage denials for gender-related treatments.⁷⁴

Insurance denials for services related to the care of patients who identify as TGD are a significant barrier. Although the Office for Civil Rights of the US Department of Health and Human Services explicitly stated in 2012 that the nondiscrimination provision in the Patient Protection and Affordable Care Act includes people who identify as gender diverse,^{75,76} insurance claims for gender affirmation, particularly among youth who identify as TGD, are frequently denied.^{54,77} In 1 study, it was found that approximately 25% of individuals

who identified as transgender were denied insurance coverage because of being transgender.³¹ The burden of covering medical expenses that are not covered by insurance can be financially devastating, and even when expenses are covered, families describe high levels of stress in navigating and submitting claims appropriately.⁷⁸ In 2012, a large gender center in Boston, Massachusetts, reported that most young patients who identified as transgender and were deemed appropriate candidates for recommended gender care were unable to obtain it because of such denials, which were based on the premise that gender dysphoria was a mental disorder, not a physical one, and that treatment was not medically or surgically necessary.²⁴ This practice not only contributes to stigma, prolonged gender dysphoria, and poor mental health outcomes,⁷⁷ but it may also lead patients to seek nonmedically supervised treatments that are potentially dangerous.²⁴ Furthermore, insurance denials can reinforce a socioeconomic divide between those who can finance the high costs of uncovered care and those who cannot.^{24,77}

The transgender youth group in Seattle likely reflected the larger TGD population when they described how obstacles adversely affect self-esteem and contribute to the perception that they are undervalued by society and the health care system.^{74,77} Professional medical associations, including the AAP, are increasingly calling for equity in health care provisions regardless of gender identity or expression.^{1,8,23,72} There is a critical need for investments in research on the prevalence, disparities, biological underpinnings, and standards of care relating to gender-diverse populations. Pediatric providers who work with state government and insurance officials can play an essential role in advocating for

stronger nondiscrimination policies and improved coverage.

There is a lack of quality research on the experience of youth of color who identify as transgender. One theory suggests that the intersection of racism, transphobia, and sexism may result in the extreme marginalization that is experienced among many women of color who identify as transgender,⁷⁹ including rejection from their family and dropping out of school at younger ages (often in the setting of rigid religious beliefs regarding gender),⁸⁰ increased levels of violence and body objectification,⁸¹ 3 times the risk of poverty compared with the general population,³¹ and the highest prevalence of HIV compared with other risk groups (estimated as high as 56.3% in 1 meta-analysis).³⁰ One model suggests that pervasive stigma and oppression can be associated with psychological distress (anxiety, depression, and suicide) and adoption of risk behaviors by such youth to obtain a sense of validation toward their complex identities.⁷⁹

FAMILY ACCEPTANCE

Research increasingly suggests that familial acceptance or rejection ultimately has little influence on the gender identity of youth; however, it may profoundly affect young people's ability to openly discuss or disclose concerns about their identity. Suppressing such concerns can affect mental health.⁸² Families often find it hard to understand and accept their child's gender-diverse traits because of personal beliefs, social pressure, and stigma.^{49,83} Legitimate fears may exist for their child's welfare, safety, and acceptance that pediatric providers need to appreciate and address. Families can be encouraged to communicate their concerns and questions. Unacknowledged concerns can contribute to shame and hesitation in regard to offering support and understanding.⁸⁴

which is essential for the child's self-esteem, social involvement, and overall health as TGD.^{48,85–87} Some caution has been expressed that unquestioning acceptance per se may not best serve questioning youth or their families. Instead, psychological evidence suggests that the most benefit comes when family members and youth are supported and encouraged to engage in reflective perspective taking and validate their own and the other's thoughts and feelings despite divergent views.^{49,82}

In this regard, suicide attempt rates among 433 adolescents in Ontario who identified as “trans” were 4% among those with strongly supportive parents and as high as 60% among those whose parents were not supportive.⁸⁵ Adolescents who identify as transgender and endorse at least 1 supportive person in their life report significantly less distress than those who only experience rejection. In communities with high levels of support, it was found that nonsupportive families tended to increase their support over time, leading to dramatic improvement in mental health outcomes among their children who identified as transgender.⁸⁸

Pediatric providers can create a safe environment for parents and families to better understand and listen to the needs of their children while receiving reassurance and education.⁸³ It is often appropriate to assist the child in understanding the parents' concerns as well. Despite expectations by some youth with transgender identity for immediate acceptance after “coming out,” family members often proceed through a process of becoming more comfortable and understanding of the youth's gender identity, thoughts, and feelings. One model suggests that the process resembles grieving, wherein the family separates from their expectations for their child to embrace a new reality. This process may proceed through stages of shock,

denial, anger, feelings of betrayal, fear, self-discovery, and pride.⁸⁹ The amount of time spent in any of these stages and the overall pace varies widely. Many family members also struggle as they are pushed to reflect on their own gender experience and assumptions throughout this process. In some situations, youth who identify as TGD may be at risk for internalizing the difficult emotions that family members may be experiencing. In these cases, individual and group therapy for the family members may be helpful.^{49,78}

Family dynamics can be complex, involving disagreement among legal guardians or between guardians and their children, which may affect the ability to obtain consent for any medical management or interventions. Even in states where minors may access care without parental consent for mental health services, contraception, and sexually transmitted infections, parental or guardian consent is required for hormonal and surgical care of patients who identify as TGD.^{72,90} Some families may take issue with providers who address gender concerns or offer gender-affirming care. In rare cases, a family may deny access to care that raises concerns about the youth's welfare and safety; in those cases, additional legal or ethical support may be useful to consider. In such rare situations, pediatric providers may want to familiarize themselves with relevant local consent laws and maintain their primary responsibility for the welfare of the child.

SAFE SCHOOLS AND COMMUNITIES

Youth who identify as TGD are becoming more visible because gender-diverse expression is increasingly admissible in the media, on social media, and in schools and communities. Regardless of whether a youth with a gender-diverse

identity ultimately identifies as transgender, challenges exist in nearly every social context, from lack of understanding to outright rejection, isolation, discrimination, and victimization. In the US Transgender Survey of nearly 28 000 respondents, it was found that among those who were out as or perceived to be TGD between kindergarten and eighth grade, 54% were verbally harassed, 24% were physically assaulted, and 13% were sexually assaulted; 17% left school because of maltreatment.³¹ Education and advocacy from the medical community on the importance of safe schools for youth who identify as TGD can have a significant effect.

At the time of this writing,* only 18 states and the District of Columbia had laws that prohibited discrimination based on gender expression when it comes to employment, housing, public accommodations, and insurance benefits. Over 200 US cities have such legislation. In addition to basic protections, many youth who identify as TGD also have to navigate legal obstacles when it comes to legally changing their name and/or gender marker.⁵⁴ In addition to advocating and working with policy makers to promote equal protections for youth who identify as TGD, pediatric providers can play an important role by developing a familiarity with local laws and organizations that provide social work and legal assistance to youth who identify as TGD and their families.

School environments play a significant role in the social and emotional development of children. Every child has a right to feel safe

and respected at school, but for youth who identify as TGD, this can be challenging. Nearly every aspect of school life may present safety concerns and require negotiations regarding their gender expression, including name/pronoun use, use of bathrooms and locker rooms, sports teams, dances and activities, overnight activities, and even peer groups. Conflicts in any of these areas can quickly escalate beyond the school's control to larger debates among the community and even on a national stage.

The formerly known Gay, Lesbian, and Straight Education Network (GLSEN), an advocacy organization for youth who identify as LGBTQ, conducts an annual national survey to measure LGBTQ well-being in US schools. In 2015, students who identified as LGBTQ reported high rates of being discouraged from participation in extracurricular activities. One in 5 students who identified as LGBTQ reported being hindered from forming or participating in a club to support lesbian, gay, bisexual, or transgender students (eg, a gay straight alliance, now often referred to as a genders and sexualities alliance) despite such clubs at schools being associated with decreased reports of negative remarks about sexual orientation or gender expression, increased feelings of safety and connectedness at school, and lower levels of victimization. In addition, >20% of students who identified as LGBTQ reported being blocked from writing about LGBTQ issues in school yearbooks or school newspapers or being prevented or discouraged by coaches and school staff from participating in sports because of their sexual orientation or gender expression.⁹¹

One strategy to prevent conflict is to proactively support policies and protections that promote inclusion and safety of all students. However, such policies are far from

consistent across districts. In 2015, GLSEN found that 43% of children who identified as LGBTQ reported feeling unsafe at school because of their gender expression, but only 6% reported that their school had official policies to support youth who identified as TGD, and only 11% reported that their school's antibullying policies had specific protections for gender expression.⁹¹ Consequently, more than half of the students who identified as transgender in the study were prevented from using the bathroom, names, or pronouns that aligned with their asserted gender at school. A lack of explicit policies that protected youth who identified as TGD was associated with increased reported victimization, with more than half of students who identified as LGBTQ reporting verbal harassment because of their gender expression. Educators and school administrators play an essential role in advocating for and enforcing such policies. GLSEN found that when students recognized actions to reduce gender-based harassment, both students who identified as transgender and cisgender reported a greater connection to staff and feelings of safety.⁹¹ In another study, schools were open to education regarding gender diversity and were willing to implement policies when they were supported by external agencies, such as medical professionals.⁹²

Academic content plays an important role in building a safe school environment as well. The 2015 GLSEN survey revealed that when positive representations of people who identified as LGBTQ were included in the curriculum, students who identified as LGBTQ reported less hostile school environments, less victimization and greater feelings of safety, fewer school absences because of feeling unsafe, greater feelings of connectedness to their school

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@aap.org.

community, and an increased interest in high school graduation and postsecondary education.⁹¹ At the time of this writing, * 8 states had laws that explicitly forbade teachers from even discussing LGBTQ issues.⁵⁴

MEDICAL EDUCATION

One of the most important ways to promote high-quality health care for youth who identify as TGD and their families is increasing the knowledge base and clinical experience of pediatric providers in providing culturally competent care to such populations, as recommended by the recently released guidelines by the Association of American Medical Colleges.⁹³ This begins with the medical school curriculum in areas such as human development, sexual health, endocrinology, pediatrics, and psychiatry. In a 2009–2010 survey of US medical schools, it was found that the median number of hours dedicated to LGBTQ health was 5, with one-third of US medical schools reporting no LGBTQ curriculum during the clinical years.⁹⁴

During residency training, there is potential for gender diversity to be emphasized in core rotations, especially in pediatrics, psychiatry, family medicine, and obstetrics and gynecology. Awareness could be promoted through the inclusion of topics relevant to caring for children who identify as TGD in the list of core competencies published by the American Board of Pediatrics, certifying examinations, and relevant study materials. Continuing education and maintenance of certification activities can include topics relevant to TGD populations as well.

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@aap.org.

RECOMMENDATIONS

The AAP works toward all children and adolescents, regardless of gender identity or expression, receiving care to promote optimal physical, mental, and social well-being. Any discrimination based on gender identity or expression, real or perceived, is damaging to the socioemotional health of children, families, and society. In particular, the AAP recommends the following:

1. that youth who identify as TGD have access to comprehensive, gender-affirming, and developmentally appropriate health care that is provided in a safe and inclusive clinical space;
2. that family-based therapy and support be available to recognize and respond to the emotional and mental health needs of parents, caregivers, and siblings of youth who identify as TGD;
3. that electronic health records, billing systems, patient-centered notification systems, and clinical research be designed to respect the asserted gender identity of each patient while maintaining confidentiality and avoiding duplicate charts;
4. that insurance plans offer coverage for health care that is specific to the needs of youth who identify as TGD, including coverage for medical, psychological, and, when indicated, surgical gender-affirming interventions;
5. that provider education, including medical school, residency, and continuing education, integrate core competencies on the emotional and physical health needs and best practices for the care of youth who identify as TGD and their families;
6. that pediatricians have a role in advocating for, educating, and developing liaison relationships

with school districts and other community organizations to promote acceptance and inclusion of all children without fear of harassment, exclusion, or bullying because of gender expression;

7. that pediatricians have a role in advocating for policies and laws that protect youth who identify as TGD from discrimination and violence;
8. that the health care workforce protects diversity by offering equal employment opportunities and workplace protections, regardless of gender identity or expression; and
9. that the medical field and federal government prioritize research that is dedicated to improving the quality of evidence-based care for youth who identify as TGD.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
GACM: gender-affirmative care model
GLSEN: Gay, Lesbian, and Straight Education Network
LGBTQ: lesbian, gay, bisexual, transgender, or questioning
TGD: transgender and gender diverse

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Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment



WHAT'S KNOWN ON THIS SUBJECT: Puberty suppression has rapidly become part of the standard clinical management protocols for transgender adolescents. To date, there is only limited evidence for the long-term effectiveness of this approach after gender reassignment (cross-sex hormones and surgery).



WHAT THIS STUDY ADDS: In young adulthood, gender dysphoria had resolved, psychological functioning had steadily improved, and well-being was comparable to same-age peers. The clinical protocol including puberty suppression had provided these formerly gender-dysphoric youth the opportunity to develop into well-functioning young adults.

abstract

BACKGROUND: In recent years, puberty suppression by means of gonadotropin-releasing hormone analogs has become accepted in clinical management of adolescents who have gender dysphoria (GD). The current study is the first longer-term longitudinal evaluation of the effectiveness of this approach.

METHODS: A total of 55 young transgender adults (22 transwomen and 33 transmen) who had received puberty suppression during adolescence were assessed 3 times: before the start of puberty suppression (mean age, 13.6 years), when cross-sex hormones were introduced (mean age, 16.7 years), and at least 1 year after gender reassignment surgery (mean age, 20.7 years). Psychological functioning (GD, body image, global functioning, depression, anxiety, emotional and behavioral problems) and objective (social and educational/professional functioning) and subjective (quality of life, satisfaction with life and happiness) well-being were investigated.

RESULTS: 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. Improvements in psychological functioning were positively correlated with postsurgical subjective well-being.

CONCLUSIONS: A clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons, including puberty suppression, followed by cross-sex hormones and gender reassignment surgery, provides gender dysphoric youth who seek gender reassignment from early puberty on, the opportunity to develop into well-functioning young adults. *Pediatrics* 2014;134:696–704

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KEY WORDS

gender dysphoria, transgenderism, adolescents, psychological functioning, puberty suppression, longitudinal outcomes

ABBREVIATIONS

ABCL—Adult Behavior Checklist
ASR—Adult Self-Report
BDI—Beck Depression Inventory
BIS—Body Image Scale
CBCL—Child Behavior Checklist
CGAS—Children's Global Assessment Scale
CSH—cross-sex hormones
GD—gender dysphoria
GnRHa—gonadotropin-releasing hormone analogs
GRS—gender reassignment surgery
SHS—Subjective Happiness Scale
STAI—Spielberger's Trait Anxiety Scale
SWLS—Satisfaction With Life Scale
TPI—Spielberger's Trait Anger Scale
UGDS—Utrecht Gender Dysphoria Scale
YSR—Youth Self-Report

Dr de Vries conceptualized the study, clinically assessed the participants, drafted the initial manuscript, and reviewed and revised the manuscript; Dr McGuire conceptualized the study, planned and carried out the analyses, assisted in drafting the initial manuscript, and reviewed and revised the manuscript; Dr Steensma conceptualized the study, coordinated and supervised data collection, and reviewed and revised the manuscript; Dr Wagenaar coordinated and invited participants for assessments and reviewed and revised the manuscript; Drs Doreleijers and Cohen-Kettenis conceptualized the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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(Continued on last page)



Transgender adolescents experience an incongruence between their assigned gender and their experienced gender and may meet the Diagnostic and Statistical Manual of Mental Disorders 5 criteria for gender dysphoria (GD).¹ Fifteen years ago, pubertal delay was introduced as an aid in the treatment of a gender dysphoric adolescent.² Although not without debate, blocking pubertal development has rapidly become more widely available^{3–7} and is now part of the clinical management guidelines for GD.^{8–12}

Gonadotropin-releasing hormone analogs (GnRHa) are a putatively fully reversible¹³ medical intervention intended to relieve distress that gender dysphoric adolescents experience when their secondary sex characteristics develop. A protocol designed by Cohen-Kettenis and Delemarre-van de Waal¹⁴ (sometimes referred to as “the Dutch model”)^{4,7} considers adolescents, after a comprehensive psychological evaluation with many sessions over a longer period of time, eligible for puberty suppression, cross-sex hormones (CSH), and gender reassignment surgery (GRS) at the respective ages of 12, 16, and 18 years when there is a history of GD; no psychosocial problems interfering with assessment or treatment, for example, treatment might be postponed because of continuous moving from 1 institution to another or repeated psychiatric crises; adequate family or other support; and good comprehension of the impact of medical interventions.¹² Puberty suppression is only started after the adolescent actually enters the first stages of puberty (Tanner stages 2–3), because although in most prepubertal children GD will desist, onset of puberty serves as a critical diagnostic stage, because the likelihood that GD will persist into adulthood is much higher in adolescence than in the case of childhood GD.^{15,16}

Despite the apparent usefulness of puberty suppression, there is only limited evidence available about the effective-

ness of this approach. In the first cohort of adolescents who received GnRHa, we demonstrated an improvement in several domains of psychological functioning after, on average, 2 years of puberty suppression while GD remained unchanged.¹⁶ The current study is a longer-term evaluation of the same cohort, on average, 6 years after their initial presentation at the gender identity clinic. This time, we were not only interested in psychological functioning and GD, but added as important outcome measures objective and subjective well-being (often referred to as “quality of life”), that is, the individuals’ social life circumstances and their perceptions of satisfaction with life and happiness.^{17–19} After all, treatment cannot be considered a success if GD resolves without young adults reporting they are healthy, content with their lives, and in a position to make a good start with their adult professional and personal lives.²⁰ Because various studies show that transgender youth may present with psychosocial problems,^{21,22} a clinical approach that includes both medical (puberty suppression) and mental health support (regular sessions, treatment when necessary, see Cohen-Kettenis et al¹²) aims to improve long-term well-being in all respects.

In the present longitudinal study, 3 primary research questions are addressed. Do gender dysphoric youth improve over time with medical intervention consisting of GnRHa, CSH, and GRS? After gender reassignment, how satisfied are young adults with their treatment and how do they evaluate their objective and subjective well-being? Finally, do young people who report relatively greater gains in psychological functioning also report a higher subjective well-being after gender reassignment?

METHODS

Participants and Procedure

Participants included 55 young adults (22 transwomen [natal males who

have a female gender identity] and 33 transmen [natal females who have a male gender identity]) of the first cohort of 70 adolescents who had GD who were prescribed puberty suppression at the Center of Expertise on Gender Dysphoria of the VU University Medical Center and continued with GRS between 2004 and 2011. These adolescents belonged to a group of 196 consecutively referred adolescents between 2000 and 2008, of whom 140 had been considered eligible for medical intervention and 111 were prescribed puberty suppression (see de Vries et al¹⁶). The young adults were invited between 2008 and 2012, when they were at least 1 year past their GRS (vaginoplasty for transwomen, mastectomy and hysterectomy with ovariectomy for transmen; many transmen chose not to undergo a phalloplasty or were on a long waiting list). Nonparticipation ($n = 15$, 11 transwomen and 4 transmen) was attributable to not being 1 year postsurgical yet ($n = 6$), refusal ($n = 2$), failure to return questionnaires ($n = 2$), being medically not eligible (eg, uncontrolled diabetes, morbid obesity) for surgery ($n = 3$), dropping out of care ($n = 1$), and 1 transfemale died after her vaginoplasty owing to a postsurgical necrotizing fasciitis. Between the 55 participants and the 15 nonparticipating individuals, Student’s t tests revealed no significant differences on any of the pretreatment variables. A similar lack of differences was found between the 40 participants who had complete data and the 15 who were missing some data.

Participants were assessed 3 times: pre-treatment (T0, at intake), during treatment (T1, at initiation of CSH), and post-treatment (T2, 1 year after GRS). See Table 1 for age at the different time points. The VU University Medical Center medical ethics committee approved the study, and all participants gave informed consent.

TABLE 1 Age at Different Treatment Milestones and Intelligence by Gender

Variable	All Participants ^a (N = 55)		Transwomen (Natal Males) (N = 22)	Transmen (Natal Females) (N = 33)
Age, y	Mean (SD)	Range	Mean (SD)	Mean (SD)
At assessment PreT	13.6 (1.9)	11.1–17.0	13.6 (1.8)	13.7 (2.0)
At start of GnRHa	14.8 (1.8)	11.5–18.5	14.8 (2.0)	14.9 (1.9)
At start of CSH	16.7 (1.1)	13.9–19.0	16.5 (1.3)	16.8 (1.0)
At GRS	19.2 (0.9)	18.0–21.3	19.6 (0.9)	19.0 (0.8)
At assessment PostT	20.7 (1.0)	19.5–22.8	21.0 (1.1)	20.5 (0.8)
Full-scale intelligence ^b	99.0 (14.3)	70–128	97.8 (14.2)	100.4 (14.3)

PostT, post-treatment; PreT, pre-treatment.

^a Comparisons between those who had complete data (n = 40) and those who had missing data on the CBCL/ABCL (n = 15) reveal no significant differences between the groups in age at any point in the study or in natal sex.^b WISC-R, the WISC-III, or the WAIS-III at first assessment, depending on age and time.^{45–47}

Measures

Time was the predominate independent variable. Other demographic characteristics were incorporated in some models, including, age, natal sex, Full Scale Intelligence, and parent marital status; where significantly different they are reported.

Gender Dysphoria/Body Image

There was 1 indicator measuring GD (Utrecht Gender Dysphoria Scale [UGDS]) and 3 indicators measuring body image (Body Image Scale [BIS] with primary, secondary, and neutral subscales). Higher UGDS (12 items, 1–5 range, total score ranging from 12–60) total scores indicate higher levels of GD, for example, “I feel a continuous desire to be treated as a man/woman.”²³ There are separate versions of the UGDS for males and females with mostly different items, permitting no gender difference analyses. BIS (30 items, 1–5 range) higher scores indicate more dissatisfaction with primary sex characteristics (important gender-defining body characteristics, eg, genitals, breasts), secondary sex characteristics (less obvious gender-defining features, eg, hips, body hair), and neutral (hormonally unresponsive) body characteristics (eg, face, height).²⁴ The male and the female BIS are identical except for the sexual body parts. The UGDS and the BIS of the natal gender were administered at T0 and T1. At T1, we chose the UGDS of the assigned gender, because no physical changes had occurred yet and some were still

treated as their assigned gender. This way, however, decreased GD caused by social transitioning was not measured. At T2 young adults filled out the versions of their affirmed gender.

Psychological Functioning

There were 10 indicators assessing psychological functioning. To assess global functioning, the Children’s Global Assessment Scale (CGAS) was used.²⁵ The Beck Depression Inventory (BDI; 21 items, 0–3 range) indicates presence and severity of depressive symptoms.²⁶ Spielberger’s Trait Anger (TPI) and Spielberger’s Trait Anxiety (STAI; 10 and 20 items, respectively, 1–4 range) scales of the State-Trait Personality Inventory were administered to assess the tendency to respond with anxiety or anger, respectively, to a threatening or annoying situation.^{27,28}

Behavioral and emotional problems were assessed by the total, internalizing, and externalizing T scores as well as clinical range scores for these 3 indices (T score >63) of the Child/Adult Behavior Checklist (CBCL at T0 and T1, ABCL at T2), the Youth/Adult Self-Report (YSR at T0 and T1, ASR at T2).^{29–31} Items referring to GD in the CBCL/YSR and ABCL/ASR were scored as 0 (for more explanation, see Cohen-Kettenis et al³²).

Objective and Subjective Well-Being (T2 Only)

A self-constructed questionnaire was used to ask the young adults about their current life circumstances, such

as living conditions, school and employment, and social support (objective well-being), and satisfaction with treatment (subjective well-being). Three instruments further assessed subjective well-being. To measure quality of life, the WHOQOL-BREF (quality of life measure developed by the World Health Organization) was administered (24 items, 4 domains: Physical Health, Psychological Health, Social Relationships, and Environment, 1–5 range with higher scores indicating better quality of life).¹⁷ The Satisfaction With Life Scale (SWLS, 5 items, 5–35 range, 20 being neutral) was used to assess life satisfaction.¹⁸ Higher scores on the Subjective Happiness Scale (SHS, 4 items, 7-point Likert scale, average score 1–7) reflect greater happiness.¹⁹

Data Analyses

General Linear Models examined the repeated measures with an analysis of variance-based model, incorporating continuous and categorical predictors, and correcting for the unbalanced cell sizes. Linear and quadratic effects of the 14 indicators across 3 time points, with time as the within-subjects factor, and sex as a between-subjects factor in a second set of analyses are reported in Tables 2 and 3 and Fig 1. A linear effect signifies an overall change across T0 to T2. A quadratic effect signifies that the change was not continuous, such as when an indicator does not improve from T0 to T1 but improves from T1 to T2. It is possible to have both a significant linear and quadratic effect on the same

TABLE 2 Gender Dysphoria and Body Image of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)

	N ^a	T0	T1	T2	T0–T2	Time	Time × Sex
		Mean (SD)	Mean (SD)	Mean (SD)	<i>t</i> test <i>P</i>	Linear Effect Quadratic Effect <i>P</i>	Linear Effect Quadratic Effect <i>P</i>
UGDS	33	53.51 (8.29)	54.39 (7.70)	15.81 (2.78)	<.001		
MtF	11	47.07 (11.05)	48.95 (10.80)	17.27 (2.57)	<.001	<.001 <.001	n/a
FtM	22	56.74 (3.74)	57.11 (3.40)	15.08 (2.64)	<.001	<.001 <.001	n/a
Body Image (BIS)							
Primary sex characteristics	45	4.13 (0.59)	4.05 (0.60)	2.59 (0.82)	<.001	<.001 <.001	.01 .45
MtF	17	4.03 (0.68)	3.82 (0.56)	2.07 (0.74)	<.001		
FtM	28	4.18 (0.53)	4.13 (0.60)	2.89 (0.71)	<.001		
Secondary sex characteristics	45	2.73 (0.72)	2.86 (0.67)	2.27 (0.56)	<.001	<.001 <.001	.10 <.001
MtF	17	2.63 (0.60)	2.34 (0.68)	1.93 (0.63)	<.001		
FtM	28	2.80 (0.72)	3.18 (0.43)	2.48 (0.40)	.05		
Neutral body characteristics	45	2.35 (0.68)	2.49 (0.53)	2.23 (0.49)	.29	.29 .01	.007 .01
MtF	17	2.57 (0.70)	2.29 (0.50)	2.09 (0.56)	.014		
FtM	28	2.21 (0.64)	2.61 (0.52)	2.32 (0.44)	.40		

FtM, female to male transgender; MtF, male to female transgender; n/a, not applicable.

^a Participants who had complete data at all 3 waves were included. Some assessments were added to the study later, yielding fewer total participants for those scales.

indicator. Other potential between-subjects factors (age, total IQ, parental marital status) were examined but excluded owing to a lack of relationship with the 14 indicators at T0. The 1 exception, age predicting secondary sex characteristics, is described below in the findings. We compared T2 sample means to population norms for subjective well-being using 1-sample *t* tests from previously published validation studies. Finally, we examined T2 subjective well-being correlations with residual change scores from T0 to T2 on the 14 indicators (an indicator of who improved relatively more or less over time).

All measures used were self-reported, except the CGAS (attending clinician) and the CBCL/ASR (parents). Each participant was given all measures at each of 3 assessments. Numbers varied across indicators owing to the later inclusion of the YSR, CGAS, BDI, TPI, and STAI, yielding 8 persons who had missing data at T0 and a clinician error yielding missing data at T1 for 10 participants on the UGDS. Dutch versions were used (see de Vries et al¹⁶).

RESULTS

Gender Dysphoria and Body Satisfaction

Figure 1 and Table 2 show that GD and body image difficulties persisted through puberty suppression (at T0 and T1) and remitted after the administration of CSH and GRS (at T2) (significant linear effects in 3 of 4 indicators, and significant quadratic effects in all indicators). Time by sex interactions revealed that transwomen reported more satisfaction over time with primary sex characteristics than transmen and a continuous improvement in satisfaction with secondary and neutral sex characteristics. Transmen reported more dissatisfaction with secondary and neutral sex characteristics at T1 than T0, but improvement in both from T1 to T2. Age was a significant covariate with secondary sex characteristics (the only significant demographic covariate with any outcome indicator in the study), indicating that older individuals were more dissatisfied at T0, but the age gap in body satisfaction narrowed over time ($F(1, 42) = 8.18; P < .01$).

Psychological Functioning

As presented in Table 3, significant linear effects showed improvement over time in global functioning (CGAS), CBCL/ABCL total, internalizing and externalizing *T* scores, and YSR/ASR total and internalizing *T* scores. Quadratic effects revealed decreases from T0 to T1 followed by increases from T1 to T2 in depression and YSR/ASR internalizing *T* scores. Quadratic trends revealed decreases from T0 to T1, followed by increases from T1 to T2 in depression and YSR/ASR internalizing *T* scores. For all CBCL/ABCL and YSR/ASR indicators except YSR/ASR externalizing, the percentage in the clinical range dropped significantly (McNemar's test, *P* value <0.05) from T0 to T1, from T0 to T2, or from T1 to T2.

Over time, transmen showed reduced anger, anxiety, and CBCL/ABCL externalizing *T* scores, whereas transwomen showed stable or slightly more symptomatology on these measures. Transwomen improved in CBCL/ABCL total *T* scores in a quadratic fashion (all the improvement between T1 and T2),

TABLE 3 Psychological Functioning of Adolescents at Intake (T0), While on Puberty Suppression (T1), and After Gender Reassignment (T2)

	N ^a	T0	T1	T2	T0–T2	Time		Time × Sex	
						<i>t</i> test	Linear Effect Quadratic Effect	Linear Effect Quadratic Effect	
		Mean (SD)	Mean (SD)	Mean (SD)	<i>P</i>				
Global functioning (CGAS)	32	71.13 (10.46)	74.81 (9.86)	79.94 (11.56)	<.001				
MtF	15	74.33 (7.53)	78.20 (9.56)	82.40 (8.28)	<.001				
FtM	17	67.65 (11.87)	70.65 (9.89)	76.29 (14.48)	.02				
Depression (BDI)	32	7.89 (7.52)	4.10 (6.17)	5.44 (8.40)	.21				
MtF	12	4.73 (4.20)	2.25 (3.54)	3.38 (4.40)	.12				
FtM	20	10.09 (8.34)	5.05 (7.08)	6.95 (9.83)	.32				
Anger (TPI)	32	17.55 (5.72)	17.22 (5.61)	16.01 (5.28)	.20				
MtF	12	14.17 (3.01)	14.00 (3.36)	5.58 (3.92)	.18				
FtM	20	19.55 (5.96)	19.25 (5.69)	16.56 (6.06)	.05				
Anxiety (STAI)	32	39.57 (10.53)	37.52 (9.87)	37.61 (10.39)	.45				
MtF	12	31.87 (7.42)	31.71 (8.36)	35.83 (10.22)	.14				
FtM	20	44.41 (9.06)	41.59 (9.03)	39.20 (10.53)	.12				
CBCL–ABCL									
Total <i>T</i> score	40	60.20 (12.66)	54.70 (11.58)	48.10 (9.30)	<.001				
% Clinical		38 _x	20 _y	5 _y					
MtF	15	57.40 (12.76)	49.67 (12.29)	48.13 (12.58)	.002				
FtM	25	61.88 (12.56)	57.72 (10.23)	48.08 (6.95)	<.001				
Int <i>T</i> score	40	60.83 (12.36)	54.42 (10.58)	50.45 (10.04)	<.001				
% Clinical		30 _x	12.5 _y	10 _y					
MtF	15	59.40 (10.03)	50.93 (11.15)	48.73 (12.61)	<.001				
FtM	25	61.68 (13.70)	56.52 (9.86)	51.48 (8.25)	<.001				
Ext <i>T</i> score	40	57.85 (13.73)	53.85 (12.77)	47.85 (8.59)	<.001				
% Clinical		40 _x	25 _x	2.5 _y					
MtF	15	52.53 (14.11)	47.87 (12.07)	46.33 (10.95)	.10				
FtM	25	61.04 (12.71)	57.44 (12.01)	48.76 (6.89)	<.001				
YSR-ASR									
Total <i>T</i> score	43	54.72 (12.08)	49.16 (11.16)	48.53 (9.46)	.005				
% Clinical		30 _x	14 _{xy}	7 _y					
MtF	17	50.65 (12.19)	45.94 (12.24)	47.24 (12.28)	.28				
FtM	26	57.38 (11.47)	51.27 (10.08)	49.38 (7.21)	.01				
Int <i>T</i> score	43	55.47 (13.08)	48.65 (12.33)	50.07 (11.15)	.03				
% Clinical		30 _x	9.3 _y	11.6 _{xy}					
MtF	17	54.00 (12.31)	47.59 (14.26)	48.12 (12.54)	.04				
FtM	26	56.42 (13.86)	49.35 (11.13)	51.35 (10.19)	.17				
Ext <i>T</i> score	43	52.77 (12.47)	49.44 (9.59)	49.44 (9.37)	.14				
% Clinical		21 _x	11.6 _x	7 _x					
MtF	17	46.00 (11.58)	44.71 (9.53)	50.24 (11.18)	.17				
FtM	26	57.16 (11.14)	52.54 (8.43)	48.92 (8.18)	.006				

FtM, female to male transgender; MtF, male to female transgender.

_{xy} Percent clinical range, shared subscripts indicate no significant difference in values. In no case was an increase in percent in the clinical range significant from 1 time point to any other time point, indicating an overall decline or stability of clinical symptoms over time.

^a Participants who had complete data at all 3 waves were included. Some assessments were added to the study later, yielding fewer total participants for those scales.

whereas transmen improved steadily across the 3 time points (linear effect only).

Objective Well-Being

At T2, the participants were vocationally similar to the Dutch population except they were slightly more likely to live with parents (67% vs 63%), and more likely,

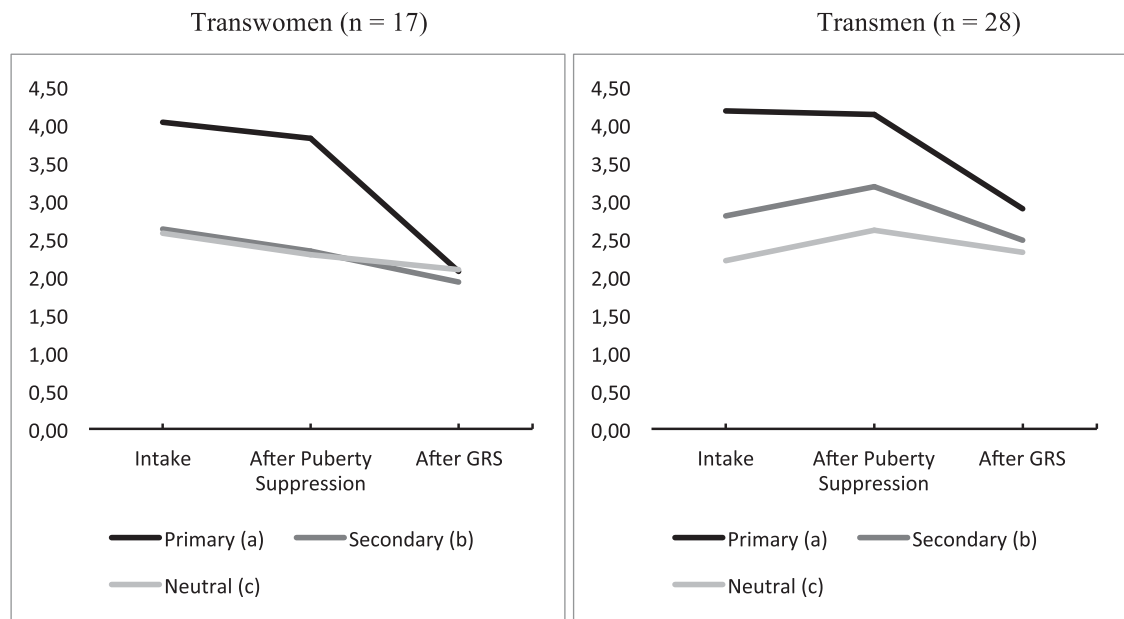
when studying, to be pursuing higher education (58% vs 31%).³³

Families were supportive of the transitioning process: 95% of mothers, 80% of fathers, and 87% of siblings. Most (79%) young adults reported having 3 or more friends, were satisfied with their male (82%) and female peers (88%), and almost all (95%) had received support

from friends regarding their gender reassignment. After their GRS, many participants (89%) reported having been never or seldom called names or harassed. The majority (71%) had experienced social transitioning as easy.

Subjective Well-Being

None of the participants reported regret during puberty suppression, GSH



Eta Squared for Linear and Quadratic Effects

- (a) Primary sex characteristics
Time: .79 ($P < .001$), .66 ($P < .001$),
Time $\times$ sex: .14 ($P = .01$), .01 ($P = .45$),
- (b) Secondary sex characteristics
Time: .31 ($P < .001$), .30 ($P < .001$),
Time $\times$ sex: .06 ($P = .10$), .22 ($P < .001$)
- (c) Neutral body characteristics
Time: .07 ($P < .001$), .09 ($P = .29$)
Time $\times$ sex: .16 ($P = .007$), .15 ($P = .01$)

FIGURE 1

BIS²³ for transwomen and transmen at T0 (pretreatment, at intake), T1 (during treatment, at initiation of cross-gender hormones), and T2 (post-treatment, 1 year after GRS).

treatment, or after GRS. Satisfaction with appearance in the new gender was high, and at T2 no one reported being treated by others as someone of their assigned gender. All young adults reported they were very or fairly satisfied with their surgeries.

Mean scores on WHOQOL-BREF, the SWLS, and the SHS are presented in Table 4, together with scores from large validation and reliability studies of these measures,^{17,19,34} revealing similar scores in all areas except WHOQOL-Environment subdomain, which was higher for the participants than the norm. There were some differences across gender; transwomen scored higher than transmen on the SWLS (mean = 27.7; SD = 5.0 vs mean = 23.2; SD = 6.0; t (52)

= 2.82; $P < .01$) and on the psychological subdomain of the WHOQOL (mean = 15.77; SD = 2.0 vs mean = 13.92; SD = 2.5; t (53) = 2.95; $P < .01$).

Correlations With Residual Change Scores

The residual change scores of secondary sex characteristics, global functioning, depression, anger, anxiety, and YSR total, internalizing and externalizing from T0 to T2, were significantly correlated with the 6 T2 quality of life indicators. Most correlation coefficients were within the moderate to large magnitude (eg, 0.30–0.60), except depression, which was highly correlated (0.60–0.80) (see Table 5).

DISCUSSION

Results of this first long-term evaluation of puberty suppression among transgender adolescents after CSH treatment and GRS indicate that not only was GD resolved, but well-being was in many respects comparable to peers.

The effectiveness of CSH and GRS for the treatment of GD in adolescents is in line with findings in adult transsexuals.^{35,36} Whereas some studies show that poor surgical results are a determinant of postoperative psychopathology and of dissatisfaction and regret,^{37,38} all young adults in this study were generally satisfied with their physical appearance and none regretted treatment. Puberty suppression had caused their bodies to

TABLE 4 Subjective Well-Being: Quality of Life, Satisfaction With Life, and Subjective Happiness Mean Scores With Scores From Validation Studies

	<i>N</i>	Mean (SD)	Range	Validation Studies Scores Mean (SD)	Comparison <i>P</i>
WHOQOL ^a Physical	55	15.22 (2.49)	8.6–20.0	15.0 (2.9) ^b	.56
WHOQOL Psychological	55	14.66 (2.44)	6.67–20.0	14.3 (2.8) ^b	.24
WHOQOL Social Relations	55	14.91 (2.35)	9.3–20.00	14.5 (3.4) ^b	.18
WHOQOL Environment	55	15.47 (2.06)	10.5–20.00	13.7 (2.6) ^b	<.001
SWLS	54	24.98 (6.0)	9.0–35.0	26.18 (5.7) ^c	.16
SHS	54	4.73 (0.77)	2.75–6.0	4.89 (1.1) ^d	.17

^a WHOQOL, Bref, Skevington et al.¹⁶^b International field trial, ages 21 to 30 years, Skevington et al.¹⁶^c Dutch young adults, Arindell et al.³³^d US Public College Students, Lyubomirsky.¹⁸

not (further) develop contrary to their experienced gender.

Psychological functioning improved steadily over time, resulting in rates of clinical problems that are indistinguishable from general population samples (eg, percent in the clinical range dropped from 30% to 7% on the YSR/ASR³⁰) and quality of life, satisfaction with life, and subjective happiness comparable to same-age peers.^{17,19,34} Apparently the clinical protocol of a multidisciplinary team with mental health professionals, physicians, and surgeons gave these formerly gender dysphoric youth the opportunity to develop into well-functioning young adults. These individuals, of whom an even higher percentage than the general population were pursuing higher education, seem different from the

transgender youth in community samples with high rates of mental health disorders, suicidality and self-harming behavior, and poor access to health services.^{21,22,39,40}

In this study, young adults who experienced relatively greater improvements in psychological functioning were more likely to also report higher levels of subjective postsurgical well-being. This finding suggests value to the protocol that involves monitoring the adolescents' functioning, physically and psychologically, over many years, and providing more support whenever necessary.

This clinic-referred sample perceived the Environmental subdomain (with items like "access to health and social care" and "physical safety and secu-

rity") of the WHOQOL-BREF as even better than the Dutch standardization sample.¹⁷ Whereas in some other contexts transgender youth may experience gender-related abuse and victimization,^{22,41,42} the positive results may also be attributable to supportive parents, open-minded peers, and the social and financial support (treatment is covered by health insurance) that gender dysphoric individuals can receive in the Netherlands.

Both genders benefitted from the clinical approach, although transwomen showed more improvement in body image satisfaction (secondary sex characteristics) and in psychological functioning (anger and anxiety). None of the transmen in this study had yet had a phalloplasty because of waiting lists or

TABLE 5 Correlations Between Residual Change in Psychological Functioning Over Time and Young Adult Subjective Well-Being

	WHOQOL BREF					
	Physical	Psychological	Social	Environment	SWLS	SHS
Gender dysphoria (UGDS)	0.01 (.97)	0.05 (.75)	−0.09 (.57)	−0.02 (.89)	0.06 (.71)	0.30 (.04)
Body image subscales (BIS)						
Primary sex characteristics	−0.22 (.14)	−0.25 (.09)	−0.35 (.02)	−0.04 (.78)	−0.22 (.14)	−0.21 (.17)
Secondary sex characteristics	−0.39 (.006)	−0.45 (<.001)	−0.47 (<.001)	−0.34 (.02)	−0.35 (.02)	−0.26 (.08)
Neutral body characteristics	−0.21 (.16)	−0.27 (.07)	−0.15 (.32)	−0.28 (.06)	−0.26 (.08)	−0.16 (.28)
Psychological functioning						
Global functioning (CGAS)	0.60 (<.001)	0.52 (.002)	0.52 (.002)	0.27 (.14)	0.58 (<.001)	0.50 (.004)
Depression (BDI)	−0.76 (<.001)	−0.72 (<.001)	−0.51 (.002)	−0.49 (.003)	−0.61 (<.001)	−0.77 (<.001)
Trait anger (TPI)	−0.37 (.03)	−0.18 (.31)	−0.22 (.20)	−0.29 (.09)	−0.33 (.07)	−0.35 (.05)
Trait anxiety (STAI)	−0.58 (<.001)	−0.64 (<.001)	−0.38 (.03)	−0.44 (.01)	−0.49 (.004)	−0.57 (<.001)
CBCL–ABCL						
Total <i>T</i> score	−0.20 (.20)	−0.12 (.45)	−0.07 (.65)	−0.14 (.35)	−0.32 (.03)	−0.16 (.29)
Internalizing <i>T</i> score	−0.29 (.06)	−0.29 (.06)	−0.23 (.14)	−0.12 (.44)	−0.48 (<.001)	−0.36 (.02)
Externalizing <i>T</i> score	−0.13 (.40)	−0.05 (.75)	0.16 (.29)	−0.20 (.19)	−0.15 (.36)	0.00 (.99)
Youth Self Report (YSR–ASR)						
Total <i>T</i> score	−0.53 (<.001)	−0.45 (.002)	−0.33 (.03)	−0.42 (.005)	−0.52 (<.001)	−0.55 (<.001)
Internalizing <i>T</i> score	−0.62 (<.001)	−0.61 (<.001)	−0.47 (<.001)	−0.40 (.007)	−0.66 (<.001)	−0.60 (<.001)
Externalizing <i>T</i> score	−0.23 (.13)	−0.10 (.53)	−0.07 (.67)	−0.37 (.02)	−0.22 (.15)	−0.35 (.02)

P values are in parentheses.

a desire for improved surgery techniques. This finding warrants further study of the specific concerns of young transmen.

Despite promising findings, there were various limitations. First, the study sample was small and came from only 1 clinic. Second, this study did not focus on physical side effects of treatment. Publications on physical parameters of the same cohort of adolescents are submitted or in preparation. A concurring finding exists in the 22-year follow-up of the well-functioning first case now at age 35 years who has no clinical signs of a negative impact of earlier puberty suppression on brain development, metabolic and endocrine parameters, or bone mineral density.⁴³ Third, despite the absence of pretreatment differences on measured indicators, a selection bias could exist between adolescents of the original cohort that participated in this study compared with nonparticipants.

Age criteria for puberty suppression and CSH are under debate, although they worked well for adolescents in the current study. Especially in natal females, puberty will often start before the age of 12 years. Despite the fact that developing evidence suggests that cognitive and affective cross-gender identification, social role transition, and age at assessment are related to persistence of childhood GD into adolescence, predicting individual persistence at a young age will always remain difficult.⁴⁴ The age criterion of 16 years for the start of CSH may be problematic especially for transwomen, as growth in height continues as long as cross-sex steroids are not provided (causing the growth plates to close). Therefore, psychological maturity and the capacity to give full informed consent may surface as the required criteria for puberty suppression and CSH⁴⁵ in cases that meet other eligibility criteria.

CONCLUSIONS

Results of this study provide first evidence that, after CSH and GRS, a treatment protocol including puberty suppression leads to improved psychological functioning of transgender adolescents. While enabling them to make important age-appropriate developmental transitions, it contributes to a satisfactory objective and subjective well-being in young adulthood. Clinicians should realize that it is not only early medical intervention that determines this success, but also a comprehensive multidisciplinary approach that attends to the adolescents' GD as well as their further well-being and a supportive environment.

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ORIGINAL RESEARCH

Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria

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ABSTRACT

Introduction. Puberty suppression by gonadotropin-releasing hormone analogs (GnRHa) is prescribed to relieve the distress associated with pubertal development in adolescents with gender dysphoria (GD) and thereby to provide space for further exploration. However, there are limited longitudinal studies on puberty suppression outcome in GD. Also, studies on the effects of psychological support on its own on GD adolescents' well-being have not been reported.

Aim. This study aimed to assess GD adolescents' global functioning after psychological support and puberty suppression.

Methods. Two hundred one GD adolescents were included in this study. In a longitudinal design we evaluated adolescents' global functioning every 6 months from the first visit.

Main Outcome Measures. All adolescents completed the Utrecht Gender Dysphoria Scale (UGDS), a self-report measure of GD-related discomfort. We used the Children's Global Assessment Scale (CGAS) to assess the psychosocial functioning of adolescents.

Results. At baseline, GD adolescents showed poor functioning with a CGAS mean score of 57.7 ± 12.3 . GD adolescents' global functioning improved significantly after 6 months of psychological support (CGAS mean score: 60.7 ± 12.5 ; $P < 0.001$). Moreover, GD adolescents receiving also puberty suppression had significantly better psychosocial functioning after 12 months of GnRHa (67.4 ± 13.9) compared with when they had received only psychological support (60.9 ± 12.2 , $P = 0.001$).

Conclusion. Psychological support and puberty suppression were both associated with an improved global psychosocial functioning in GD adolescents. Both these interventions may be considered effective in the clinical management of psychosocial functioning difficulties in GD adolescents. **Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. J Sex Med 2015;12:2206–2214.**

Key Words. Gender Dysphoria; Adolescents; Psychosocial Functioning; Puberty Suppression

¹Joint last authors.

The study was conducted in the Gender Identity Development Service, Tavistock and Portman NHS Foundation Trust, Tavistock Centre, 120 Belsize Lane, London NW3 5BA.

Introduction

Gender dysphoria (GD) individuals experience a marked incongruence between their assigned gender and their experienced gender [1]. GD refers to this stressful condition resulting in clinically significant distress or impairment in

important areas of functioning [2,3]. When supporting and treating children and adolescents with GD, health professionals should broadly conform to the Standards of Care of the World Professional Association for Transgender Health (WPATH) [4]. These guidelines indicate that psychological support should focus on exploring gender identity, role, and expression; addressing the negative impact of GD and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; promoting resilience. Psychological interventions such as individual, couple, family, or group therapy should be provided within a multidisciplinary gender identity specialty service [4].

Studies indicate that cross-sex hormonal treatment (CSHT) improves well-being in GD adults [5,6]. However, it has been observed that despite many years of psychotherapy the GD of most adolescents does not often abate. Rather, once these young persons, who are already experiencing considerable distress over their gender identity, undergo the pubertal development of their biological sex, their psychological well-being deteriorates significantly [7]. Because this risk can be so great, the need for an early intervention has become paramount.

Delemarre-van de Waal and Cohen-Kettenis have proposed an early intervention approach, the Dutch model [8], which aims to eliminate the exposure to unwanted pubertal hormones, limit GD, and improve the ability to “pass” as the desired gender in adulthood. It considers adolescents, after a comprehensive psychological evaluation with many sessions over a longer period of time, eligible for puberty suppression, cross-sex hormonal treatment (CSHT), and gender reassignment surgery (GRS) at the respective ages of 12, 16, and 18 years when there is a history of GD; no psychosocial problems interfering with assessment or treatment; adequate family or other support; and good comprehension of the impact of medical interventions. According to this protocol, suppressing puberty and allowing young individuals the opportunity to explore their gender identity would provide some relief from the distress associated with the development of secondary characteristics [8]. Consistently, some studies indicate that puberty suppression leads to a better psychosocial outcome [2,9].

Since the release of the Dutch model, there has been disagreement about the appropriateness of treatment in minors. Some practitioners have questioned the ethics and safety of this intervention.

Conversely, other health care professionals have argued they have an obligation to alleviate suffering and it would be unethical to allow a patient to suffer through the distress of pubertal development when there is a way of preventing it [10]. Anyway, puberty suppression by gonadotropin-releasing hormone analogs (GnRHa) has increasingly become accepted in clinical management of adolescents with GD. Even if further studies are needed, GnRHa are considered a safe and putatively reversible intervention which should be provided to people in need of it, especially if allowing puberty to progress appears likely to harm the young person [7].

There are limited longitudinal studies on the psychosocial functioning of GD adolescents after puberty suppression [2,9]. Also, studies on the effects of psychological support on its own on GD adolescents’ psychosocial functioning have not been reported.

Aims

The aim of this study was to assess GD adolescents’ psychosocial functioning in follow-up evaluations. Based on previous literature [2,9] and our clinical experience, we hypothesized a poor general functioning at baseline, an improvement after psychological support, and a further improvement after the beginning of the GnRHa.

Methods

Study Design and Participants

This longitudinal study was conducted at the Gender Identity Development Service (GIDS) in London. The health care pathway provided at the GIDS is described in Figure 1. A consecutive series of 436 adolescents (mean age = 15.74 ± 1.38 years; natal male/natal female ratio = 1:1.7) were referred between 2010 and 2014 to the GIDS. 201 adolescents (mean age = 15.52 ± 1.41 years; natal male/natal female ratio = 1:1.6) completed the diagnostic procedure (about 6 months) and were invited to take part in the follow-up evaluations. No GD adolescent refused to participate and all participants and their parents gave informed consent. By clinical interview, all adolescents fulfilled DSM-IV-TR criteria in use at the time for Gender Identity Disorder. The GIDS has adopted the WPATH Standards of Care [4]. There were no significant differences in socio-demographic characteristics as well as baseline CGAS scores

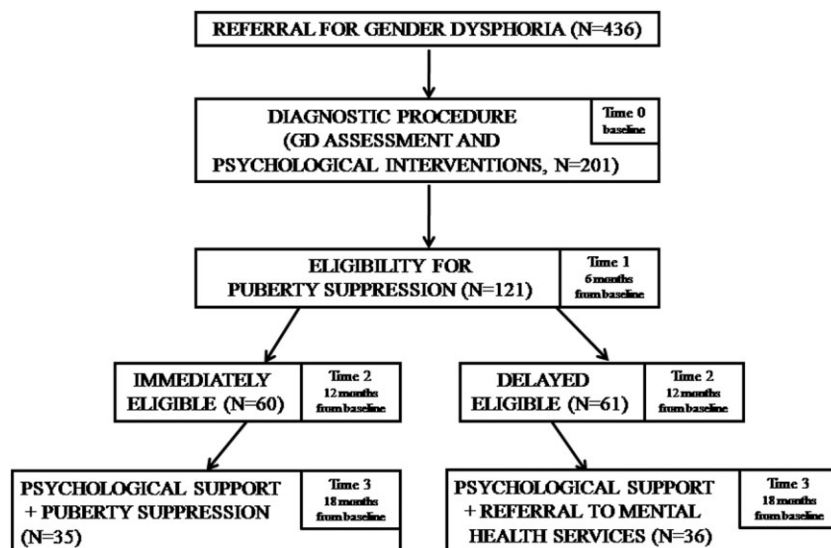


Figure 1 Health care pathway at the Gender Identity Development Service (GIDS)

between adolescents with a GD diagnosis enrolled in this study ($N = 201$) and adolescents who did not complete the diagnostic procedure ($N = 235$; all $P > 0.1$).

Psychological Support

The GIDS has developed a standardized psychological assessment which is part of the diagnostic procedure, in accordance with the WPATH guidelines [4]. This model emphasizes the early recognition and non-judgmental acceptance of gender identity problems as well as the importance of ameliorating associated behavioral, emotional and relationship difficulties [11]. Ample room is given to adolescents to explore different options for gender expression. Together with their families GD adolescents are supported in making difficult decisions regarding the extent to which they are allowed to express a gender role that is consistent with their gender identity. Also the timing of changes in gender role and possible social transition are extensively explored. This ensures that decisions about gender expression and the treatment of GD are thoughtfully and recurrently considered. Health care professionals help families to make decisions regarding the timing and process of any gender role changes for their young children. Information is provided to parents to weigh the potential benefits and challenges of choices.

The aims outlined are achieved through various psychotherapeutic interventions, ranging from individual to family and group therapy, which are carried out on a regular basis (at least once a month). Social and educational interventions are

also provided if necessary. All these interventions are well coordinated and integrated in a comprehensive management plan agreed with local services (The Network Model). Moreover, the care pathway provides continuous psychological support to the patients' emotional and behavioral changes that may occur during the puberty suppression treatment. All adolescents received psychological support for the entire duration of the study.

Eligibility for Puberty Suppression

In accordance with the WPATH Standards of Care [4], adolescents were able to commence puberty suppression with GnRHa if they met the following criteria: (i) a presence of GD from early childhood on; (ii) an increase of the GD after the first pubertal changes; (iii) an absence of psychiatric comorbidity that interferes with the diagnostic work-up or treatment; (iv) adequate psychological and social support during treatment; and (v) a demonstration of knowledge and understanding of the effects of GnRHa, cross-sex hormone treatment, surgery, and the social consequences of sex reassignment. All GD adolescents were considered eligible for puberty suppression. Eligible adolescents were divided into two groups: immediately eligible and delayed eligible adolescents, consistently with Cohen-Kettenis and colleagues [12]. Immediately eligible adolescents started GnRHa at the end of the diagnostic procedure (0.75 ± 0.59 years from baseline). On the contrary, some adolescents were considered delayed eligible and continued to receive psychological support without

any type of physical intervention until they felt ready to make a decision in collaboration with their families and the clinicians. In those specific cases clinicians needed more time to make the decision of starting GnRHa because of possible comorbid psychiatric problems and/or psychological difficulties. If concomitant problems were observed (e.g., psychiatric problems, substantial problems with peers, or conflicts with parents or siblings), the young person was referred to a local mental health service. All possible medical and/or psychosocial interventions were well coordinated, integrated in a comprehensive management plan agreed with local services, and tended to be individualized in relation to the psychopathology/difficulty. The primary aim was for the child and the family to function better. After being assessed and, if necessary, treated for a psychiatric comorbidity, all delayed eligible GD individuals received puberty suppression. The interval from the start of the diagnostic procedure to the start of puberty suppression took about 1.5 years (1.5 ± 0.63 years from baseline). None of the delayed eligible individuals received puberty suppression at the time of this study.

Main Outcome Measures

Socio-Demographic Information

The data collected included: natal gender (male–female ratio), age (at assessment, at start of GnRHa), education level (yes/no), living arrangement (both parents, one parents, other), living in the chosen gender (partly, i.e., by wearing clothing and having a hairstyle that reflects gender identity/completely, i.e., by also using a name and pronouns congruent with gender identity/no), and change of name (yes/no).

GD-Related Discomfort

The Utrecht GD Scale (UGDS) was used to measure adolescents' GD-related discomfort. This is a 12-item questionnaire specifically developed to measure GD in a dimensional way. In particular, the UGDS focuses on core aspects of GD and gender identity. The adolescents are asked to rate their agreement on a 5-point scale. The total score ranges from 12 to 60. Higher UGDS total scores indicate high level of GD [13]. The scale has shown a high reliability (a Cronbach's alpha of 0.66–0.80 in one sample, and 0.78–0.92 in another); as reported by the authors, the lower alphas on the scale were only found among control

subjects, which may be related to the lower variability of GD in these groups [13]. Cronbach's alpha for UGDS in our sample was 0.76–0.88. The UGDS has also shown a good discriminant validity, when adolescents and adults with and without a GD diagnosis were compared.

Measure of Global Psychosocial Functioning

The Children's Global Assessment Scale (CGAS) was used to assess adolescents' psychosocial functioning. The CGAS is one of the most widely used rating scales designed to measure how children and adolescents function psychosocially in daily life [14]. This clinical-rated instrument is divided into 10-point intervals and ranges from 1 to 100, with higher scores indicating better psychosocial functioning. The CGAS is useful to assess psychosocial/psychiatric outcomes, socio-cognitive competence and changes because of treatment [15]. In particular, it has been used in several longitudinal and epidemiological studies in clinical and non-clinical populations, naturalistic cohorts [16], and young GD individuals [9]. The inter-rater reliability was tested by Shaffer and his colleagues [14] before publication of CGAS, in order to minimize variation because of clinician background. Test–retest has been described in different studies with raters' consistence over time [16].

All CGAS were administered by qualified psychologists, psychotherapists, and psychiatrists who attended training and intra-class correlation assessment ($0.76 \leq \text{Cronbach's } \alpha \leq 0.94$). Participants were assessed at baseline (Time 0) and every following 6 months, for a total of four evaluations over an 18-month period. Follow-up evaluations were performed 6 months from the baseline (Time 1: after 6 months of psychological support); 12 months from the baseline (Time 2: after 12 months of psychological support for delayed eligible GD adolescents, and after 12 months of psychological support + 6 months of puberty suppression for immediately eligible GD adolescents); 18 months from the baseline (Time 3: after 18 months of psychological support for delayed eligible GD adolescents, and after 18 months of psychological support + 12 months of puberty suppression for immediately eligible GD adolescents).

Participants were compared with a sample of young individuals without observed psychological/psychiatric symptoms ($N = 169$), using the same methodology of this study, the CGAS scale [16]. This sample was part of a large naturalistic cohort

of children/adolescents who attended child and adolescent mental health services (CAMHS; N = 12,613) in Stockholm in order to be evaluated for their psychosocial functioning.

Statistical Analysis

Chi-squared and independent *t*-tests were used to test for possible differences in socio-demographic characteristics and CGAS scores between natal men and natal women; adolescents who did not complete the diagnostic procedure and adolescents who received a GD diagnosis; immediately eligible and delayed eligible individuals. Dependent and independent *t*-tests were used to test for possible differences in CGAS scores between baseline and follow-up evaluations, in both immediately eligible and delayed eligible individuals.

Finally, independent *t*-tests were used to compare GD adolescents' CGAS scores with CGAS scores from a sample of children/adolescents without observed psychological/psychiatric symptoms [16].

Ethics

The study received ethical approval from the National Research Ethics Service (NRES) Committee London-Camden and Islington.

Results

Socio-Demographic Characteristics of the Sample

Socio-demographic characteristics of the sample (N = 201) are reported in Table 1. The majority of GD adolescents were living with one parent, were in education, were living as a member of the desired gender, and had changed their names. However, compared with natal women, a higher proportion of natal men did not live with their biological parents, had left school, were not living as a member of the desired gender, and had not changed their names. Moreover, natal women reported a significantly higher GD-related discomfort than natal men. Natal men and women did not differ in their age, both at assessment and when GnRHa was started (Table 1).

Table 1 General characteristics of 201 adolescents with gender dysphoria

	All participants	Natal men	Natal women	Statistical comparisons <i>t</i> -test; <i>P</i> value
Age in years, M (SD)				
Baseline	15.52 (1.41)	15.61 (1.70)	15.46 (1.22)	0.73; 0.47
Range	12–17	12–17	12–17	
At start of GnRHa	16.48 (1.26)	16.64 (1.22)	16.39 (1.28)	0.74; 0.46
Range	13–17	13–17	13–17	
Living arrangement, N (%)				χ^2 ; <i>P</i>
Both parents	78 (41.5)	25 (33.7)	53 (44.2)	8.95; 0.01
One parent	100 (53.2)	35 (51.5)	65 (54.2)	
Other*	10 (5.3)	8 (11.8)	2 (1.6)	
No details	13	8	5	3.47; 0.06
Education				
Yes	168 (89.8)	56 (83.6)	112 (93.3)	20.52; <0.001
No	19 (10.2)	11 (16.4)	8 (6.7)	
No details	14	9	5	
Living in role				
Completely	117 (62.6)	29 (42.6)	88 (73.9)	23.14; <0.001
Partly	27 (14.4)	12 (17.7)	15 (12.6)	
No	43 (23.0)	27 (39.7)	16 (13.5)	
No details	14	8	6	
Change name				
Yes	107 (57.5)	23 (33.8)	84 (71.2)	
No	79 (42.5)	45 (66.2)	34 (28.8)	
No details	15	8	7	
	Mean (SD)	Mean (SD)	Mean (SD)	<i>t</i> -test; <i>P</i> value
UGDS†	54.7 (6.8)	51.6 (9.7)	56.1 (4.3)	4.07; <0.001
CGAS at baseline	57.7 (12.3)	55.4 (12.7)	59.2 (11.8)	2.15; 0.03

*Living in children's home, living with other family's members

†Data available in 160 individuals, 50 natal men (31.25%), 110 natal women (68.75%)

M (SD) = mean (standard deviation); UGDS = Utrecht Gender Dysphoria Scale; CGAS = Children's Global Assessment Scale; GnRHa = gonadotropin-releasing hormone analogs

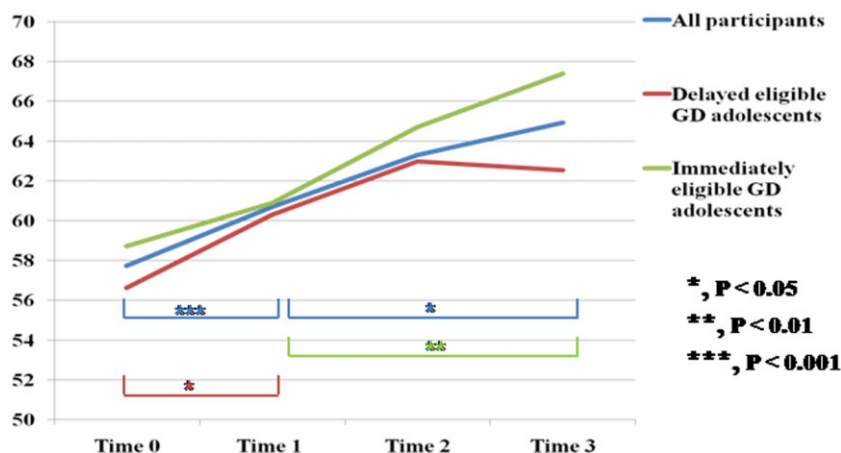


Figure 2 Gender dysphoria adolescents' psychosocial functioning (CGAS) at baseline, after psychological support, and after puberty suppression

CGAS, Children's Global Assessment Scale; Time 0, baseline; Time 1, 6 months from baseline (after 6 months of psychological support); Time 2, 12 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression); Time 3, 18 months from baseline (delayed eligible GD adolescents, after 18 months of psychological support; immediately eligible GD adolescents, after 18 months of psychological support + 12 months of puberty suppression)

CGAS at Baseline

GD adolescents' CGAS at baseline (Time 0, $M = 57.7 \pm 12.3$) revealed a score suggestive of "variable functioning with sporadic difficulties or symptoms in several but not all social areas" (range 50–59). Natal men had a significantly lower functioning than natal women at baseline ($P = 0.03$; Table 1). CGAS scores were not associated with any demographic variable, in both natal men and women (all $P > 0.1$). GD adolescents' CGAS scores at baseline were significantly lower ($t = 7.4$, $P < 0.001$) than that found in a sample of children/adolescents without observed psychological/psychiatric symptoms ($N = 169$, 67.1 ± 12) [16].

CGAS at Follow-Up

Compared with baseline, GD adolescents' psychosocial functioning was increasingly higher at each of the following evaluations (Figure 2). In particular, CGAS scores were significantly higher after 6 months of psychological support (Time 0 vs. Time 1, $P < 0.001$). Also there was a further significant improvement 18 months from baseline (Time 1 vs. Time 3, $P = 0.02$; Table 2).

Delayed eligible GD adolescents, who received only psychological support for the entire duration of the study, had a significantly better psychosocial functioning after six months of psychological support (Time 0 vs. Time 1, $P = 0.05$). However,

despite scoring better at the following evaluations they did not show any further significant improvement in their psychosocial functioning (Table 2). Also, the delayed eligible group continued to score lower than a sample of children/adolescents without observed psychological/psychiatric symptoms [16], even after 18 months of psychological support (Time 3, $t = 2.0$, $P = 0.04$).

On the contrary, the immediately eligible group, who at baseline had a higher, but not significantly different psychosocial functioning than the delayed eligible group, did not show any significant improvement after 6 months of psychological support. However, immediately eligible adolescents had a significantly higher psychosocial functioning after 12 months of puberty suppression compared with when they had received only psychological support (Time 1 vs. Time 3 $P = 0.001$; Table 2). Also, their CGAS scores after 12 months of puberty suppression (Time 3) coincided almost perfectly with those found in a sample of children/adolescents without observed psychological/psychiatric symptoms ($t = 0.01$, $P = 0.99$) [16].

There were no significant differences in CGAS scores between GD natal men and women in all the follow-up evaluations (all $P > 0.1$). Also delayed eligible and immediately eligible GD adolescents did not differ in their demographic variables (all $P > 0.1$). Finally, even if at the end of the

Table 2 Gender dysphoria adolescents' psychosocial functioning (CGAS) at baseline, after psychological support, and after puberty suppression

	Time 0	Time 1	Time 2	Time 3	Statistical comparisons
	N	N	N	N	
	M/F ratio	M/F ratio	M/F ratio	M/F ratio	
	M (SD)	M (SD)	M (SD)	M (SD)	t-test; P value
All participants	N = 201 1:1.6 57.73 (12.27)	N = 201 1:1.6 60.68 (12.47)	N = 121 1:1.6 63.31 (14.41)	N = 71 1:1.6 64.93 (13.85)	4.87*; <0.001 3.70†; <0.001 4.11‡; <0.001 1.73§; 0.08 2.40¶; 0.02 0.76**; 0.45
Delayed eligible GD adolescents	N = 100 1:1.6 56.63 (13.14)	N = 100 1:1.6 60.29 (12.81)	N = 61 1:1.6 62.97 (14.10)	N = 36 1:1.6 62.53 (13.54)	1.99*; 0.05 2.89†; 0.005 2.29‡; 0.02 1.24§; 0.22 0.89¶; 0.37 0.15**; 0.88
Immediately eligible GD adolescents	N = 101 1:1.7 58.72 (11.38)	N = 101 1:1.7 60.89 (12.17)	N = 60 1:1.7 64.70 (13.34)	N = 35 1:1.7 67.40 (13.93)	1.31*; 0.19 3.02†; 0.003 3.66‡; <0.001 1.85§; 0.07 2.63¶; 0.001 0.94**; 0.35
Statistical comparisons t-test; P value	1.21††; 0.23	0.34††; 0.73	0.69†; 0.49	1.49†; 0.14	

*Comparison between baseline and Time 1

†Comparison between baseline and Time 2

‡Comparison between baseline and Time 3

§Comparison between Time 1 and Time 2

¶Comparison between Time 1 and Time 3

**Comparison between Time 2 and Time 3

††Comparison between delayed eligible GD adolescents and immediately eligible GD adolescents

CGAS = Children's Global Assessment Scale; M/F = natal male/natal female; M (SD) = mean (standard deviation)

follow-up study (Time 3) the immediately eligible group had a 5-point higher CGAS score than the delayed eligible group, this difference failed to reach significance, possible because of sample size (Table 2).

Discussion

Results from this study indicate that psychological support is associated with a better psychosocial functioning in GD adolescents, especially if presenting psychological/psychiatric problems. Moreover, puberty suppression was associated with a further improvement in global functioning. Finally, global functioning improved steadily over time in GD adolescents receiving both psychological support and GnRHa.

Medical and surgical interventions are considered to be necessary components of effective management in GD adults. These partially reversible/irreversible treatments aim to align the individuals' physical appearance with their internal gender identity and have been shown to improve the patients' psychosocial well-being [3,5,6]. GD ado-

lescents may experience psychosocial problems at puberty onset because of an intensification of feelings of incongruence between self-perception and their natal gender [2,9]. Therefore, in the pre-pubertal population, the suppression of puberty using continuous GnRHa is a fully reversible treatment which has the fundamental benefit for children of gaining time to reflect over their gender identity, have a real-life experience living as the other gender (i.e., in dress and behavior) and determine whether or not they desire the transition [12,13]. Preventing the development of a body contrary to the experienced gender, puberty suppression allows GD adolescents to experience a smooth transition into their desired gender role. This translates into an improvement in many aspects of their psychosocial functioning, such as mood improvement and school integration [2,9]. Consistently, these results underline the importance of puberty suppression for GD adolescents' well-being.

The GD adolescents' improved global functioning after only 6 months of psychological support may have different explanations. First, it

could indicate that the timely addressing of psychosocial problems contributes to enhanced psychological well-being. Second, as also reported in previous studies among both GD adults and adolescents [2,3,5,9], our clinical experience suggests that patients attending a gender unit are pleased in the knowledge that the puberty suppression will be performed within a reasonable time and refer a distress reduction because of their accepted and understood requirements. Moreover, the initiation of the puberty suppression may have a psychological meaning which *per se* could be fundamental in reducing distress. In any case, data are too limited to express conclusively.

Both natal men and women benefited from the clinical approach, although natal men had a significantly worse functioning than natal women at baseline. It is even more important if we consider that natal men reported more social difficulties than natal women (higher dropout from school and more frequently not living with their parents). Interestingly, natal women reported significantly more GD-related discomfort than natal men. As already suggested [2], with a mean of 15 years most natal women had developed their breasts and had their menarche, which are likely to be associated with higher levels of distress. Therefore, natal men and women may need to be thought about separately and may require different interventions. Also, as the revised Dutch model [8] encourages considering GD individuals eligible for puberty suppression when they are 12 years old, studies are ongoing at our service to explore the possible benefit of further reducing the age for being eligible for puberty suppression. Even if the absence of a control group in our study does not allow us to pronounce conclusively on these comparisons, GD adolescents undergoing puberty suppression in addition to the psychological support result in psychosocial functioning levels that are impossible to differentiate from a sample of peers. These additional findings further indicate the effectiveness of both psychological support and puberty suppression in enabling young GD individuals to reach a satisfactory psychosocial functioning.

In the present study, there are some limitations. Even if psychosocial functioning is of crucial importance to identify clinical or socio-cognitive difficulties [17], we focused only on a measure of psychosocial well-being. Also, the study sample was relatively small and came from only one clinic. Most importantly, despite the findings seem to suggest a cumulative and

increasing over time positive effect of psychological support and GnRHa on young GD patients' well-being, results could have also different explanations because of the study design. For instance, getting older has been positively associated with maturity and well-being [18]. Ideally, a blinded randomized controlled trial design should have been performed. However, it is highly unlikely that adolescents would be motivated to participate. Also, disallowing puberty suppression, resulting in irreversible development of secondary sex characteristics, may be considered unethical [2]. Moreover, we cannot be conclusive on the higher GD-related distress in natal women compared with natal men. There are different versions of the UGDS scale for men and women, with specific items reversely coded because of gender. These differences do not allow drawing strong conclusions from the gender difference analysis.

Conclusions

In conclusion, this study confirms the effectiveness of puberty suppression for GD adolescents. Recently, a long-term follow-up evaluation of puberty suppression among GD adolescents after CSHT and GRS has demonstrated that GD adolescents are able to maintain a good functioning into their adult years [2]. The present study, together with this previous research [2], indicate that both psychological support and puberty suppression enable young GD individuals to reach a psychosocial functioning comparable with peers.

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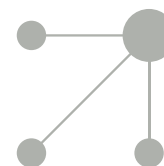
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ORIGINAL ARTICLE

Psychosocial assessment in transgender adolescents[☆]

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KEYWORDS

Transgender;
Adolescent;
Gender dysphoria;
Gender identity

Abstract

Objectives: To evaluate the psychosocial status of the patients who attend a paediatric endocrinology clinic due to gender incongruity (GI), and to establish the impact on this after one-year of cross hormonal therapy (CHT).

Material and methods: An analytical and prospective study conducted on adolescents between 14 and 18 years old with GI, and who attended the Endocrinology Clinic during 2018–2019. The sample included 23 transgender cases (16 male and 7 female cases) and 30 cisgender controls. Study variables were collected at T0 (pre-treatment) and T1 (after one year of CHT) and included sociodemographic data, Utrecht test, SDQ-Cas test, family APGAR test, STAI scale-anxiety Grade, and BDI-II depression assessment test.

Results: A significant improvement ($P < .05$) was found between T0 and T1 in the transgender group in terms of emotional symptoms, behaviour problems, hyperactivity symptoms, pro-social conduct, as well as in the degree of anxiety and depression measured by the SDQ-Cas test, the STAI and the BDI-II scale. There were significant differences in these scales between the transgender group and the controls at T0, however, the scores equalised at T1. The families in this sample of transgender patients provided a very favourable environment according to the scores obtained on the family APGAR scale.

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PALABRAS CLAVE

Transgénero;
Adolescente;
Disforia de género;
Identidad de género

Conclusions: The rates of anxiety, emotional and behaviour distress, depressive symptomatology, as well as the feeling of gender dysphoria of these transgender patients were similar to those of non-transsexual population of the same age after one year of CHT initiated at ages between 14 and 18 years old.

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Evaluación psicosocial en adolescentes transgénero**Resumen**

Objetivos: Evaluar el estado psicosocial de los pacientes que acuden a consulta de endocrinología pediátrica por incongruencia de género y determinar el impacto en este sentido de la terapia hormonal cruzada (THC) después de un año.

Material y métodos: Se trata de un estudio analítico, prospectivo realizado en adolescentes con incongruencia de género de entre 14 y 18 años que acuden a endocrinología infantil durante 2018-2019. Tamaño muestral: 23 casos transgénero (16 masculinos y 7 femeninos) y 30 controles cis. Variables del estudio en T0 (pretratamiento) y T1 (tras un año de THC): datos sociodemográficos, Test de Utrecht, Test SDQ-Cas, APGAR familiar, Escala STAI, Test de evaluación de depresión BDI-II.

Resultados: Se encuentra mejoría significativa ($p < 0,05$) entre T0 y T1 en el grupo trans en cuanto a los síntomas emocionales, los problemas de conducta, los síntomas de hiperactividad y la conducta prosocial, así como en el grado de ansiedad y depresión. Existen diferencias significativas entre el grupo trans y los controles en T0 igualándose las puntuaciones en T1 en las escalas evaluadas. Las familias de nuestra muestra de pacientes transgénero proporcionan un entorno muy favorable según las puntuaciones obtenidas en la escala del APGAR familiar.

Conclusiones: Los índices de ansiedad, estrés emocional y comportamental, sintomatología depresiva, así como el sentimiento de disforia de género de nuestra muestra de pacientes transgénero fueron similares a los de población no transexual de su misma edad tras un año de THC iniciada en edades comprendidas entre los 14-18 años.

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Introduction

Transgender individuals are individuals whose gender identity or gender expression does not conform to that typically associated with the sex to which they were at birth, in the absence of an underlying mental disorder or chromosomal abnormality that could be the cause of this experience. The concept of gender dysphoria featured in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and the International Classification of Diseases, Tenth Revision (ICD-10)^{1,2} refers to the distress caused by this incongruence between gender identity and the sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics),^{3,4} and not all transgender individuals experience it. During the development of the International Classification of Diseases, Eleventh Revision (ICD-11), the World Health Organization (WHO) redefined gender identity-related health, replacing categories like "transsexualism" and introducing the concept of "gender incongruence". This category is included in the so-called Z codes, which are codes used to define a variety of psychosocial factors or life events and do not fit into a diagnostic category.⁵

In transgender adolescents, puberty suppression at an early age (Tanner stages 2 and 3) seeks to alleviate the suffering caused by the development of secondary sex characteristics, to widen the temporal window for decision-making, as at this stage the treatment is still reversible, and to facilitate social transition to the new gender role.^{6,7} Thus, a study conducted in the Netherlands by Cohen-Kettenis et al in transgender youth that had undergone puberty suppression analysed behavioural problems, depression, anxiety and overall functioning and found considerable improvement in every scale following treatment.^{8,9}

In a study published in *Pediatrics*, Spack et al. reported similar outcomes applying the 'Dutch model' to those found by De Vries and Cohen-Kettenis in 2014.¹⁰

Outside the works we have just mentioned, the literature on the psychosocial impact of hormone therapy in transgender youth is scarce. More specifically, no such study has been conducted in Spain, and none of those conducted elsewhere included a control group. For this reason, the objectives of our study were to assess the psychosocial status of patients seeking care in the paediatric endocrinology clinic for gender incongruence and the impact on psychosocial status of cross-sex hormone therapy (CSHT) at 1 year of treatment.

Materials and methods

Study design

We conducted a prospective analytical study in adolescents with gender incongruence aged 14–18 years managed as new patients in the paediatric endocrinology clinic of the Hospital Clínico San Carlos. In our unit, the hormone therapy approach used for male-to-female (MTF) transition starts with gonadotropin-releasing hormone (GnRH) analogues in the intermediate pubertal stages (Tanner 2–3), adding CSHT with oral estradiol starting from age 14 years, with the specific timing determined on a case-by-case basis. The approach to female-to-male (FTM) transition starts with GnRH analogues in the intermediate pubertal stages with addition of CSHT with intramuscular testosterone starting from age 14 years. We analysed the cases of 23 trans patients (16 FTM and 7 MTF) and 30 cisgender controls matched for age, ethnicity and socioeconomic status. We recruited both cases and controls in the paediatric endocrinology clinic of the Hospital Clínico San Carlos simply by requesting that they volunteer to participate in the study. We followed up patients in both groups for a year after initiation of CHST in the trans cases.

Variables under study at T0 (before hormone therapy) and T1 (1 year after initiation of cross-sex hormone therapy)

1. *Sociodemographic characteristics*. Family: age, country of origin, ethnicity, educational attainment and income level.
Personal: age, country of origin, ethnicity, sexual orientation and past use of mental health services.
2. *Severity of gender dysphoria – Utrecht Gender Dysphoria Scale (UGDS)*.¹¹ Filled out for the sex assigned at birth at T0 and the self-identified gender at T1.
3. *Patient strengths and difficulties – Strengths and Difficulties Questionnaire, Spanish Version (SDQ-Cas)*.¹² This questionnaire detects potential emotional and behavioural problems in children and adolescents. A score of more than 20 is considered indicative of risk of having a disorder (normal: 0–15; borderline: 16–19, abnormal: 20–40).
4. *Family functioning – Family APGAR test*.¹³ The family APGAR test assesses how family members perceive overall family functioning. It is interpreted as follows: functional, 17–20 points; mildly dysfunctional, 16–13 points; moderately dysfunctional, 12–10 point; severely dysfunctional, <9 points.
5. *Level of anxiety – State-Trait Anxiety Inventory*.¹⁴ This instrument is based on a theoretical model with 2 components: state anxiety and trait anxiety. It is composed of 2 separate self-report subscales, each with 20 items, to assess these components. Specific cut-off points have not been established for its interpretation, and instead the result is reported as the percentile corresponding to the raw score.
6. *Mood – Beck Depression Inventory II (BDI-II)*.¹⁵ The 21 items of the inventory describe the most frequent symptoms found in patients with depression (psychologi-

cal or affective-cognitive items, and somatic-vegetative items). The instrument was developed mainly for use in clinical practice as a means to assess severity of depression in adolescent and adult patients. The ranges used to interpret the score are: no depression, 0–9; mild depression, 10–18; moderate depression, 19–29; severe depression, >30.

Inclusion criteria

- Adolescents with gender incongruence at a stage of pubertal development of Tanner 2 or higher that were willing to participate.
- Absence of psychiatric comorbidity that could affect the experience of gender dysphoria.
- Having demonstrated an understanding of the potential risks and benefits of CSHT.

Ethical considerations

We obtained the written informed consent of the parents and the assent of the minor as a requisite for participation in the study. We provided an informational document and explained the protocol in detail to all participants. We did not include any personally identifiable information in the study dataset. Thus, the study adhered to international regulations for data protection and current Spanish law on personal data protection. The protocol was approved by the Ethics and Clinical Research Committee of the Hospital Clínico San Carlos de Madrid.

Statistical analysis

We did a descriptive analysis of all study variables, using measures of central tendency and dispersion for quantitative variables and absolute and relative frequency distributions for quantitative variables. We used the mean and standard deviation (SD) to summarise quantitative variables. We compared the mean scores at baseline (T0) in both groups using the two-sample t test and the changes in scores between baseline (T0) and 1 year of treatment (T1) by one-way repeated measures analysis of variance (ANOVA), introducing the group variable as an intergroup factor and the T0 and T1 timepoints as an intragroup factor. We set a level of significance of 5% for all tests. Data were handled and analysed with the software SPSS 23.0.

Results

We analysed data for 53 participants aged 14–18 years, of whom 23 were trans gender (16 [69%] trans male and 7 [31%] trans female) and 30 were healthy cisgender controls (12 [40%] female and 18 [60%] male). All were Caucasian of Spanish descent except for 2 trans participants, 1 Asian participant of Chinese descent and 1 black participant from Colombia. We did not find significant differences in the socioeconomic status between the trans participants and the cis controls ($P = .2$). Approximately 40% to 50% of participants in each group were of middle socioeconomic status and had parents with a university education (Table 1).

Table 1 Sociodemographic characteristics.

	Trans group	Cis group	
Mean age (range)	16 (14–18 years)	16 (14–18 years)	NS
Sex assigned at birth	Female (69%), male (31%)	Female (60%), male (40%)	NS
Caucasian and of Spanish descent	91%	100%	NS
Parents with university education	52%	40%	NS
Previous use of mental health services	30.4%	30%	NS
Sexual orientation	Heterosexual (65%), homosexual (13%), bisexual (21%)	Heterosexual (90%), homosexual (10%), bisexual (0%)	$P < .05$

Table 2 Results of the Strengths and Difficulties Questionnaire in trans adolescents and the control group before hormone therapy (T0) and at 1 year of cross-sex hormone therapy (T1).

Variable	Trans					Cis					Group comparison	
	T0		T1		P	T0		T1		P	T0	T1
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		P	P
Prosocial	8	1.6	9	1.2	<0.001	7.7	1.2	7.5	1.2	.3	.4	<.001
Emotional symptoms	5.2	1.6	3.4	1.2	<0.001	3.7	1	3.7	1	1	<.001	.3
Conduct problems	2.7	0.8	1.8	1	<0.001	2.3	1.2	2.6	1.6	.1	.1	.05
Hyperactivity	4	1.9	2.6	1.8	<0.001	3.8	0.9	3.9	0.8	.8	.5	.002
Peer problems	2.6	1.3	2.3	0.8	0.1	1.3	0.4	1	0.2	.07	<.001	<.001
Total difficulties	14.7	3.3	10.3	2.9	<0.001	11.3	2.3	11.3	2.3	.9	<.001	.1

Cis, cisgender control group; SD, standard deviation; Trans, transgender case group.

We found that 30.4% of the trans participants ($n=7$) and 30% of the cis controls ($n=9$) had previously used mental health services, while only 1 trans participant (4.3%) had ever received psychiatric medication (Table 1).

The trans participants had a supportive social environment, as 100% had disclosed their transgender identity to their parents and 82% (19 out of 22) had disclosed it in their respective schools. In addition, 95% (22 out of 23) reported being addressed by their chosen names at home and 82% in their school.

Severity of Gender Dysphoria-Utrecht Scale

Participants in the trans group had a mean score in the UGDS of 57.1 ± 4.1 at T0 (the cut-off point to identify dysphoria is 40 points, out of a total possible maximum of 60 points) compared to a mean score of 14.7 ± 3.2 at T1, which evinced significant improvement at 12 months of treatment ($P < .001$). Every trans participant had gender dysphoria at T0 and none had gender dysphoria at T1 applying the cut-off point established for definition of gender dysphoria in this scale.

Strengths and Difficulties Questionnaire

The mean overall score in the trans group was in the upper range of normal at T0 (14.7 ± 3.3), with a significant

improvement at T1 (10.3 ± 2.8 DE) ($P < .001$). When we compared the trans and cis groups at T0, we found significant differences, with a mean difference in the questionnaire score of 3.3 ± 0.7 ($P < .001$), a difference that was nearly reversed after 1 year of treatment (-1.0 ± 0.7 ; $P = .153$), so that emotional symptoms and conduct problems had both become comparable to those of the control group at T1. Tables 2 and 3 summarise the scores in the SDQ.

When we analysed each of the 5 groups of difficulties that compose the SDQ, we found significant improvement between T0 and T1 in the trans group in the areas of emotional symptoms, conduct problems, hyperactivity and prosocial behaviour ($P < .001$), with no significant change in the area of peer relationship problems, with similar scores at T0 and T1.

Table 3 Percentage of trans participants with SDQ scores in the normal, borderline and abnormal range at T0 and T1.

SDQ in trans group	T0	T1
Normal (0–15 points)	61% ($n=14$)	95.6% ($n=22$)
Borderline (16–19 points)	34.7% ($n=8$)	4.3% ($n=1$)
Abnormal (20–40 points)	4.3% ($n=1$)	0%

Table 4 Results of the State-Trait Anxiety Inventory (STAI) in the trans adolescent group and the cis adolescent control group before hormone therapy (T0) and at 1 year of cross-sex hormone therapy (T1).

Variable	Trans					Cis					Group comparison	
	T0		T1		P	T0		T1		P	T0	T1
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		P	P
STAI-S	33.3	9.1	16.8	8.1	<0.001	11.8	3.8	12.3	3.8	0.6	< 0.001	0.008
STAI-T	33	7.2	18.5	8.4	<0.001	14.2	4.8	14.2	4.8	0.9	< 0.001	0.02

Cis, cisgender control group; SD, standard deviation; STAI-S, STAI state anxiety subscale; STAI-T, STAI trait anxiety subscale; Trans, transgender case group.

Table 5 State anxiety subscale percentiles in the trans group.

STAI-State in trans group	Mean (SD)	Percentile
T0	33.3 (9.1)	75th–85th
T1	16.8 (8.1)	<50th

SD, standard deviation; STAI, State-Trait Anxiety Inventory.

Table 6 Trait anxiety subscale percentiles in the trans group.

STAI-Trait in trans group	Mean (SD)	Percentile
T0	33.0 (7.2)	p 85–95
T1	18.5 (8.4)	<p50

SD, standard deviation; STAI, State-Trait Anxiety Inventory.

Family environment: Family Apgar test

We found a mean score of 17.9 at T0 and of 18 at T1 in the trans group, both within the normal range. We did not find differences between T0 and T1 or between the case and control groups.

Anxiety assessment: State-Trait Anxiety Inventory

State anxiety in the trans group improved significantly, with the mean score decreasing by 16.5 ± 1.1 points ($P < .001$), corresponding to a decrease from the 75th to 85th percentile at T0 to below the 50th percentile at T1. On the other hand, participants in the control group had similar scores at T0 and T1 (Tables 4 and 5).

Comparing the trans and cis groups at T0, we found a difference in the mean score of 21.5 ± 1.8 ($P < .001$), and there was still a mean difference at T1, in this case of 4.6 ± 1.6 points ($P < .008$), which indicated a higher level of anxiety in cases compared to controls at 1 year despite treatment (Table 4).

Trait anxiety decreased by a mean of 14.5 ± 0.9 points between T0 and T1 in the trans group ($P < .001$), with no difference between time points in the control group. We found a decrease from the 85th to 90th percentile at T0 to below the 50th percentile at T1. In contrast, controls had similar scores at T0 and T1, as was also the case with the state anxiety.

Comparing the trans and cis groups at T0, we found a mean difference of 18.8 ± 1.6 points ($P < .001$), and we also found differences between groups at T1, with a mean difference of 4.3 ± 1.8 points ($P < .02$). As was the case with state anxiety, while there was improvement in the score for trait anxiety, the level of anxiety continued to be higher in the trans group compared to the control group at T1 (Tables 4–6).

Assessment of depression: Beck Depression Inventory II

We found a decrease in symptoms of depression between T0 and T1 in the trans group, with a mean difference in the BDI-II score of 9.5 ± 0.6 points ($P < .001$), while there were no differences in the control group (Table 7). The mean score at T0 was 19.3 (at the lower limit of moderate depression) and decreased to 9.7 at T1 (at the lower limit of mild depression). In the cis control group, the mean at T0 was within the normal range and it remained normal at T1 (Table 7). In the trans group, we observed clear improvement at T1 at every level of depression (Table 8).

Comparing the trans and cis groups at T0, we found a mean difference of 12.0 ± 1.3 points in the score ($P < .001$) that had decreased to 2.4 ± 0.7 points at T1 ($P < .034$). Trans participants had more depression symptoms compared to controls at T0 and, despite improvement, also at T1 (Table 7).

Discussion

In many cases, both families and the health professionals that habitually work with trans adolescents need to make decisions without the support of clear scientific evidence. But, as any professional that works with trans youth and their families knows, in a population that faces this level of discrimination^{16–18} and in which self-harm, suicidal ideation, anxiety and other problems are so prevalent, the risk associated with not performing any kind of intervention is very high.^{19–21}

Medical treatment of transgender adolescents has been a controversial issue since it was first reported in the Netherlands in 1998.²² Since 2013, our paediatric endocrinology clinic offers multidisciplinary treatment to patients with adolescent-onset gender dysphoria, with collaboration of social workers, psychologists, psychiatrists, gynaecologists, dermatologists, paediatricians and endocrinologists. At

Table 7 Results of the Beck Depression Inventory II in the trans and cis groups, before hormone therapy (T0) and at 1 year of cross-sex hormone therapy (T1).

Variable	Trans					Cis					Group comparison	
	T0		T1		P	T0		T1		P	T0	T1
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		P	P
BDI-II	19.3	5.5	9.7	3.9	<.001	7.2	3.9	7.4	3.6	.7	<.001	.034

BDI, Beck Depression Inventory; SD, standard deviation.

Table 8 Percentage of trans participants with BDI-II scores in the normal, mild depression, moderate depression and severe depression range at T0 and T1.

BDI-II in trans group	T0	T1
Normal (0–9)	0%	69.5%
Mild (10–18)	60.8%	26.0%
Moderate (19–29)	34.7%	4.3%
Severe (>30)	4.3%	0%

present, our clinic manages 50 patients receiving hormone therapy for this indication, mostly following the latest recommendations of the World Professional Association for Transgender Health,³ with a model similar to the one recommended by Hembree⁴ and the Cohen-Kettenis group.⁸ That is, patients that have reached a stage of pubertal development of at least Tanner 2 or 3, without psychiatric comorbidity that could play a role in gender dysphoria, with adequate social, family and psychological support and that have demonstrated an understanding of the risks and benefits of hormone therapy.

At present, the scientific community does not consider transgender identities pathological. Removing transgender identities from the classification of psychiatric disorders and placing related problems in the Z codes is a solution that allows their depathologisation, including them in the classification criteria related to factors that have an impact on health status.⁵ Until recently, the few manuals available to guide the management of trans patients mainly focused on the incongruence between the sex assigned at birth and the gender identity of the individual, and particularly on the distress caused by this discrepancy.² This distress may or may not be directly associated with the possibility of freely expressing gender identity, being able to transition if so desired, the support received by the family and the general social environment and the degree of transphobia experienced. In our study, all trans participants experienced gender dysphoria at T0, which had resolved in all at 1 year of CSHT, which demonstrates that this dysphoria is not a necessary condition in transgender individuals and is not always present in transgender youth.

In our sample, the families of transgender participants provided a highly supportive environment, as demonstrated by the family APGAR scores. This could explain the highly favourable outcomes observed at 1 year of treatment with CSHT. The support of families and physicians is essential to the adequate and healthy neuropsychological development of transgender adolescents.^{6,7,23} Initiation of CSHT and

the associated physical changes at younger ages than currently recommended in management protocols (16 years) may have psychological benefits, given the particular importance of fitting in the peer group during adolescence. In fact, we found excellent results in the SDQ, with a significant improvement between T0 and T1 in the trans group in emotional symptoms, conduct problems, hyperactivity and prosocial behaviour, which were comparable to those of the control group at T1 (Tables 2 and 3).

We know that a high proportion of transgender youth experience anxiety and depression, and there is evidence in the literature on the mental health of trans children and youth whose desired identities are affirmed and supported by their families. In this sense, the family plays an essential role in improving the lives of these minors, acting as a protective factor against depression, which is why it is important to implement strategies that promote the support of families due to their impact on mental health.^{24–31}

We found substantial improvement in the mean scores and percentiles in the STAI state anxiety and trait anxiety scales in the trans group after 1 year of CSHT. We also found differences at T0 compared to the control group that had improved at T1, as the differences had decreased, although not disappeared (Tables 4 and 5). We also found substantial improvement in the BDI-II scores. Before initiation of hormone therapy, all trans participants had scores corresponding to some level of depression. After 1 year of CSHT, 70% had scores in the normal range. These findings suggest that initiation of CSHT at earlier ages than recommended at present, with adequate family support in general or specifically expressed in the decision of allowing an early social transition, may be associated with better mental health outcomes in transgender children.

Our findings are consistent with those of the longitudinal study published in *Pediatrics* by Annelou de Vries in 2014.⁸ The levels of anxiety, emotional distress and behavioural disturbances and depressive symptoms and the experience of gender dysphoria in transgender participants were similar or better compared to those of their cisgender peers matched for age at 1 year of CSHT. Based on this body of evidence, it is essential for paediatric providers to have updated knowledge and an unbiased attitude on this reality, the concerns regarding the future impact of these interventions and the lack of evidence on their long-term adverse effects.³² We ought to mention the recent position statement of the Asociación Española de Pediatría (Spanish Association of Paediatrics) on the approach to gender diverse and transgender identities in children and adolescents.³³ This document does not simply adopt the depathologising perspective that is increasingly espoused by health professionals, but pushes

beyond, calling for a necessary shift in social perception, as it considers that diversity in gender identity and expression enriches humankind.

Keeping in mind that age should not be the main criterion for initiation of hormone therapy in transgender minors, we, as other authors before us, hope for the development of more flexible management protocols.³⁴

Limitations of the study

Selection bias: the selected sample is a key element in any study, and use of an inadequate sampling method is one of the most frequent sources of error in designing a study, as most statistical methods in use assume that the data source is a random sample. The simplest and most appropriate way of selecting a sample is completely random selection, but under real world conditions this is nearly impossible to do. We resorted to obtaining a convenience sample of individuals that volunteered to participate. Without forgetting that the sample in our study may not be representative of the general adolescent transgender population, as many transgender adolescents do not have a supportive family and many others do not need referral to a paediatric endocrinology clinic, we do not believe that the internal validity of our study was affected by the sampling method.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation

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BACKGROUND AND OBJECTIVES: Gonadotropin-releasing hormone analogues are commonly prescribed to suppress endogenous puberty for transgender adolescents. There are limited data regarding the mental health benefits of this treatment. Our objective for this study was to examine associations between access to pubertal suppression during adolescence and adult mental health outcomes.

abstract

METHODS: Using a cross-sectional survey of 20 619 transgender adults aged 18 to 36 years, we examined self-reported history of pubertal suppression during adolescence. Using multivariable logistic regression, we examined associations between access to pubertal suppression and adult mental health outcomes, including multiple measures of suicidality.

RESULTS: Of the sample, 16.9% reported that they ever wanted pubertal suppression as part of their gender-related care. Their mean age was 23.4 years, and 45.2% were assigned male sex at birth. Of them, 2.5% received pubertal suppression. After adjustment for demographic variables and level of family support for gender identity, those who received treatment with pubertal suppression, when compared with those who wanted pubertal suppression but did not receive it, had lower odds of lifetime suicidal ideation (adjusted odds ratio = 0.3; 95% confidence interval = 0.2–0.6).

CONCLUSIONS: This is the first study in which associations between access to pubertal suppression and suicidality are examined. There is a significant inverse association between treatment with pubertal suppression during adolescence and lifetime suicidal ideation among transgender adults who ever wanted this treatment. These results align with past literature, suggesting that pubertal suppression for transgender adolescents who want this treatment is associated with favorable mental health outcomes.

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Dr Turban conceptualized and designed the study, drafted the initial manuscript, and incorporated all revisions and comments; Ms King conducted statistical analyses and reviewed and revised the manuscript for important intellectual content, with a focus on statistical aspects of the manuscript; Dr Carswell assisted in the design of the study and in interpretation of the data analyses and critically reviewed and revised the manuscript for important intellectual content, with a focus on relevant clinical endocrinology; Dr Keuroghlian supervised and contributed to the conceptualization and design of the study and the design of the statistical analyses and reviewed and revised the manuscript for important intellectual content as it relates to mental health considerations for transgender people; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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WHAT'S KNOWN ON THIS SUBJECT: Gonadotropin-releasing hormone analogues are commonly used to suppress endogenous puberty for transgender adolescents. Small studies have revealed that pubertal suppression results in favorable mental health outcomes. No studies to date have examined associations between pubertal suppression and suicidality.

WHAT THIS STUDY ADDS: In this study, using the largest survey of transgender adults to date, we show that access to pubertal suppression during adolescence is associated with lower odds of lifetime suicidal ideation among transgender young adults.

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According to the Centers for Disease Control and Prevention's Youth Risk Behavior Surveillance System, ~1.8% of adolescents in the United States identify as transgender.¹ These youth suffer mental health disparities that include higher rates of internalizing psychopathology (ie, anxiety and depression) and suicidality, theorized to be due to a combination of dysphoria toward their bodies and minority stress.²⁻⁵ In a large study of transgender adults in the United States, 40% endorsed a lifetime suicide attempt.⁶

Over the past 2 decades, protocols have been developed to provide transgender adolescents with gender-affirming medical interventions that align their bodies with their gender identities. Most prominent among these are the Endocrine Society guidelines⁷ and the World Professional Association for Transgender Health (WPATH) Standards of Care.⁸ Both sets of guidelines recommend that transgender adolescents be offered gonadotropin-releasing hormone analogues (GnRHs), colloquially referred to as "puberty blockers," once they reach Tanner 2 of puberty. These medications are provided as subcutaneous implants or are administered as either 1- or 3-month depot injections. GnRHa therapy effectively halts the production of gonadal sex steroids (testosterone and estrogen) by persistently activating and thereby desensitizing the gonadotropin-releasing hormone receptor, which in turn leads to suppression of luteinizing hormone and follicle-stimulating hormone release from the anterior pituitary gland.⁹ This process inhibits endogenous puberty for the duration of GnRHa use. Once further pubertal development is delayed, youth are able to explore gender identities without the pressure of dysphoria associated with gender-incongruent physical development.¹⁰ GnRHa therapy is unique among

gender-affirming medical interventions in that the resultant pubertal suppression is fully reversible, with the resumption of endogenous puberty after their discontinuation.^{7,8}

Since the publication of the WPATH Standards of Care and the Endocrine Society guidelines, the use of pubertal suppression for transgender youth has become more common in the United States.⁹ There are limited data, however, regarding the mental health outcomes of pubertal suppression. To date, there have been 2 published studies in which the effects of this treatment on the mental health of transgender youth were examined. In the first study, the authors assessed changes in mental health among 55 Dutch adolescents who received pubertal suppression.¹¹ This study, which notably lacked a control group, revealed that internalizing psychopathology improved after treatment with pubertal suppression. In the second study, researchers followed a group of 201 adolescents with gender dysphoria and found that those who received pubertal suppression in addition to psychological support ($n = 101$) had superior global functioning, measured by the Children's Global Assessment Scale, when compared with those who received psychological support alone ($n = 100$).¹²

In the current study, we use the largest survey of transgender people to date, a community-recruited sample of transgender adults in the United States, to conduct the first-ever investigation into associations between pubertal suppression and suicidality.

Transgender youth present to clinicians with a range of concerns. Some have minimal body dysphoria and do not desire pubertal suppression, whereas others report

significant dysphoria around the physical changes related to puberty. Because not all transgender and gender-diverse youth desire medical interventions, we examined only those youth who desired pubertal suppression because these are the young people who would present to care and for whom clinicians would need to decide about whether to initiate pubertal suppression. We specifically examined measures of past-year suicidality, lifetime suicidality, past-month severe psychological distress, past-month binge drinking, and lifetime illicit drug use. We hypothesized that among those who wanted pubertal suppression, those who received it would have superior mental health outcomes when compared with those who wanted but did not receive it.

METHODS

Study Design and Data Source

The 2015 US Transgender Survey (USTS) was conducted over a 1-month period in 2015 by the National Center for Transgender Equality (NCTE). It is, to our knowledge, the largest existing data set of transgender adults and includes data regarding demographics, past gender-affirming medical treatment, family support, and mental health outcomes. Participants were recruited through community outreach in collaboration with >400 lesbian, gay, bisexual, and transgender organizations and were provided with a Web address to complete the survey online. Details regarding outreach efforts are further described in the NCTE report on the survey.⁶ The USTS protocol was approved by the University of California, Los Angeles Institutional Review Board. For the purposes of the current study, data were obtained via a data-sharing agreement with the NCTE, and the current protocol was reviewed by The Fenway Institute

Institutional Review Board and determined to not comprise human subjects research.

Study Population

The USTS data set contains responses from 27 715 US transgender adults, with respondents from all 50 states, the District of Columbia, American Samoa, Guam, Puerto Rico, and US military bases overseas. Given that pubertal suppression for transgender youth was not available in the United States until 1998,⁴ only participants who were 17 or younger in 1998 would have had health care access to GnRHa for pubertal suppression. We thus restricted the analysis to participants who were 36 or younger at the time of the survey, resulting in a sample of 20 619 participants. Data were further restricted to those who selected “puberty blocking hormones (usually used by youth ages 9–16)” in response to the question “Have you ever wanted any of the health care listed below for your gender identity or gender transition? (Mark all that apply).” Response options for this question were “counseling/therapy,” “hormone treatment/HRT,” “puberty blocking hormones (usually used by youth ages 9–16),” or “none of the above.” This resulted in a sample of 3494 individuals between the ages of 18 and 36 who ever wanted pubertal suppression as part of their gender-affirming medical care.

Exposures

Exposure to pubertal suppression was defined as selecting “puberty blocking hormones (usually used by youth ages 9–16)” in response to the question “Have you ever had any of the health care listed below for your gender identity or gender transition? (Mark all that apply).” Response options for this question were “counseling/therapy,” “hormone treatment/HRT,” “puberty blocking hormones (usually used by youth ages 9–16),” and “none of the above.”

Participants who reported having pubertal suppression were also asked, “At what age did you begin taking Puberty Blocking Hormones?” Those who reported beginning treatment after age 17 were excluded to only include participants who likely had pubertal suppression during active endogenous puberty. The vast majority of adolescents would have reached Tanner 5, the final stage of puberty, by age 17.^{13,14}

Outcomes

Comparing those who received pubertal suppression with those who did not, we examined past-month severe psychological distress (defined as a score of ≥ 13 on the Kessler Psychological Distress Scale [K6], a cutoff previously validated among US adults¹⁵), past-month binge drinking (operationalized as drinking ≥ 5 standard alcoholic beverages during 1 occasion; the rationale for this threshold when studying alcohol use among transgender people has been discussed previously¹⁶), lifetime illicit drug use (not including marijuana), past-year suicidal ideation, past-year suicidal ideation with a plan, past-year suicide attempts, past-year suicide attempts resulting in inpatient care, lifetime suicidal ideation, and lifetime suicide attempts.

Control Variables

Demographic variables collected included age, age of social transition, age of initiation of gender-affirming hormone therapy, current gender identity, sex assigned at birth, sexual orientation, race, education level, employment status, relationship status, total household income at the time of data collection in 2015, family support for gender identity, and current hormone treatment.

Statistical Analysis

Data were analyzed by using SPSS software version 25 (IBM SPSS Statistics, IBM Corporation, Armonk,

NY). Descriptive statistics were conducted and are presented as frequency (percentage) or mean (SD). Analysis of variance and χ^2 tests were used to assess significance by age, gender identity, sex assigned at birth, race, education level, employment status, relationship status, total household income, family support for gender identity, and current hormone treatment between those who received pubertal suppression and those who did not. We used univariate logistic regression to examine associations between receiving pubertal suppression and each mental health outcome, as well as between age and both ever wanting and receiving pubertal suppression. $P < .05$ defined statistical significance. Multivariable logistic regression models were adjusted for using the demographic variables associated with each outcome at the level of $P \leq .20$. Because all outcomes were associated with level of family support, sexual orientation, education level, employment status, and total household income, all models were adjusted for these variables. Lifetime suicide attempts were associated with gender identity, and this model was therefore additionally adjusted for this variable. Past-month severe psychological distress and past-year suicidal ideation were additionally associated with age, gender identity, and relationship status, and therefore models were adjusted for these variables as well. Race was found to be associated with lifetime suicidal ideation and lifetime suicide attempts; therefore models were therefore additionally adjusted for race.

RESULTS

Of the 20 619 survey respondents 18 to 36 years of age, 3494 (16.9%) reported that they had ever wanted pubertal suppression. Of those who wanted pubertal suppression, only 89 (2.5%) had

received this treatment. The following variables were found to be associated with those who wanted and received pubertal suppression compared with those who wanted pubertal suppression but did not receive it: younger age, age of social transition, age of initiation of hormone therapy, feminine gender identity, male sex assigned

at birth, heterosexual sexual orientation, higher total household income, and greater family support of gender identity (Table 1).

In univariate analyses, when comparing those who received pubertal suppression with those who did not, receiving pubertal

suppression was associated with decreased odds of past-year suicidal ideation, lifetime suicidal ideation, and past-month severe psychological distress (Table 2). After controlling for demographic variables from Table 1, pubertal suppression was associated with decreased odds of lifetime suicidal ideation. Raw

TABLE 1 Sample Demographics

	All (N = 3494)	Have You Ever Had [Pubertal Suppression] for Your Gender Identity or Gender Transition?			
		Yes (n = 89; 2.5%)	No (n = 3405; 97.5%)	F	P
n (%) n (%) n (%)					
Age	23.4 (5.0)	21.7 (4.7)	23.4 (5.0)	10.3	.001*
Age of social transition	20.0 (5.5)	15.2 (4.5)	20.1 (5.5)	67.5	<.001*
Age began hormone therapy	22.1 (4.5)	15.7 (2.4)	22.5 (4.3)	217.4	<.001*
Gender identity				25.5 ^a	<.001*
Woman		23 (25.8)	617 (18.2)		
Man		19 (21.3)	383 (11.3)		
Transgender woman		25 (28.1)	720 (21.3)		
Transgender man		16 (18.0)	795 (23.5)		
Nonbinary or genderqueer		6 (6.7)	866 (25.6)		
Sex assigned at birth				4.4 ^a	.04*
Female		39 (43.8)	1874 (55.0)		
Male		50 (56.2)	1531 (45.0)		
Sexual orientation				36.5 ^a	<.001*
Heterosexual or straight		27 (30.3)	350 (10.3)		
Asexual		9 (10.1)	437 (12.8)		
Pansexual or queer		36 (40.4)	1784 (52.4)		
Gay or lesbian		12 (13.5)	539 (15.8)		
Not listed		5 (5.6)	295 (8.7)		
Race, n (%)				3.5 ^a	.06
Racial minority		28 (31.5)	782 (23.0)		
Not racial minority (white or European American)		61 (68.5)	2623 (77.0)		
Education level				2.9 ^a	.41
Less than high school		9 (10.1)	220 (6.5)		
High school graduate or GED		20 (22.5)	683 (20.1)		
Some college or associate degree		39 (43.8)	1729 (50.8)		
Bachelor's degree or higher		21 (23.6)	773 (22.7)		
Employment status				0.6 ^a	.45
Employed		51 (79.7)	1976 (75.6)		
Unemployed		13 (20.3)	638 (24.4)		
Relationship status				0.5 ^a	.47
Partnered		35 (40.2)	1447 (44.1)		
Unpartnered		52 (59.8)	1834 (55.9)		
Total household income, \$				21.9 ^a	<.001*
<25 000		21 (26.3)	1153 (38.3)		
25 000–49 999		13 (16.3)	652 (21.7)		
50 000–99 000		14 (17.5)	630 (20.9)		
>100 000		32 (40.0)	574 (19.1)		
Family support for gender identity				24.3 ^a	<.001*
Supportive		71 (81.6)	1551 (55.8)		
Neutral		11 (12.6)	573 (20.6)		
Unsupportive		5 (5.7)	658 (23.7)		
Current hormone treatment		87 (97.8)	1617 (96.3)	0.5 ^a	.48

Descriptive statistics for transgender adults in the United States who ever wanted pubertal suppression for their gender identity or gender transition when comparing those who received this treatment with those who did not receive this treatment (total N = 3494). Percentages were calculated from the total of nonmissing values.

*Indicates statistical significance.

^a χ^2 .

TABLE 2 Mental Health Outcomes Among Those Who Received Pubertal Suppression

	Univariate Analyses		Multivariable Analyses	
	OR (95% CI)	P	aOR (95% CI)	P
Suicidality, past 12 mo				
Ideation	0.6 (0.4–0.8)	.006*	0.6 (0.3–1.1)	0.09
Ideation with plan	0.9 (0.5–1.6)	.73		
Ideation with plan and attempt	1.2 (0.6–2.3)	.64		
Attempt resulting in inpatient care	2.8 (0.8–9.4)	.09		
Suicidality, lifetime				
Ideation	0.3 (0.2–0.5)	<.001*	0.3 (0.2–0.6)	0.001*
Attempts	0.7 (0.4–1.0)	.08		
Mental health and substance use				
Past-month severe psychological distress, K6 $\geq$ 13	0.5 (0.3–0.8)	.001*	0.8 (0.4–1.4)	0.38
Past-month binge drinking	0.3 (0.8–2.0)	.29		
Lifetime illicit drug use	1.1 (0.7–1.8)	.67		

Univariate and multivariable analyses of mental health outcomes among transgender adults in the United States who ever wanted pubertal suppression when comparing those who received this treatment with those who did not. Multivariable logistic regression models were adjusted for using the demographic variables associated with each outcome at the level of $P \leq .20$. Because all outcomes were associated with family support, sexual orientation, education level, employment status, and total household income, all models were adjusted for these variables. Lifetime suicide attempts were associated with gender identity, and this model was additionally adjusted for this variable. Past-month severe psychological distress and past-year suicidal ideation were additionally associated with age, gender identity, and relationship status, and thus these models were adjusted for these variables as well. Race was found to be associated with lifetime suicidal ideation and lifetime suicide attempts, and thus these models were additionally adjusted for race. Models for psychological distress and past-year suicidal ideation were also adjusted for age, gender identity, and relationship status. aOR, adjusted odds ratio.

* Indicates statistical significance.

frequency outcomes are presented in Table 3.

To examine associations between age, ever wanting, and ever receiving pubertal suppression, we divided participants into 2 age groups with the cutoff point at the median, 18 to 22 and 23 to 36, in light of the skewed distribution of age.¹⁷ The younger age group had increased odds both of ever wanting pubertal

suppression (odds ratio [OR] = 1.4, $P < .001$, 95% confidence interval [CI]: 1.3–3.5) and of receiving pubertal suppression (OR = 2.1, $P = .001$, 95% CI: 1.4–3.4).

Among those who had ever received pubertal suppression, 60% reported traveling <25 miles for gender-affirming health care, 29% traveled between 25 and 100 miles, and 11% traveled >100 miles.

DISCUSSION

This study is the first in which the association between access to pubertal suppression and measures of suicidality is examined. Treatment with pubertal suppression among those who wanted it was associated with lower odds of lifetime suicidal ideation when compared with those who wanted pubertal suppression but did not receive it. Suicidality is of particular concern for this population because the estimated lifetime prevalence of suicide attempts among transgender people is as high as 40%.⁶ Approximately 9 of 10 transgender adults who wanted pubertal suppression but did not receive it endorsed lifetime suicidal ideation in the current study (Table 3). Access to pubertal suppression was associated with male sex assignment at birth, heterosexual sexual orientation, higher total household income, and higher level of family support for gender identity.

Results from this study suggest that the majority of transgender adults in the United States who have wanted pubertal suppression did not receive it. Of surveyed transgender adults in

TABLE 3 Raw Frequencies of Outcome Variables

	Have You Ever Had [Pubertal Suppression] for Your Gender Identity or Gender Transition?	
	Yes ($n = 89$; 2.5%)	No ($n = 3405$; 97.5%)
	n (%)	n (%)
Suicidality (past 12 mo)		
Ideation	45 (50.6)	2204 (64.8)
Ideation with plan	25 (55.6)	1281 (58.2)
Ideation with plan and attempt	11 (24.4)	473 (21.5)
Attempt resulting in inpatient care	5 (45.5)	108 (22.8)
Suicidality (lifetime)		
Ideation	67 (75.3)	3062 (90.2)
Attempts	37 (41.6)	1738 (51.2)
Mental health and substance use		
Past-month severe psychological distress (K6 $\geq$ 13)	32 (37.2)	1847 (55.1)
Past-month binge drinking	26 (29.2)	825 (24.3)
Lifetime illicit drug use	24 (27.3)	850 (25.3)

Raw frequencies of mental health outcomes among transgender adults in the United States who ever wanted pubertal suppression. Percentages were calculated from the total of nonmissing values.

the current study, 16.9% reported ever desiring pubertal suppression as part of their gender-related care; however, only 2.5% of these respondents indicated they had in fact received this wanted treatment. This was the case even for the youngest survey respondents, who were 18 years old at the time of data collection in 2015. Only 4.7% of 18-year-olds who wanted the treatment reported receiving it.

Although rates both of desiring and of receiving pubertal suppression were higher among younger respondents, results from the current study indicate that still only 29.2% of the youngest participants in the study (ie, those who were 18 years of age in the year 2015) reported ever desiring pubertal suppression as part of gender-related care. No individuals <18 years of age were captured by this data set; future research should investigate the rate of desiring pubertal suppression among younger populations. Some respondents may have simply never been aware of the possibility of puberty suppression while still within the range of developmentally suitable candidates for receiving this treatment, or they may have believed that they were not suitable candidates. This finding may also reflect the diversity of experience among transgender and gender-diverse people, highlighting that not all will want every type of gender-affirming intervention.^{7,8} Future research is needed to understand why younger participants reported desiring pubertal suppression at higher rates; we hypothesize that this is likely due in part to recent increased public awareness about and access to gender-affirming interventions.⁵

Access to pubertal suppression was associated with a greater total household income. Without insurance, the annual cost of GnRHa therapy ranges from \$4000 to \$25 000.¹⁸ Among adolescents treated with pubertal suppression at

the Boston Children's Hospital Gender Management Service before 2012, <20% obtained insurance coverage.¹⁹ More recently, insurance coverage for these medications has increased: a study from 2 academic medical centers in 2015 revealed that insurance covered the cost of GnRHa therapy in 72% of cases.¹⁸ This is 1 potential explanation for why younger age was found to be associated with accessing pubertal suppression in the current study (Table 1). It is also plausible that those who receive pubertal suppression experience more improvement in mental health, which in turn may contribute to greater socioeconomic advancement.²⁰ This study's cross-sectional design limits further interpretation.

Participants who endorsed a heterosexual sexual orientation were more likely to have received pubertal suppression. This is in line with past research revealing that nonheterosexual transgender people are less likely to access gender-affirming surgical interventions.²¹ Some clinicians may be biased against administering pubertal suppression to patients whose sexual orientation identities do not align with society's heteronormative assumptions.²¹ In the current study, nonbinary and genderqueer respondents were also less likely to have accessed pubertal suppression, suggesting that clinicians may additionally be uncomfortable with delivering this treatment to patients whose gender identities defy more traditional binary categorization. Of note, because research on gender-affirming hormonal interventions for adolescents has been focused on transgender youth with binary gender identities,¹¹ some clinicians have reservations about prescribing pubertal suppression interventions to nonbinary youth in the event of a potentially prolonged state of low sex-steroid milieu.

Family support was also associated with receiving pubertal suppression among those who wanted this treatment. This finding is unsurprising given that most states require parental consent for adolescents to receive pubertal suppression.²² Past studies have revealed that family support of gender identity is associated with favorable mental health outcomes.⁶ Of note, treatment with pubertal suppression in the current study was associated with lower odds of lifetime suicidal ideation, even after adjustment for family support (Table 2).

We did not detect a difference in the odds of lifetime or past-year suicide attempts or attempts resulting in hospitalization. It is possible that we were underpowered to detect these differences given that suicide attempt items were less frequently endorsed than suicidal ideation items (Table 3). Given this study's retrospective self-report survey design, we were unable to capture information regarding completed suicides, which may have also reduced the number of suicide attempts we were able to account for. Given that suicidal ideation alone is a known predictor of future suicide attempts and deaths from suicide, the current results warrant particular concern.²³

This study adds to the existing literature^{11,12} on the relationship of pubertal suppression to favorable mental health outcomes. The theoretical basis for these improved mental health outcomes is that pubertal suppression prevents irreversible, gender-noncongruent changes that result from endogenous puberty (eg, bone structure, voice changes, breast development, and body hair growth) and that may cause significant distress among transgender youth. Pubertal suppression allows these adolescents more time to decide if they wish to either induce exogenous gender-congruent puberty or allow

endogenous puberty to progress.^{7,8} Some have also theorized that gender-affirming medical care may have mental health benefits that are separate from its physical effects because it provides implied affirmation of gender identity from clinicians, which may in turn buffer against minority stress.²⁴

Strengths of this study include its large sample size and representation of a broad geographic area of the United States. It is the first study in which associations between pubertal suppression for transgender youth and suicidality are examined. Limitations include the study's cross-sectional design, which does not allow for determination of causation. Longitudinal clinical trials are needed to better understand the efficacy of pubertal suppression. Because the 2015 USTS data do not contain the relevant variables, we were unable to examine associations between access to pubertal suppression and degree of body dysphoria in this study. Notably, past studies have revealed that body image difficulties persist through pubertal suppression and remit only after administration of gender-affirming hormone therapy with estrogen or testosterone.¹¹ It is also limited by its nonprobability sample design. Future researchers should work toward the collection of population-based survey data that include variables related to gender-

affirming medical interventions. Of note, because pubertal suppression for transgender youth is a relatively recent intervention, some participants might not have known that these interventions existed and thus would not have reported ever wanting them. Had these individuals known about pubertal suppression, it is possible that they might have desired it. Because we do not have data on whether individuals who did not desire pubertal suppression would have wanted it had they known about it, we restricted our analysis to those who reported ever desiring pubertal suppression. Reverse causation cannot be ruled out: it is plausible that those without suicidal ideation had better mental health when seeking care and thus were more likely to be considered eligible for pubertal suppression. The Endocrine Society guidelines for pubertal suppression eligibility recommend that other mental health concerns be "reasonably well controlled."⁷ Because this study includes only adults who identify as transgender, it does not include outcomes for people who may have initiated pubertal suppression and subsequently no longer identify as transgender. Notably, however, a recent study from the Netherlands of 812 adolescents with gender dysphoria revealed that only 1.9% of adolescents who initiated pubertal suppression discontinued

this treatment without proceeding to gender-affirming hormone therapy with estrogen or testosterone.²⁵

CONCLUSIONS

Among transgender adults in the United States who have wanted pubertal suppression, access to this treatment is associated with lower odds of lifetime suicidal ideation. This study strengthens recommendations by the Endocrine Society and WPATH for this treatment to be made available for transgender adolescents who want it.

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ABBREVIATIONS

CI: confidence interval
GnRHa: gonadotropin-releasing hormone analogue
K6: Kessler Psychological Distress Scale
NCTE: National Center for Transgender Equality
OR: odds ratio
USTS: US Transgender Survey
WPATH: World Professional Association for Transgender Health

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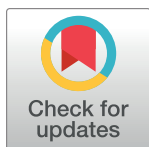
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RESEARCH ARTICLE

Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults

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Abstract

Objective

To examine associations between recalled access to gender-affirming hormones (GAH) during adolescence and mental health outcomes among transgender adults in the U.S.

Methods

We conducted a secondary analysis of the 2015 U.S. Transgender Survey, a cross-sectional non-probability sample of 27,715 transgender adults in the U.S. Using multivariable logistic regression adjusting for potential confounders, we examined associations between access to GAH during early adolescence (age 14–15), late adolescence (age 16–17), or adulthood (age ≥ 18) and adult mental health outcomes, with participants who desired but never accessed GAH as the reference group.

Results

21,598 participants (77.9%) reported ever desiring GAH. Of these, 8,860 (41.0%) never accessed GAH, 119 (0.6%) accessed GAH in early adolescence, 362 (1.7%) accessed GAH in late adolescence, and 12,257 (56.8%) accessed GAH in adulthood. After adjusting for potential confounders, accessing GAH during early adolescence (aOR = 0.4, 95% CI = 0.2–0.6, $p < .0001$), late adolescence (aOR = 0.5, 95% CI = 0.4–0.7, $p < .0001$), or adulthood (aOR = 0.8, 95% CI = 0.7–0.8, $p < .0001$) was associated with lower odds of past-year suicidal ideation when compared to desiring but never accessing GAH. In post hoc analyses, access to GAH during adolescence (ages 14–17) was associated with lower odds of past-year suicidal ideation (aOR = 0.7, 95% CI = 0.6–0.9, $p = .0007$) when compared to accessing GAH during adulthood.

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Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: Dr. Turban reports receiving textbook royalties from Springer Nature and Dr. Keuroghlian reports receiving textbook royalties from McGraw Hill. Dr. Turban has received expert witness payments from the ACLU.

Conclusion

Access to GAH during adolescence and adulthood is associated with favorable mental health outcomes compared to desiring but not accessing GAH.

Introduction

A recent representative sample of adolescents in the United States (U.S.) found that 1.8% identified as transgender [1]. Unfortunately, these young people face a range of mental health disparities, including elevated rates of anxiety, depression, and suicide attempts [2]. Suicide attempt prevalence among transgender young adults has been estimated to be as high as 40% [3]. These disparities are generally thought to be due to two processes: gender minority stress and dysphoria related to one's body developing in ways that are incongruent with one's gender identity (i.e., a person's psychological sense of their own gender) [2].

Gender minority stress refers to the ways in which society's mistreatment of transgender people results in worse mental and physical health outcomes. This includes distal factors (gender-related discrimination, gender-related rejection, gender-related victimization, and non-affirmation of gender identity), as well as subsequent proximal factors (internalized transphobia, negative expectations, and concealment) [4]. Creating safe and affirming social environments for transgender adolescents is thus considered paramount in preventing adverse mental health outcomes [5].

In addition to creating safe and affirming environments, care for transgender people often involves the provision of gender-affirming medical interventions to alleviate the psychological distress related to one's body developing in ways that do not align with one's gender identity [6, 7]. This may include pubertal suppression for younger adolescents and gender-affirming hormones (GAH, e.g., estrogen and testosterone) from adolescence onward to induce physical changes that match the person's gender identity [6–8]. Some adolescents may undergo gender-affirming surgery to reduce psychological distress [9, 10]. Of note, past Endocrine Society guidelines recommended that GAH not be considered until an adolescent reaches age 16 [11]. More recent guidelines state that initiation of GAH can be considered as early as age 14, to allow transgender adolescents to undergo puberty at ages more comparable to their peers, and to reduce the risk of delayed bone development due to prolonged pubertal suppression [7]. In this article, we therefore consider two age groups of adolescents who initiated GAH: those who started GAH during late adolescence (i.e., between their 16th and 18th birthdays) and those who started GAH during early adolescence (i.e., between their 14th and 16th birthdays).

To date, there have been six longitudinal cohort studies examining the impact of GAH initiation during adolescence on mental health [12–17]. These studies have generally found improvement in mental health following adolescent GAH initiation, including decreases in internalizing psychopathology, improved general wellbeing, and decreased suicidality. Of note, these studies did not include a comparison group of adolescents who did not access GAH. Furthermore, these studies did not examine separately those who initiated GAH during early or late adolescence, nor did they compare initiation of GAH during adolescence with initiation of GAH during adulthood.

The impact of GAH initiated in adolescence on the mental health of transgender adults is of particular policy relevance today, as several U.S. states have introduced legislation to limit access to GAH for transgender adolescents, despite opposition from major medical organizations including The American Medical Association, The American Academy of Pediatrics,

The American Psychiatric Association, The American Academy of Child & Adolescent Psychiatry, The Endocrine Society, The Pediatric Endocrine Society, and others [18]. This is an area of active policy debate where additional quantitative data are needed to guide policy decisions. Parents of transgender youth have been particularly concerned about these restrictive legislative efforts, with a parent in one recent qualitative study noting, “this could mean death for my child” [19].

The current study uses the largest survey of transgender people conducted to date to examine associations between recalled access to GAH during early adolescence (ages 14–15), late adolescence (ages 16–17), or adulthood (age ≥ 18), and adult mental health outcomes including measures of suicidality. It is the first study of GAH initiation during adolescence that includes a comparison group of those who desired but never accessed GAH. It is also the first to compare access to GAH during adolescence with access to GAH during adulthood. Given the large sample size, we were able to adjust for a wide range of potential confounding variables known to be associated with mental health outcomes for transgender people. We hypothesized that access to GAH during both early and late adolescence would be associated with more favorable mental health outcomes reported in adulthood, when compared to desiring but never accessing GAH.

Methods

Study population

The 2015 U.S. Transgender Survey (USTS) is the largest existing dataset of transgender people to date [3]. The cross-sectional non-probability survey was conducted between August and September of 2015. Transgender adults ages 18 years or older were recruited in collaboration with over 400 community organizations and completed measures online. The final survey had 27,715 participants from all 50 U.S. states, as well as Washington D.C., Puerto Rico, and U.S. territories abroad. Because not all transgender people necessarily desire GAH, we restricted the current study to participants who reported ever desiring GAH for gender affirmation, as this is a more clinically relevant group. This was assessed by choosing “hormone therapy/HRT (an acronym for ‘Hormone Replacement Therapy’)” in response to the question, “Have you ever wanted any of the health care listed below for your gender identity or gender transition? (Mark all that apply).” Options included “counseling/therapy,” “hormone treatment/HRT,” “puberty blocking hormones (usually used by youth ages 9–16),” and “none of the above.” This resulted in inclusion of 21,598 participants.

Ethical considerations

The protocol for the USTS was approved by the University of California Los Angeles Institutional Review Board. The protocol for the current study was reviewed by The Fenway Institute Institutional Review Board. All participants provided informed consent for study participation.

Age of initiation of GAH

Participants were divided into four categories. The first group, “wanted but never accessed GAH” (No GAH), reported never accessing GAH despite desiring these medications. The second group consisted of participants who reported they first accessed GAH during early adolescence, defined as the period between their 14th and 16th birthdays (GAH 14–15), which corresponds to the age group most recently added to the Endocrine Society Guidelines [7]. The third group consisted of participants who reported they first accessed GAH during late

adolescence, defined as the period between their 16th and 18th birthdays (GAH 16–17), corresponding to the narrower age group in the prior, 2009 Endocrine Society Guidelines [11]. The fourth group consisted of participants who reported they first accessed GAH after their 18th birthday (GAH $\geq$ 18).

Outcomes

Severe psychological distress in the month prior to the survey was defined as a score $\geq$ 13 on the Kessler-6 Psychological Distress Scale [20]. Binge drinking in the month prior to the survey was defined as drinking 5 or more standard alcoholic drinks on a single occasion, a threshold for use in research with transgender adults that has been discussed in prior reports [21]. Lifetime illicit drug use (excluding marijuana) was also assessed as a binary “yes” or “no” self-report outcome. Measures of suicidality were examined, including suicidal ideation during the year prior to the survey, suicidal ideation with plan during the prior year, suicide attempt during the prior year, and suicide attempt requiring hospitalization during the prior year [8]. All suicidality measures were binary outcome variables in which participants reported “yes” or “no.”

Demographic and other potential confounding variables

Demographic and other potential confounding variables that are known to be associated with adverse mental health outcomes among transgender people were collected for participants and included age at time of survey completion (U.S. census categories), gender identity, sex assigned at birth, sexual orientation, race/ethnicity (U.S. census categories), level of family support for gender identity (unsupportive, neutral, supportive, or not asked because participant had not disclosed being transgender to their family) [22], relationship status, level of education, employment status, household income, having ever received pubertal suppression (e.g., treatment with gonadotropin-releasing hormone agonists) [8], having ever been exposed to gender identity conversion efforts [23], and having experienced any harassment based on gender identity in K-12 (verbal, physical, or sexual) [5].

Statistical analyses

All statistical analyses were performed with SAS 9.4. The data in the analytic sample had minimal missing data for both exposure and outcome variables. Each control variable had under 8% missing data within all comparison groups. Therefore no imputation was performed, since listwise deletion with missingness as high as 10% can be acceptable under particular assumptions of missingness [24].

Analyses were performed for the three age groups of participants who accessed GAH and participants who desired but never accessed GAH, on demographic variables listed above. Variables were analyzed with Rao-Scott χ^2 tests. Logistic regression tests were used to identify demographics and other potential confounding variables associated with each outcome.

Multivariable logistic regression was then performed, comparing mental health outcomes for participants who reported access to GAH during early adolescence, late adolescence, or adulthood with those for participants who desired but never accessed GAH. Models were fit to test associations with mental health outcomes, after adjusting for demographic and potential confounding variables that were found to be associated with each outcome. All hypothesis tests were 2-sided. The percentage decrease in adjusted odds for the outcomes was calculated from the model coefficients for each age group.

In order to account for multiple comparisons, a modified Bonferroni correction was applied for the approximately 50 comparisons performed. A significance threshold of 0.001 (.05/50) was used for our analyses.

After all aforementioned analyses were completed, we identified further analyses of interest that were not included in the original study design, and therefore not included in the Bonferroni correction. In these post hoc analyses, we compared access to GAH during adolescence (ages 14–17) to access during adulthood (ages ≥ 18), and access to GAH during early adolescence (ages 14–15) to access during late adolescence (ages 16–17).

Results

Demographic differences & potential confounding variables

In total, 21,598 participants (77.9%) reported ever desiring GAH. Of these, 8,860 (41.0%) never accessed GAH, 119 (0.6%) reported access to GAH in early adolescence, 362 (1.7%) reported access to GAH in late adolescence, and 12,257 (56.8%) reported access to GAH in adulthood. Significant differences were found based on age at time of study participation, gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, relationship status, level of education, employment status, household income, having ever received pubertal suppression, having ever been exposed to gender identity conversion efforts, and having experienced verbal, physical, or sexual harassment based on gender identity in K-12 ([Table 1](#)).

GAH during early adolescence

The median age of participants who reported accessing GAH during early adolescence was 21.0 (IQR 18.0–35.0). After adjusting for demographic and potential confounding variables, recalled access to GAH during early adolescence was associated with lower odds of past-month severe psychological distress (aOR = 0.3, 95% CI = 0.2–0.4, $p < .0001$) and past-year suicidal ideation (aOR = 0.4, 95% CI = 0.2–0.6, $p < .001$) when compared to desiring GAH but never accessed them. For participants who recalled GAH access in early adolescence, these results represent a 222% decrease in adjusted odds for past-month severe psychological distress and a 135% decrease for past-year suicidal ideation. We detected no difference for other mental health variables measured ([Table 2](#)).

GAH during late adolescence

The median age of participants who reported accessing GAH during late adolescence was 19.0 (IQR 18.0–22.0). After adjusting for demographic and potential confounding variables, recalled access to GAH during late adolescence was associated with lower odds of past-month severe psychological distress (aOR = 0.3, 95% CI = 0.3–0.4, $p < .0001$) and past-year suicidal ideation (aOR = 0.5, 95% CI = 0.4–0.7, $p < .0001$) when compared to desiring GAH but never accessing them. These results represent a 153% decrease in the adjusted odds for past-month severe psychological distress and a 62% decrease for past-year suicide ideation. We detected no difference for other mental health variables measured ([Table 2](#)).

GAH during adulthood

The median age of participants who reported accessing GAH during adulthood was 31.0 (IQR 25.0–45.0). After adjusting for demographic and potential confounding variables, participants who recalled access to GAH during adulthood had lower odds of past-month severe psychological distress (aOR = 0.6, 95% CI = 0.5–0.6, $p < .0001$) and past-year suicidal ideation

Table 1. Sample demographics.

Total N = 21,598		No GAH n = 8860 n (%)	GAH 14–15 n = 119 n (%)	GAH 16–17 n = 362 n (%)	GAH ≥ 18 n = 12257 n (%)	p
Age (Census)						<0.001
	18–24	5315 (60.0)	75 (63.03)	297 (82.04)	2856 (23.30)	
	25–44	2653 (29.9)	23 (19.33)	54 (14.92)	6285 (51.28)	
	45–64	753 (8.5)	19 (15.97)	11 (3.04)	2660 (21.70)	
	65+	139 (1.57)	2 (1.68)	0 (0.00)	456 (3.72)	
Gender Identity						<0.001
	Trans man / male	02620 (29.57)	00048 (40.34)	00214 (59.12)	04713 (38.45)	
	Trans woman / female	02324 (26.23)	00054 (45.38)	00109 (30.11)	06340 (51.73)	
	AFAB GQ/NB	02829 (31.93)	00013 (10.92)	00035 (9.67)	00834 (6.80)	
	AMAB GQ/NB	00766 (8.65)	00004 (3.36)	00004 (1.10)	00330 (2.69)	
	Other	00321 (3.62)	00000 (0.00)	00000 (0.00)	00040 (0.33)	
Sex Assigned at Birth						<0.001
	Female	05475 (61.79)	00061 (51.26)	00249 (68.78)	05561 (45.37)	
	Male	03385 (38.21)	00058 (48.74)	00113 (31.22)	06696 (54.63)	
Sexual Orientation						<0.001
	Asexual	01220 (13.77)	00006 (5.04)	00022 (6.08)	00771 (06.29)	
	Bisexual	01391 (15.70)	00007 (5.88)	00056 (15.47)	01900 (15.50)	
	Gay/Lesbian/Same Gender Loving	01337 (15.09)	00022 (18.49)	00064 (17.68)	02535 (20.68)	
	Heterosexual/Straight	00743 (8.39)	00031 (26.05)	00071 (19.61)	02019 (16.47)	
	Pansexual	01875 (21.16)	00021 (17.65)	00066 (18.23)	01877 (15.31)	
	Queer	01573 (17.75)	00019 (15.97)	00058 (16.02)	02525 (20.60)	
	Other	00721 (08.14)	00013 (10.92)	00025 (6.91)	00630 (5.14)	
Race / Ethnicity						<0.001
	Alaska Native/American Indian	00105 (1.19)	00002 (1.68)	00003 (0.83)	00149 (1.22)	
	Asian/Native Hawaiian/Pacific Islander	00273 (3.08)	00008 (6.72)	00010 (2.76)	00292 (2.38)	
	Biracial/Multiracial	00475 (5.36)	00009 (7.56)	00027 (7.46)	00571 (4.66)	
	Black/African American	00210 (2.37)	00011 (9.24)	00016 (4.42)	00378 (3.08)	
	Latin/Hispanic	00499 (5.63)	00008 (6.72)	00025 (6.91)	00572 (4.67)	
	White/Middle Eastern/North African	07298 (82.37)	00081 (68.07)	00281 (77.62)	10295 (83.99)	
Family Support of Gender Identity						<0.001
	Not Asked (Not Out to Family as Transgender)	03067 (34.64)	00003 (2.52)	00015 (4.14)	00901 (7.36)	
	Neutral	01564 (17.66)	00012 (10.08)	00032 (8.84)	01980 (16.16)	
	Supportive	02904 (32.80)	00091 (76.47)	00291 (80.39)	07321 (59.77)	

(Continued)

Table 1. (Continued)

Total N = 21,598		No GAH n = 8860 n (%)	GAH 14–15 n = 119 n (%)	GAH 16–17 n = 362 n (%)	GAH ≥ 18 n = 12257 n (%)	p
Relationship Status	Unsupportive	01319 (14.90)	00013 (10.92)	00024 (6.63)	02047 (16.71)	
	Missing	6 (0.07)	0 (0.00)	0 (00.00)	8 (0.08)	
						<0.001
Education	Partnered	04028 (46.90)	00049 (43.36)	00135 (38.03)	06257 (52.99)	
	Unpartnered	04560 (53.10)	00064 (56.64)	00220 (61.97)	05551 (47.01)	
	Other	272 (3.07)	6 (5.04)	7 (1.93)	449 (3.66)	
						<0.001
Employment Status	Bachelor's degree or higher	02219 (25.05)	00023 (19.33)	00048 (13.26)	05911 (48.23)	
	Some college (no degree)/Associate's	04555 (51.41)	00061 (51.26)	00171 (47.24)	05199 (42.42)	
	High school grad (including GED)	01617 (18.25)	00023 (19.33)	00099 (27.35)	00975 (7.95)	
	Less than high school	00469 (5.29)	00012 (10.08)	00044 (12.15)	00172 (1.40)	
						<0.001
Household Income	Employed	05213 (59.10)	00060 (50.85)	00189 (52.50)	08788 (72.01)	
	Out of the labor force	02038 (23.10)	00039 (33.05)	00108 (30.00)	02283 (18.71)	
	Unemployed	01570 (17.80)	00019 (16.10)	00063 (17.50)	01133 (9.28)	
	Excluded (status unclear)	4 (0.05)	0 (0)	2 (00.55)	2 (0.02)	
	Missing	35 (0.40)	1 (0.48)	0 (0)	51 (0.42)	
						<0.001
Ever Received Pubertal Suppression	\$1 to \$9,999	01163 (14.75)	00016 (14.81)	00041 (12.65)	01160 (10.10)	
	\$10,000 to \$24,999	01714 (21.73)	00013 (12.04)	00053 (16.36)	02252 (19.62)	
	\$100,000 or more	01136 (14.40)	00023 (21.30)	00079 (24.38)	02064 (17.98)	
	\$25,000 to \$49,999	01717 (21.77)	00028 (25.93)	00059 (18.21)	02652 (23.10)	
	\$50,000 to \$100,000	01772 (22.47)	00024 (22.22)	00071 (21.91)	03035 (26.44)	
	No income	00385 (4.88)	00004 (3.70)	00021 (6.48)	00317 (2.76)	
	Excluded	275 (3.10)	7 (5.88)	11 (3.04)	313 (2.55)	
	Missing	698 (7.88)	4 (3.36)	27 (7.46)	464 (3.79)	
						<0.001
Ever Experienced Gender Identity Conversion Efforts	Yes	00031 (0.36)	00041 (34.45)	00044 (12.15)	00221 (01.80)	
	No	08659 (99.64)	00078 (65.55)	00318 (87.85)	12036 (98.20)	
	Missing	00170 (1.92)	0 (0.00)	0 (0.00)	0 (0.00)	
						<0.001

(Continued)

Table 1. (Continued)

Total N = 21,598		No GAH	GAH 14–15	GAH 16–17	GAH ≥ 18	p
		n = 8860	n = 119	n = 362	n = 12257	
		n (%)	n (%)	n (%)	n (%)	
	Yes	00998 (11.28)	00031 (26.27)	00092 (25.48)	02208 (18.03)	
	No	07852 (88.72)	00087 (73.73)	00269 (74.52)	10037 (81.97)	
	Missing	10 (0.11)	1 (0.84)	1 (0.28)	12 (0.10)	
K–12 Harassment						<0.001
	Verbal, physical or sexual	2026 (22.9)	80 (67.2)	226 (62.4)	2612 (21.3)	
	None	6834 (77.1)	39 (32.8)	136 (37.6)	9645 (78.7)	

Descriptive statistics for transgender adults in the U.S. who ever desired gender-affirming hormones (GAH) for their gender identity or gender transition, comparing those who never accessed this treatment (No GAH), those who accessed GAH between their 14th and 16th birthdays (GAH 14–15), those who accessed GAH after their 16th birthday and before their 18th birthday (GAH 16–18) and those who accessed GAH after their 18th birthday (GAH ≥ 18).

Abbreviations: AFAB (assigned female at birth), AMAB (assigned male at birth), GQ/NB (gender queer or non-binary).

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(aOR = 0.8, 95% CI = 0.7–0.8, $p < .0001$) when compared to those who desired GAH but never accessed them. Access to GAH during adulthood was associated with an 81% decrease in adjusted odds of past-month severe psychological distress and a 21% decrease in past-year suicidal ideation. Access to GAH during adulthood was also associated with greater odds of past-month binge drinking (aOR = 1.2, 95% CI = 1.1–1.3, $p < .0001$) and lifetime illicit drug use (aOR = 1.7, 95% CI = 1.6–1.8, $p < .0001$) when compared to desiring but never accessing GAH. Results indicated an adjusted odds increase of 20% for past-month binge drinking and 70% increase for lifetime illicit drug use. We detected no difference for other mental health variables measured (Table 2).

Raw frequencies of outcome variables

Raw frequencies for outcome variables are shown in Table 3.

Post hoc analyses

GAH during adolescence vs. GAH during adulthood. After adjusting for demographic and potential confounding variables, access to GAH during adolescence (ages 14–17) was associated with lower odds of past-month severe psychological distress (aOR = 0.6, 95% CI = 0.5–0.8, $p < .0001$), past-year suicidal ideation (aOR = 0.7, 95% CI = 0.6–0.9, $p = .0007$), past-month binge drinking (aOR = 0.7, 95% CI = 0.5–0.9, $p = .001$), and lifetime illicit drug use (aOR = 0.7, 95% CI = 0.5–0.8, $p = .0003$) when compared to access to GAH during adulthood. We detected no difference for other mental health variables measured (Table 4).

Access to GAH during early vs. late adolescence. After adjusting for demographic and potential confounding variables, we detected no difference in odds of any mental health variables measured when comparing access to GAH during early adolescence with access to GAH during late adolescence (Table 4).

Lifetime but no past year suicidality. Due to the cross-sectional nature of the study, it was possible that we detected an association between favorable mental health outcomes and access to GAH because people with better mental health were more likely to be able to access GAH. Given that baseline mental health status could confound associations between access to GAH and mental health outcomes, in post hoc analyses we examined two outcome measures

Table 2. Outcomes for participants who accessed gender-affirming hormones (estrogen or testosterone).

	Participants who Accessed GAH											
	N = 12,598											
	Accessed GAH at Age 14 or 15				Accessed GAH at Age 16 or 17				Accessed GAH at Age $\geq$ 18			
	n = 119				n = 362				n = 12257			
	OR (95% CI)	p	aOR (95% CI)	p	OR (95% CI)	p	aOR (95% CI)	p	OR (95% CI)	p	aOR (95% CI)	p
Suicidality (Past 12 months)												
Past-year suicidal ideation ^a	0.5 (0.3–0.7)	.0001	0.4 (0.2–0.6)	< .0001	1.0 (0.8–1.2)	.73	0.5 (0.4–0.7)	< .0001	0.5 (0.5–0.6)	< .0001	0.8 (0.7–0.8)	< .0001
Past-year suicidal ideation with plan ^b	1.3 (0.8–2.4)	.31	0.8 (0.4–1.6)	.58	1.1 (0.9–1.5)	.41	0.9 (0.7–1.2)	.49	0.8 (0.8–0.9)	< .0001	0.9 (0.8–1.0)	.09
Past-year suicide attempt ^c	1.0 (0.5–2.2)	.99	0.4 (0.2–1.1)	.08	1.4 (1.0–2.0)	.04	0.9 (0.6–1.4)	.79	0.8 (0.8–0.9)	.002	1.0 (0.9–1.1)	.89
Past-year suicide attempt requiring inpatient hospitalization ^d	--	--	--	--	2.2 (1.2–4.0)	.01	2.2 (1.2–4.2)	.01	1.4 (1.1–1.7)	.002	1.2 (0.9–1.5)	.26
Mental Health & Substance Use												
Past-month severe psychological distress (K6 $\geq$ 13) ^e	0.5 (0.3–0.7)	.0004	0.3 (0.2–0.4)	< .0001	0.6 (0.5–0.8)	< .0001	0.3 (0.3–0.4)	< .0001	0.4 (0.3–0.4)	< .0001	0.6 (0.5–0.6)	< .0001
Past-month binge drinking ^e	1.6 (1.1–2.3)	.02	1.6 (1.0–2.4)	.04	0.8 (0.6–1.1)	.17	0.9 (0.6–1.1)	.27	1.2 (1.1–1.2)	< .0001	1.2 (1.1–1.3)	< .0001
Lifetime illicit drug use ^f	1.8 (1.2–2.6)	.003	1.5 (1.0–2.2)	.08	1.2 (1.0–1.6)	.08	1.3 (1.0–1.6)	.07	2.1 (1.9–2.2)	< .0001	1.7 (1.6–1.8)	< .0001

Mental health outcomes of transgender adults who recalled access to gender-affirming hormones (GAH) during various age groups. Reference group for all analyses is participants who desired GAH but did not access them. All models adjusted for age, partnership status, employment status, K-12 harassment, and having experienced gender identity conversion efforts.

Abbreviations: OR (odds ratio), aOR (adjusted odds ratio), 95% CI (95% confidence interval).

^a Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, and total household income.

^b Model also adjusted for sexual orientation, race/ethnicity, educational attainment, and total household income.

^c Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, total household income, and having received pubertal suppression.

^d Model also adjusted for family support of gender identity. Only one participant in the GAH < 16 group endorsed a past-year suicide attempt requiring inpatient hospitalization, precluding calculation of an aOR for this outcome.

^e Model also adjusted for gender identity, sex assigned at birth, sexual orientation, family support of gender identity, educational attainment, and total household income.

^f Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, and educational attainment.

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relevant to this question of temporality: lifetime but no past-year suicidal ideation, and lifetime but no past-year suicide attempt. We found that access to GAH in adulthood was associated with greater odds of lifetime but no past-year suicidal ideation (aOR = 1.4, 95% CI = 1.3–1.5, $p < .0001$) when compared to desiring but not accessing GAH (Table 5). The association of access to GAH during late adolescence with lifetime but no past year suicidal ideation (aOR = 1.4, 95% CI = 1.1–1.8, $p = .005$) was no longer significant after Bonferroni correction, though some have noted that Bonferroni adjustment may be overly conservative, suggesting that this finding may be considered significant [25].

Discussion

In this large national cross-sectional non-probability study, transgender people who accessed GAH during early adolescence, late adolescence, or adulthood had better mental health

Table 3. Raw outcome frequencies of mental health outcomes.

Total N = 21,598	No GAH	GAH 14–15	GAH 16–17	GAH ≥ 18
	n = 8860	n = 119	n = 362	n = 12257
	n (%)	n (%)	n (%)	n (%)
Suicidality (Past 12 months)				
Past-year suicidal ideation	5144 (58.1)	48 (40.3)	40 (33.6)	5237 (42.7)
Past-year suicidal ideation with plan	2731 (30.8)	29 (24.3)	39 (32.8)	02537 (20.7)
Past-year suicide attempt	853 (9.6)	8 (6.7)	40 (33.6)	756 (6.2)
Past-year suicide attempt requiring inpatient hospitalization	220 (2.5)	1 (0.8)	40 (33.6)	247 (2.0)
Mental Health & Substance Use				
Past-month severe psychological distress (K6 ≥ 13)	4545 (51.3)	40 (33.6)	145 (40.1)	3419 (27.9)
Past-month binge drinking	2083 (23.5)	39 (32.8)	74 (20.4)	3214 (26.2)
Lifetime illicit drug use	1918 (21.6)	40 (33.6)	93 (25.7)	4455 (36.3)

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outcomes when compared to those who desired but were unable to access GAH. Given the substantial mental health disparities faced by transgender people, these results are of particular importance [26].

For each time period of GAH initiation examined (early adolescence, late adolescence, and adulthood), access to GAH was associated with lower odds of past-year suicidal ideation and past-month severe psychological distress. When we compared participants who accessed GAH during adolescence (ages 14–17) with those who accessed GAH during adulthood (18+),

Table 4. Outcomes for participants who accessed gender-affirming hormones (estrogen or testosterone).

	Accessed GAH at Age 14–17				Accessed GAH at Age 14 or 15			
	(compared to GAH access at age ≥ 18)				(compared to GAH access at age 16 or 17)			
	n = 481				n = 119			
	OR (95% CI)	p	aOR (95% CI)	p	OR (95% CI)	p	aOR (95% CI)	p
Suicidality (Past 12 months)								
Past-year suicidal ideation ^a	1.5 (1.3–1.8)	< .0001	0.7 (0.6–0.9)	.0007	0.5 (0.3–0.8)	.002	0.7 (0.4–1.2)	.16
Past-year suicidal ideation with plan ^b	1.4 (1.1–1.8)	.009	1.1 (0.8–1.5)	.51	1.2 (0.6–2.3)	.58	1.0 (0.5–1.9)	.88
Past-year suicide attempt ^c	1.6 (1.2–2.2)	.003	1.0 (0.7–1.4)	.82	0.7 (0.3–1.6)	.40	0.4 (0.1–1.3)	.12
Past-year suicide attempt requiring inpatient hospitalization ^d	1.3 (0.7–2.3)	.35	1.7 (0.9–3.2)	.08	0.2 (0.0–1.6)	.13	0.2 (0.0–2.1)	.19
Mental Health & Substance Use								
Past-month severe psychological distress (K6 ≥ 13) ^e	1.7 (1.4–2.0)	< .0001	0.6 (0.5–0.8)	< .0001	0.8 (0.5–1.2)	.26	0.7 (0.4–1.3)	.30
Past-month binge drinking ^e	0.9 (0.7–1.1)	.17	0.7 (0.5–0.9)	.001	1.9 (1.2–3.0)	.006	2.0 (1.2–3.5)	.01
Lifetime illicit drug use ^f	0.7 (0.5–0.8)	< .001	0.7 (0.5–0.8)	.0003	1.4 (0.9–2.3)	.10	1.0 (0.6–1.7)	.98

All models adjusted for age, partnership status, employment status, K-12 harassment, and having experienced gender identity conversion efforts.

Abbreviations: OR (odds ratio), aOR (adjusted odds ratio), 95% CI (95% confidence interval).

^a Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, and total household income.

^b Model also adjusted for sexual orientation, race/ethnicity, educational attainment, and total household income.

^c Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, total household income, and having received pubertal suppression.

^d Model also adjusted for family support of gender identity.

^e Model also adjusted for gender identity, sex assigned at birth, sexual orientation, family support of gender identity, educational attainment, and total household income.

^f Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, and educational attainment.

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Table 5. Lifetime but no past-year suicide ideation and attempts for participants who accessed gender-affirming hormones (estrogen or testosterone).

	Participants who Accessed GAH					
	N = 12,598					
	Accessed GAH at Age 14 or 15		Accessed GAH at Age 16 or 17		Accessed GAH at Age ≥ 18	
	n = 119		n = 362		n = 12,257	
	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p
Lifetime suicidal ideation and no past-year ideation ^a	1.3 (0.8–2.0)	.28	1.4 (1.1–1.8)	.005	1.4 (1.3–1.5)	< .0001
Lifetime suicide attempt and no past-year attempt ^b	0.8 (0.5–1.2)	.24	0.7 (0.6–1.0)	.03	1.0 (0.9–1.1)	.67

Mental health outcomes of transgender adults who recalled access to gender-affirming hormones (GAH) during various age groups. Reference group for all analyses is participants who desired GAH but did not access them. Both models adjusted for age, partnership status, employment status, K-12 harassment, and having experienced gender identity conversion efforts.

^a Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, and total household income.

^b Model also adjusted for gender identity, sex assigned at birth, sexual orientation, race/ethnicity, family support of gender identity, educational attainment, total household income, and having received pubertal suppression.

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participants who accessed GAH earlier had better mental health outcomes, including lower odds of past-year suicidal ideation, past-month severe psychological distress, past-month binge drinking, and lifetime illicit drug use. These results argue against waiting until adulthood to offer GAH to transgender adolescents and suggest that doing so may put patients at greater mental health risk.

The current study has a few advantages over past published studies in this area. While past studies have not included a comparison group of people who did not access GAH and were also underpowered to adjust for potential cofounders, this large sample size enabled comparison of participants who reported access to GAH to those who desired but did not access GAH, while adjusting for a wide range of potential confounding variables known to be associated with mental health outcomes for transgender people.

One unexpected finding was that participants who initiated GAH during adulthood, compared to those who desired but never accessed GAH, had greater odds of past-month binge drinking and lifetime illicit substance use. Transgender people often become more socially engaged following the increased confidence that results from gender affirmation, which may partly explain these results [27]. Given the high prevalence of substance use disorders in this population, clinicians ought to routinely screen for substance use disorders among transgender people, and researchers ought to focus on development of culturally responsive substance use disorder prevention and treatment interventions with transgender communities [27].

Notably, even participants who recalled access to GAH had high rates of past-year suicidal ideation. Though access to GAH during adolescence appears to be related to more favorable mental health outcomes, transgender people face a range of other psychosocial stressors that contribute to chronic minority stress, including but not limited to employment discrimination, lack of safe access to public facilities, and physical violence [4]. Future epidemiological and interventional research is needed to understand and address chronic minority stress among transgender people who access GAH as well as those who do not. For transgender adolescents, creating safe and affirming school environments appears to be of particular importance [28], in addition to providing gender-affirming medical care, as well as psychological, legal and surgical gender affirmation as needed [6].

This study also suggests that a large proportion of transgender people desire but never access GAH. Though prevalence in a non-probability sample should be interpreted with

caution, 41% of those who desired GAH in this study reported that they were unable to access them. Barriers to accessing prescribed GAH, in addition to leaving many without treatment, may also drive use of non-prescribed GAH, which is highly prevalent and associated with stigmatizing healthcare policies [29]. Future studies ought to examine if non-prescribed GAH use, when compared to prescribed GAH, is linked to worse mental health outcomes or adverse physical health outcomes (e.g., blood clot risk from estradiol use without standard medical monitoring).

Strengths and limitations

Strengths of this study include its large sample size and broad geographic representation within the U.S. The large sample size enabled adjustment for a wide range of potential confounding variables. Limitations include its non-probability cross-sectional design, which reduces generalizability and limits determination of causality. It is possible that people with better mental health status at baseline are more likely to be able to access GAH, thus confounding associations between GAH access and adult mental health outcomes measured: we therefore examined lifetime but not past-year suicidal ideation as an outcome, with results suggesting a lack of reverse causation due to such confounding. Nonetheless, this method is imperfect for investigating mental health changes following GAH, and future longitudinal studies are needed. Longitudinal waitlist control studies would be of particular value. Though a randomized controlled trial would help determine causality, many have noted that such a trial design is unethical in this context [2]. Age of GAH initiation reported by participants at time of data collection is vulnerable to recall bias. It is possible that participants in older age cohorts (45–65; 65+) were more vulnerable to recall bias; in our clinical experience, however, starting GAH is a major event in one's life, making it less susceptible to recall bias than more routine events [30]. It was unexpected that the median age at time of survey completion for participants who recalled accessing GAH in early adolescence was older than for those in the late adolescence group, which may be indicative of recall bias. Of note, though it is often presumed that GAH were not offered to adolescents in the U.S. until the past three decades, recent historical analyses have pointed out that adolescents have been receiving GAH as early as the 1970s [31]. The 2015 USTS sample is younger, with fewer racial minorities, fewer heterosexual participants, and higher educational attainment when compared with probability samples of TGD people in the U.S [32]. Because all participants identified as non-cisgender, those who initiated GAH and subsequently identified as cisgender would not necessarily be represented in this study; existing literature, however, suggests that this is a rare occurrence [2, 33].

Conclusion

This study found that transgender people who accessed GAH during early or late adolescence had a lower odds of past-month suicidal ideation and past-month severe psychological distress in adulthood, when compared to those who desired but did not access GAH, after adjusting for a range of potential confounding variables. The findings support updated 2017 recommendations from The Endocrine Society [7] and WPATH [6] that these medical interventions be made available for transgender adolescents. The results also provide additional evidence to suggest that legislation restricting transgender adolescents' access to gender-affirming medical care would result in adverse mental health outcomes [18].

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RESEARCH

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Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results

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Abstract

Background/aims: Transgender youths experience high rates of depression and suicidal ideation compared to cisgender peers. Previous studies indicate that endocrine and/or surgical interventions are associated with improvements to mental health in adult transgender individuals. We examined the associations of endocrine intervention (puberty suppression and/or cross sex hormone therapy) with depression and quality of life scores over time in transgender youths.

Methods: At approximately 6-month intervals, participants completed depression and quality of life questionnaires while participating in endocrine intervention. Multiple linear regression and residualized change scores were used to compare outcomes.

Results: Between 2013 and 2018, 50 participants (mean age 16.2 ± 2.2 yr) who were naïve to endocrine intervention completed 3 waves of questionnaires. Mean depression scores and suicidal ideation decreased over time while mean quality of life scores improved over time. When controlling for psychiatric medications and engagement in counseling, regression analysis suggested improvement with endocrine intervention. This reached significance in male-to-female participants.

Conclusion: Endocrine intervention may improve mental health in transgender youths in the US. This effect was observed in both male-to-female and female-to-male youths, but appears stronger in the former.

Keywords: Transgender, Transgender management, Transgender youth, Depression, Suicide, Suicidal ideation, Quality of life, GnRH analogue, Puberty suppression, Puberty, Testosterone, Estrogen, Cross sex hormone

Introduction

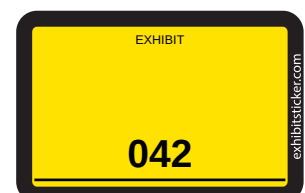
Transgender individuals have a gender identity that differs from the sex assigned at birth [1]. These individuals have a high prevalence of body image dysphoria, depression and suicidal ideation [2]. Studies in adults have

shown improvement in psychological function in adulthood from endocrine and/or surgical interventions. Specifically, studies have indicated a positive impact of cross sex steroid therapy on depression scores and quality of life in the adult transgender population [3]. Guidelines for endocrine intervention in transgender youth have existed for the past decade in the United States and longer internationally. These guidelines include suppression of puberty to provide more time before cross sex steroid

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therapy is introduced [4, 5]. Two studies have examined the impact of this strategy on depression and quality of life in youths. De Vries et al. demonstrated no improvement of gender dysphoria after puberty suppression alone but did report improvement only after both cross sex steroid therapy and gender confirmation surgery was complete in transgender individuals from the Netherlands [6]. These authors did not report findings after cross sex steroid therapy alone but before surgery. In the UK, Costa found that GnRH agonist suppression of puberty improved psychological functioning in transgender youth [7]. In the United States, there are few data concerning the impact of endocrine intervention on psychological function in transgender youth. Therefore, we conducted a longitudinal assessment of psychological wellbeing and quality of life in children and adolescents who have sought endocrine intervention to help with gender dysphoria. Herein, we report preliminary results of this ongoing study.

Objective

The aim of this study is to examine the impact that endocrine intervention [suppression of endogenous pubertal hormones utilizing GnRH agonists/anti-androgens/suppressors of menstruation (AKA “pubertal suppression”), or addition of cross-sex hormones] has on depression and quality of life scales of transgender youths as reported by the youths themselves over time.

Methods

Participants and procedure

This is a single center study approved by Stony Brook University IRB for children, adolescents and young adults aged 9–25 years. Subjects referred to the Pediatric Endocrine Department for gender dysphoria were approached to participate. Although we do not have exact numbers, the vast majority of eligible subjects agreed to take part in the study. Minor participants signed assent and participants over 18 years of age and parents of those less than 18 yr. of age signed consent to participate. Individuals with sex chromosome abnormalities and disorders of sexual differentiation were excluded from the study. At approximately 6-month intervals, participants completed the following validated assessments of mental health: The Center for Epidemiologic Studies Depression Scale (CESD-R) [8], The Patient Health Questionnaire Modified for Teens (PHQ-9_Modified for Teens) [9], Quality of Life Enjoyment and Satisfaction Questionnaire (QLES-Q-SF) [10]. Most subjects were followed by mental health professionals. Those that were not were encouraged to see a mental health professional.

Psychological measures

The CESD-R score is calculated as a sum of 20 questions, ranging from 0 (for those who say “not at all or less than one day” to all 20 questions) to a maximum score of 60 (for those who say “5–7 days” and/or “nearly every day for 2 weeks” for all 20 questions). A total CESD-R score less than 16 implies no clinical depression [8, 11]. The PHQ-9 consists of 9 questions describing symptoms of depression each rated 0 to 3 with the sum indicating level of depression: minimal 0–4, mild 5–9, moderate 10–14, moderately severe 15–19, severe 20–27. This questionnaire also asks the participants four additional questions relating to suicidal ideology and difficulty dealing with problems of life [9]. The QLES-Q-SF consists of 15 questions rating quality of life on a scale of 1–5 with 1 being poor and 5 being very good [10]. It was used rather than the Pediatric Quality of Life and Enjoyment Scale (PQLES-SF), which is based on QLES-Q-SF, because of the overlap in age inclusion of older adolescents and young adults and the intention of continuing the study into adulthood. Transyouths in the study were also asked if they were participating in psychological counseling and/or on psychiatric medication. ADHD medications were not included as psychiatric medication for this analysis.

Endocrine interventions

Endocrine interventions were introduced in accordance with the Endocrine Society and the WPATH guidelines [4, 5]. In our study, GnRH agonist and/or antiandrogens were used for male to female (MTF) participants, and suppression of menstruation (either GnRH agonist or Medroxyprogesterone) for female to male (FTM) participants. Collectively, these interventions were labeled “Puberty Suppression”. Once eligible as determined by mental health consultants, youths, parents and according to guidelines, cross sex hormones were prescribed, either testosterone for FTM or estrogen for MTF participants.

Statistical analysis

Regression analysis was used to examine the association of various treatments with outcomes experienced by transgender youths over time. Linear multiple regression was used for continuous outcomes, and multiple logistic regression was used for dichotomous outcomes. For continuous outcomes, residualized change scores were used to compare change at outcome relative to levels at baseline. This approach thus allowed us to control for the dependent variable’s level at baseline for each participant and to examine how endocrine intervention predicted change in the dependent variable over and above predicted outcome level relative to the level at baseline. Regression analyses also controlled for psychiatric medication and engagement in psychotherapy.

Results

Between December 2013 to December 2018, 116 participants entered the study. Ninety-five were naive to any endocrine intervention. Of those 95 participants, 50 completed 3 waves of questionnaires and these individuals compose the analytic sample in this report. Baseline data for this population are shown in Table 1. At wave one, none of the 50 participants were on endocrine intervention. By wave 3, 47 participants had some type of endocrine intervention (Table 2).

Mean changes over time

Mean baseline CESD-R score was 21.4 and decreased to 13.9 by wave 3 ($t(48) = 3.996$, $p < 0.001$, Fig. 1a). A score less than 16 implies no clinical depression. Mean depression scores by the PHQ-9 decreased over time as well ($t(49) = 3.753$, $p < 0.001$, Fig. 1b), while quality of life scores improved (Fig. 1c) but did not reach statistical significance ($t(48) = -1.758$, $p = .085$, Fig. 1c). Suicidal ideation decreased over time across all groups at wave 3 relative to baseline (Table 3). Thus, by all measures, depression and quality of life improved to some degree over time. Both gender subgroups demonstrated similar trends.

Regression analysis

We conducted a series of regression analyses to investigate preliminary trends in the data when controlled for reported psychiatric medications and engagement in counselling. Results are given in Table 4. Given our modest sample size, particularly when stratified by gender, most predictors did not reach statistical significance. This being said, effect sizes (R^2) values were notably large in many models. In MTF participants, only puberty suppression reached a significance level of $p < .05$ in the CESD-R. However, associations with PHQ9 and QLES-Q-SF scores approached significance. For FTM participants, only cross sex hormone therapy approached statistical significance for quality of life improvement ($p = 0.08$).

Model R^2 values ranged between small to large, even in models where the hormonal intervention's prediction of the outcome did not reach statistical significance. It is potentially noteworthy that effect sizes for endocrine

Table 2 Endocrine interventions at wave 3

Type of Intervention	% of Total (n)	% of FTM (n)	% of MTF (n)
None	6% (3)	3% (1)	12% (2)
Puberty Blocker	46% (23)	24% (8)	88% (15)
Cross Sex Hormone	70% (35)	85% (28)	41% (7)
Both	22% (11)	12% (4)	41% (7)

interventions were notably larger for MTF than FTM participants in almost every analysis. Regression models for suicidal thoughts were not estimable due to the low frequency of endorsement and small cell sizes across gender.

Discussion

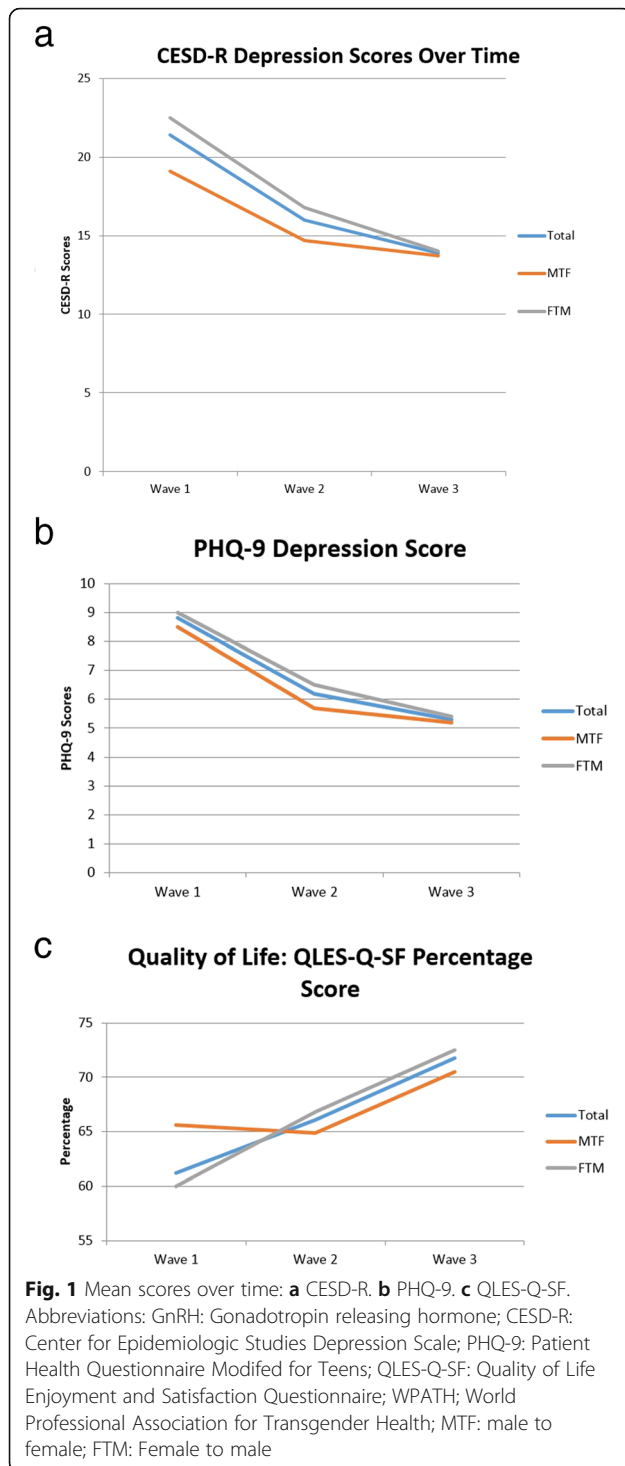
Cross-sex hormones and their effect on depression and quality of life has been extensively studied in adults. A meta-analysis by Costa and Colizza reported a reduction in anxiety and depression and improvement in quality of life with positive effect on personality and mood among transgender adults receiving cross-sex hormones therapy [3]. A 2006 cross-sectional study in California looked at adult FTM transgender participants on cross-sex hormone therapy and their quality of life. Participants who received testosterone therapy reported statistically significant higher quality of life than those who had not received hormonal therapy [12].

Adolescence is a particularly difficult time for transgender persons who experience the development of secondary sexual characteristics that are incongruous with their gender identity, and is associated with a high prevalence of depression and suicidal thoughts and gestures. Previous research has shown benefit to transgender youth in the Netherlands after cross sex steroid therapy AND gender confirmation surgery and in the UK after pubertal suppression alone [6, 7]. Our results extend these findings to transgender youths in the USA and apply prior to surgery.

Our results suggest that endocrine intervention is associated with improved mental health among transgender youth. This effect was observed in both MTF and FTM participants but appeared to be stronger in MTF. We speculate that this could be due to the following possibilities: 1. Testosterone has profound effects on

Table 1 Baseline characteristics at Wave 1

	Total	Female to Male	Male to Female
Number of participants	50	33	17
Age in Years (SD)	16.2 (2.2)	16.6 (2.5)	15.5 (1.6)
%Depressed in past year (n)	64% (32)	60.6% (20)	70.6% (12)
% Suicidal (n)	10% (5)	9.1% (3)	11.8% (2)
% In Counseling (n)	90% (45)	87.9% (29)	94.1% (16)
% On Psych Medication (n)	34% (17)	36.4% (12)	29.4% (5)



appearance. MTF participants may have experienced relief when serum testosterone concentrations are suppressed or antagonized; 2. The effects of testosterone in FTM transgender persons takes 6 to 12 months to become apparent and is not fully apparent until several years of exposure. Our study only extended for the first 12 months of endocrine intervention.

Table 3 Suicidal ideation

Suicidal Ideation Percentage: Wave 1 vs Wave 3		
	% at Wave 1 (n)	% at Wave 3 (n)
Total	10% (5)	6% (3)
MTF	11.8% (2)	5.9% (1)
FTM	9.1% (3)	6.1% (2)

Limitations and future directions

This is an ongoing study with preliminary results only presented herein. The numbers are too small to parse out the effects of pubertal suppression versus cross sex hormone therapy in the different genders. As our numbers continue to grow, we hope that we will be able to do so. As of now, we are only able to report trends.

Parental support has been shown to protect against mental health problems in transgender adolescents. Children who are socially transitioned at home, at school, and who use gender affirming pronouns represent those youths who are supported by their parents and caregivers. Being supported by family is associated with positive mental health outcomes [13]. Our data are somewhat limited by the fact that the majority of our participants had at least one supportive parent who was willing to facilitate medical and mental health intervention for the child and therefore may not apply to all transgender youths. In addition, regular visits with the medical team itself could influence depression and quality of life. Past studies have shown that having support from a multidisciplinary medical team – mental health provider, physician, surgeons – helped with quality of life and mental health [6].

Conclusions

Transgender children and adolescent are a high-risk population for suicide and depression. Our preliminary results show negative associations between depression scores/suicidal ideation and endocrine intervention, while quality of life scores showed positive associations with intervention, in transgender youths over time in the US. These results align with previous work in the Netherlands and the UK.

Table 4 Regression results when controlled for engagement in counselling and psychiatric medications

Survey	Intervention	MTF			FTM		
		b	p	R ²	b	p	R ²
CESD-R	Puberty Suppression	-2.41	0.008	0.52	-0.02	0.95	0.09
	Cross Sex Hormone	-0.56	0.27	0.21	-0.43	0.43	0.11
PHQ-9	Puberty Suppression	-1.89	0.07	0.28	-0.16	0.68	0.04
	Cross Sex Hormone	-0.92	0.07	0.29	-0.23	0.67	0.04
QOL	Puberty Suppression	1.26	0.21	0.13	0.71	0.86	0.01
	Cross Sex Hormone	0.87	0.06	0.08	0.93	0.08	0.11

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Authors' contributions

All authors contributed to the work as outlined below: Christal Achille: Primary author, helped recruit and collect data. Tenille Taggart: Worked on data entry and data analysis. Jennifer Osipoff: Recruited subjects, collected data. Kimberly Tafuri: Recruited subjects, collected data. Andrew Lane: Recruited subjects, collected data. Nicholas Eaton: Statistical analysis and interpretation. Thomas Wilson: Senior author, initial research conceptualization, IRB approval, subject recruitment, data entry and analysis and final submission. The author(s) read and approved the final manuscript.

Funding

This study is not funded.

Availability of data and materials

Data is not available as it would compromise confidentiality of the subjects participating.

Ethics approval and consent to participate

This research effort was approved by the Stony Brook University Committee on Research Involving Human Subjects. Consent and assent to participate was obtained from subjects < 18 years of age and their respective parents and consent was obtained from those over age 18 years of age.

Consent for publication

Consent for publication was included in the consent/assent.

Competing interests

The authors declare that they have no competing interests.

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Original Investigation | Pediatrics

Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care

Diana M. Tordoff, MPH; Jonathon W. Wanta, MD; Arin Collin, BA; Cesalie Stepney, PhD; David J. Inwards-Breland, MD, MPH; Kym Ahrens, MD, MPH

Abstract

IMPORTANCE Transgender and nonbinary (TNB) youths are disproportionately burdened by poor mental health outcomes owing to decreased social support and increased stigma and discrimination. Although gender-affirming care is associated with decreased long-term adverse mental health outcomes among these youths, less is known about its association with mental health immediately after initiation of care.

OBJECTIVE To investigate changes in mental health over the first year of receiving gender-affirming care and whether initiation of puberty blockers (PBs) and gender-affirming hormones (GAHs) was associated with changes in depression, anxiety, and suicidality.

DESIGN, SETTING, AND PARTICIPANTS This prospective observational cohort study was conducted at an urban multidisciplinary gender clinic among TNB adolescents and young adults seeking gender-affirming care from August 2017 to June 2018. Data were analyzed from August 2020 through November 2021.

EXPOSURES Time since enrollment and receipt of PBs or GAHs.

MAIN OUTCOMES AND MEASURES Mental health outcomes of interest were assessed via the Patient Health Questionnaire 9-item (PHQ-9) and Generalized Anxiety Disorder 7-item (GAD-7) scales, which were dichotomized into measures of moderate or severe depression and anxiety (ie, scores ≥ 10), respectively. Any self-report of self-harm or suicidal thoughts over the previous 2 weeks was assessed using PHQ-9 question 9. Generalized estimating equations were used to assess change from baseline in each outcome at 3, 6, and 12 months of follow-up. Bivariate and multivariable logistic models were estimated to examine temporal trends and investigate associations between receipt of PBs or GAHs and each outcome.

RESULTS Among 104 youths aged 13 to 20 years (mean [SD] age, 15.8 [1.6] years) who participated in the study, there were 63 transmasculine individuals (60.6%), 27 transfeminine individuals (26.0%), 10 nonbinary or gender fluid individuals (9.6%), and 4 youths who responded "I don't know" or did not respond to the gender identity question (3.8%). At baseline, 59 individuals (56.7%) had moderate to severe depression, 52 individuals (50.0%) had moderate to severe anxiety, and 45 individuals (43.3%) reported self-harm or suicidal thoughts. By the end of the study, 69 youths (66.3%) had received PBs, GAHs, or both interventions, while 35 youths had not received either intervention (33.7%). After adjustment for temporal trends and potential confounders, we observed 60% lower odds of depression (adjusted odds ratio [aOR], 0.40; 95% CI, 0.17-0.95) and 73% lower odds of suicidality (aOR, 0.27; 95% CI, 0.11-0.65) among youths who had initiated PBs or GAHs compared with youths who had not. There was no association between PBs or GAHs and anxiety (aOR, 1.01; 95% CI, 0.41, 2.51).

(continued)

Key Points

Question Is gender-affirming care for transgender and nonbinary (TNB) youths associated with changes in depression, anxiety, and suicidality?

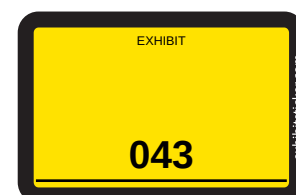
Findings In this prospective cohort of 104 TNB youths aged 13 to 20 years, receipt of gender-affirming care, including puberty blockers and gender-affirming hormones, was associated with 60% lower odds of moderate or severe depression and 73% lower odds of suicidality over a 12-month follow-up.

Meaning This study found that access to gender-affirming care was associated with mitigation of mental health disparities among TNB youths over 1 year; given this population's high rates of adverse mental health outcomes, these data suggest that access to pharmacological interventions may be associated with improved mental health among TNB youths over a short period.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.



Abstract (continued)

CONCLUSIONS AND RELEVANCE This study found that gender-affirming medical interventions were associated with lower odds of depression and suicidality over 12 months. These data add to existing evidence suggesting that gender-affirming care may be associated with improved well-being among TNB youths over a short period, which is important given mental health disparities experienced by this population, particularly the high levels of self-harm and suicide.

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Introduction

Transgender and nonbinary (TNB) youths are disproportionately burdened by poor mental health outcomes, including depression, anxiety, and suicidal ideation and attempts.¹⁻⁵ These disparities are likely owing to high levels of social rejection, such as a lack of support from parents^{6,7} and bullying,^{6,8,9} and increased stigma and discrimination experienced by TNB youths. Multidisciplinary care centers have emerged across the country to address the health care needs of TNB youths, which include access to medical gender-affirming interventions, such as puberty blockers (PBs) and gender-affirming hormones (GAHs).¹⁰ These centers coordinate care and help youths and their families address barriers to care, such as lack of insurance coverage¹¹ and travel times.¹² Gender-affirming care is associated with decreased rates of long-term adverse outcomes among TNB youths. Specifically, PBs, GAHs, and gender-affirming surgeries have all been found to be independently associated with decreased rates of depression, anxiety, and other adverse mental health outcomes.¹³⁻¹⁶ Access to these interventions is also associated with a decreased lifetime incidence of suicidal ideation among adults who had access to PBs during adolescence.¹⁷ Conversely, TNB youths who present to care later in adolescence or young adulthood experience more adverse mental health outcomes.¹⁸ Despite this robust evidence base, legislation criminalizing and thus limiting access to gender-affirming medical care for minors is increasing.^{19,20}

Less is known about the association of gender-affirming care with mental health outcomes immediately after initiation of care. Several studies published from 2015 to 2020 found that receipt of PBs or GAHs was associated with improved psychological functioning²¹ and body satisfaction,²² as well as decreased depression²³ and suicidality²⁴ within a 1-year period. Initiation of gender-affirming care may be associated with improved short-term mental health owing to validation of gender identity and clinical staff support. Conversely, prerequisite mental health evaluations, often perceived as pathologizing by TNB youths, and initiation of GAHs may present new stressors that may be associated with exacerbation of mental health symptoms early in care, such as experiences of discrimination associated with more frequent points of engagement in a largely cisnormative health care system (eg, interactions with nonaffirming pharmacists to obtain laboratory tests, syringes, and medications).²⁵ Given the high risk of suicidality among TNB adolescents, there is a pressing need to better characterize mental health trends for TNB youths early in gender-affirming care. This study aimed to investigate changes in mental health among TNB youths enrolled in an urban multidisciplinary gender clinic over the first 12 months of receiving care. We also sought to investigate whether initiation of PBs or GAHs was associated with depression, anxiety, and suicidality.

Methods

This cohort study received approval from the Seattle Children's Hospital Institutional Review Board. For youths younger than age 18 years, caregiver consent and youth assent was obtained. For youths ages 18 years and older, youth consent alone was obtained. The 12-month assessment was funded via a different mechanism than other survey time points; thus, participants were reconsented for the

12-month survey. The study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Procedures

We conducted a prospective observational cohort study of TNB youths seeking care at Seattle Children's Gender Clinic, an urban multidisciplinary gender clinic. After a referral is placed or a patient self-refers, new patients, their caregivers, or patients with their caregivers are scheduled for a 1-hour phone intake with a care navigator who is a licensed clinical social worker. Patients are then scheduled for an appointment at the clinic with a medical provider.

All patients who completed the phone intake and in-person appointment between August 2017 and June 2018 were recruited for this study. Participants completed baseline surveys within 24 hours of their first appointment and were invited to complete follow-up surveys at 3, 6, and 12 months. Youth surveys were used to assess most variables in this study; caregiver surveys were used to assess caregiver income. Participation and completion of study surveys had no bearing on prescribing of PBs or GAHs.

Measures

Mental Health Variables

We assessed 3 internalizing mental health outcomes: depression, generalized anxiety, and suicidality. Depression was assessed using the Patient Health Questionnaire 9-item scale (PHQ-9), and anxiety was assessed using the Generalized Anxiety Disorder 7-item scale (GAD-7). We dichotomized PHQ-9 and GAD-7 scores into measures of moderate or severe depression and anxiety (ie, scores ≥ 10).^{26,27} Self-harm and suicidal thoughts were assessed using PHQ-9 question 9 (eTable 1 in the [Supplement](#)).

Pharmacological Interventions

Participants self-reported if they had ever received GAHs, including estrogen or testosterone, or PBs (eg, gonadotropin-releasing hormone analogues) on each survey. We conducted a medical record review to capture prescription of androgen blockers (eg, spironolactone) and medications for menstrual suppression or contraception (ie, medroxyprogesterone acetate or levonorgestrel-releasing intrauterine device) during the study period.

Covariates

We a priori considered potential confounders hypothesized to be associated with our exposures and outcomes of interest based on theory and prior research. Self-reported gender was ascertained on each survey using a 2-step question that asked participants about their current gender and their sex assigned at birth. If a participant's self-reported gender changed across surveys, we used the gender reported most frequently by a participant (3 individuals identified as transmasculine at baseline and as nonbinary on all follow-up surveys). We collected data on self-reported race and ethnicity (available response options were Arab or Middle Eastern; Asian; Black or African American; Latinx; Native American, American Indian, or Alaskan Native or Native Hawaiian; Pacific Islander; and White), age, caregiver income, and insurance type. Race and ethnicity were assessed as potential covariates owing to known barriers to accessing gender-affirming care among transgender youth who are members of minority racial and ethnic groups. For descriptive statistics, Asian and Pacific Islander groups were combined owing to small population numbers. We included a baseline variable reflecting receipt of ongoing mental health therapy other than for the purpose of a mental health assessment to receive a gender dysphoria diagnosis. We included a self-report variable reflecting whether youths felt their gender identity or expression was a source of tension with their parents or guardians. Substance use included any alcohol, marijuana, or other drug use in the past year. Resilience was measured by the Connor-Davidson Resilience Scale (CD-RISC) 10-item score developed to measure change in an individual's state resilience over time.²⁸ Resilience scores were

dichotomized into high (ie, $\geq$ median) and low (ie, $<$ median). Prior studies of young adults in the US reported mean CD-RISC scores ranging from 27.2 to 30.1.^{29,30}

Statistical Analysis

We used generalized estimating equations to assess change in outcomes from baseline at each follow-up point (eFigure 1 in the [Supplement](#)). We used a logit link function to estimate adjusted odds ratio (aOR) for the association between variables and each mental health outcome. We initially estimated bivariate associations between potential confounders and mental health outcomes. Multivariable models included variables that were statistically significant in bivariate models. For all outcomes and models, statistical significance was defined as 95% CIs that did not contain 1.00. Reported *P* values are based on 2-sided Wald test statistics.

Model 1 examined temporal trends in mental health outcomes, with time (ie, baseline, 3, 6, and 12 months) modeled as a categorical variable. Model 2 estimated the association between receipt of PBs or GAHs and mental health outcomes adjusted for temporal trends and potential confounders. Receipt of PBs or GAHs was modeled as a composite binary time-varying exposure that compared mean outcomes between participants who had initiated PBs or GAHs and those who had not across all time points (eTable 2 in the [Supplement](#)). All models used an independent working correlation structure and robust standard errors to account for the time-varying exposure variable.

We performed several sensitivity analyses. Because our data were from an observational cohort, we first considered the degree to which they were sensitive to unmeasured confounding. To do this, we calculated the E-value for the association between PBs or GAHs and mental health outcomes in model 2. The E-value is defined as the minimum strength of association that a confounder would need to have with both exposure and outcome to completely explain away their association (eTable 4 in the [Supplement](#)).³¹ Second, we performed sensitivity analyses on several subsets of youths. We separately examined the association of PBs and GAHs with outcomes of interest, although we a priori did not anticipate being powered to detect statistically significant outcomes owing to our small sample size and the relatively low proportion of youths who accessed PBs. We also conducted sensitivity analyses using the Patient Health Questionnaire 8-item scale (PHQ-8), in which the PHQ-9 question 9 regarding self-harm or suicidal thoughts was removed, given that we analyzed this item as a separate outcome. Lastly, we restricted our analysis to minor youths ages 13 to 17 years because they were subject to different laws and policies related to consent and prerequisite mental health assessments. We used R statistical software version 3.6.2 (R Project for Statistical Computing) to conduct all analyses. Data were analyzed from August 2020 through November 2021.

Results

A total of 169 youths were screened for eligibility during the study period, among whom 161 eligible youths were approached. Nine youths or caregivers declined participation, and 39 youths did not complete consent or assent or did not complete the baseline survey, leaving a sample of 113 youths (70.2% of approached youths). We excluded 9 youths aged younger than 13 years from the analysis because they received different depression and anxiety screeners. Our final sample included 104 youths ages 13 to 20 years (mean [SD] age, 15.8 [1.6] years). Of these individuals, 84 youths (80.8%), 84 youths, and 65 youths (62.5%) completed surveys at 3, 6, and 12 months, respectively.

Our cohort included 63 transmasculine youths (60.6%), 27 transfeminine youths (26.0%), 10 nonbinary or gender fluid youths (9.6%), and 4 youths who responded "I don't know" or did not respond to the gender identity question on all completed questionnaires (3.8%) (**Table 1**). There were 4 Asian or Pacific Islander youths (3.8%), 3 Black or African American youths (2.9%); 9 Latinx youths (8.7%); 6 Native American, American Indian, or Alaskan Native or Native Hawaiian youths (5.8%); 67 White youths (64.4%); and 9 youths who reported more than 1 race or ethnicity (8.7%). Race and ethnicity data were missing for 6 youth (5.8%).

Table 1. Participant Characteristics

Characteristic	Participants, No. (%) (N = 104)
Gender	
Male or transgender male	63 (60.6)
Female or transgender female	27 (26.0)
Nonbinary or gender fluid	10 (9.6)
Don't know or missing	4 (3.8)
Race and ethnicity ^a	
Asian or Pacific Islander	4 (3.8)
Black or African American	3 (2.9)
Latinx	9 (8.7)
Native American, American Indian, or Alaskan Native or Native Hawaiian	6 (5.8)
White	67 (64.4)
More than 1 race or ethnicity chosen	9 (8.7)
Missing	6 (5.8)
Age at baseline, y	
13	8 (7.7)
14	20 (19.2)
15	18 (17.3)
16	22 (21.2)
17	22 (21.2)
18	8 (7.7)
19	5 (4.8)
20	1 (1.0)
Pharmacological intervention	
PBs ^b	19 (18.2)
GAHs ^b	64 (61.5)
Androgen blockers ^c	17 (51.5)
Menstrual suppression or contraception ^d	25 (35.2)
Depression at baseline (using PHQ-9)	
0-4 (minimal)	14 (13.5)
5-9 (mild)	27 (26.0)
10-14 (moderate)	22 (21.2)
15-19 (moderately severe)	11 (10.6)
≥20 (severe)	26 (25.0)
Missing	4 (3.8)
Anxiety at baseline (using GAD-7)	
0-4 (minimal)	20 (19.2)
5-9 (mild)	28 (26.9)
10-14 (moderate)	20 (19.2)
≥15 (severe)	32 (30.8)
Missing	4 (3.8)
Self-harm or suicidal thoughts at baseline	45 (43.2)
Receiving mental health therapy	65 (62.5)
Tension with caregiver about gender identity or expression	36 (34.6)
Any substance use	34 (32.7)
Resilience at baseline (using CD-RISC 10)	
0-10	8 (7.7)
10-20	35 (33.7)
21-30	15 (14.4)
30-40	34 (32.7)
Missing	12 (11.5)

Abbreviations: CD-RISC 10, Connor-Davidson 10-item Resilience Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; GAH, gender-affirming hormone; PB, puberty blocker; PHQ-9 Patient Health Questionnaire 9-item scale.

^a Available response options for race and ethnicity were Arab or Middle Eastern; Asian or Pacific Islander; Black or African American; Latinx; Native American, American Indian, or Alaskan Native or Native Hawaiian; Pacific Islander; and White. Asian and Pacific Islander groups were combined owing to small population sizes.

^b Self-reported receipt ever of PBs or GAHs at baseline or through the end of the study period.

^c Includes androgen blockers received during the study period; percentage is among 33 youths assigned male sex at birth.

^d Includes pharmacological interventions for menstrual suppression or contraception received during the study period; percentage is among 71 youths assigned female sex at birth.

At baseline, 7 youths had ever received PBs or GAHs (including 1 youth who received PBs, 4 youths who received GAHs, and 2 youths who received both PBs and GAHs). By the end of the study, 69 youths (66.3%) had received PBs or GAHs (including 50 youths who received GAHs only [48.1%], 5 youths who received PBs only [4.8%], and 14 youths who received PBs and GAHs [13.5%]), while 35 youths had not received either PBs or GAHs (33.7%) (eTable 3 in the [Supplement](#)). Among 33 participants assigned male sex at birth, 17 individuals (51.5%) had received androgen blockers, and among 71 participants assigned female sex at birth, 25 individuals (35.2%) had received menstrual suppression or contraceptives by the end of the study.

A large proportion of youths reported depressive and anxious symptoms at baseline. Specifically, 59 individuals (56.7%) had baseline PHQ-9 scores of 10 or more, suggesting moderate to severe depression; there were 22 participants (21.2%) scoring in the moderate range, 11 participants (10.6%) in the moderately severe range, and 26 participants (25.0%) in the severe range. Similarly, half of participants had a GAD-7 score suggestive of moderate to severe anxiety at baseline (52 individuals [50.0%]), including 20 participants (19.2%) scored in the moderate range, and 32 participants (30.8%) scored in the severe range. There were 45 youths (43.3%) who reported self-harm or suicidal thoughts in the prior 2 weeks. At baseline, 65 youths (62.5%) were receiving ongoing mental health therapy, 36 youths (34.6%) reported tension with their caregivers about their gender identity or expression, and 34 youths (32.7%) reported any substance use in the prior year. Lastly, we observed a wide range of resilience scores (median [range], 22.5 [1-38], with higher scores equaling more resiliency). There were no statistically significant differences in baseline characteristics by gender.

In bivariate models, substance use was associated with all mental health outcomes (**Table 2**). Youths who reported any substance use were 4-fold as likely to have PHQ-9 scores of moderate to severe depression (aOR, 4.38; 95% CI, 2.10-9.16) and 2-fold as likely to have GAD-7 scores of moderate to severe anxiety (aOR, 2.07; 95% CI, 1.04-4.11) or report thoughts of self-harm or suicide in the prior 2 weeks (aOR, 2.06; 95% CI, 1.08-3.93). High resilience scores (ie, $\geq$ median), compared with low resilience scores (ie, $<$ median), were associated with lower odds of moderate or severe anxiety (aOR, 0.51; 95% CI, 0.26-0.999).

There were no statistically significant temporal trends in the bivariate model or model 1 (Table 2 and **Table 3**). However, among all participants, odds of moderate to severe depression increased at 3 months of follow-up relative to baseline (aOR, 2.12; 95% CI, 0.98-4.60), which was not a significant increase, and returned to baseline levels at months 6 and 12 (**Figure**) prior to adjusting for receipt of PBs or GAHs.

We also examined the association between receipt of PBs or GAHs and mental health outcomes in bivariate and multivariable models (eFigure 2 in the [Supplement](#)). After adjusting for temporal trends and potential confounders (**Table 4**), we observed that youths who had initiated PBs or GAHs had 60% lower odds of moderate to severe depression (aOR, 0.40; 95% CI, 0.17-0.95) and 73% lower odds of self-harm or suicidal thoughts (aOR, 0.27; 95% CI, 0.11-0.65) compared with youths who had not yet initiated PBs or GAHs. There was no association between receipt of PBs or GAHs and moderate to severe anxiety (aOR, 1.01; 95% CI, 0.41-2.51). After adjusting for time-varying exposure of PBs or GAHs in model 2 (Table 4), we observed statistically significant increases in moderate to severe depression among youths who had not received PBs or GAHs by 3 months of follow-up (aOR, 3.22; 95% CI, 1.37-7.56). A similar trend was observed for self-harm or suicidal thoughts among youths who had not received PBs or GAHs by 6 months of follow-up (aOR, 2.76; 95% CI, 1.22-6.26). Lastly, we estimated E-values of 2.56 and 3.25 for the association between receiving PGs or GAHs and moderate to severe depression and suicidality, respectively (eTable 4 in the [Supplement](#)). Sensitivity analyses obtained comparable results and are presented in eTables 5 through 8 in the [Supplement](#).

Table 2. Baseline Factors Associated With Mental Health Outcomes in Bivariate Models

Factor	Moderate or severe depression (PHQ-9 ≥ 10) ^a		Moderate or severe anxiety (GAD-7 ≥ 10) ^b		Any self-harm or suicidal thoughts ^c	
	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
PBs or GAHs	0.67 (0.33-1.34)	.25	0.90 (0.49-1.66)	.74	0.47 (0.26-0.86)	.01
Time, mo						
0 (baseline)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
3	1.96 (0.99-3.90)	.05	1.46 (0.71-2.97)	.30	1.00 (0.49-2.06)	.99
6	1.01 (0.46-2.19)	.99	0.77 (0.39-1.52)	.45	1.22 (0.64-2.34)	.54
12	1.42 (0.55-3.66)	.47	0.95 (0.43-2.06)	.89	1.02 (0.41-2.52)	.97
Gender						
Male or transgender male	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Female or transgender female	1.07 (0.51-2.24)	.87	3.15 (0.92-10.8)	.07	1.20 (0.55-2.64)	.64
Nonbinary or gender fluid	2.40 (0.84-6.87)	.10	1.35 (0.67-2.72)	.40	2.17 (0.73-6.41)	.16
Race or ethnicity						
White	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
Member of minority race or ethnic group ^d	1.08 (0.51-2.28)	.84	0.86 (0.45-1.66)	.66	0.92 (0.53-1.61)	.77
Age, y						
13-15	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
16-17	1.79 (0.82-3.88)	.14	0.63 (0.29-1.39)	.25	0.86 (0.44-1.68)	.66
18-20	0.78 (0.24-2.51)	.68	1.17 (0.43-3.17)	.76	0.79 (0.36-1.74)	.55
Mental health and substance use at baseline						
Moderate or severe depression (PHQ-9 ≥ 10)	27.2 (13.4-55.4)	<.001	1.91 (0.85-4.29)	.12	1.06 (0.50-2.24)	.88
Moderate or severe anxiety (GAD-7 ≥ 10)	4.90 (2.27-10.6)	<.001	14.3 (7.31-27.9)	<.001	1.44 (0.76-2.72)	.27
Self-harm or suicidal thoughts	1.32 (0.61-2.85)	.48	1.49 (0.73-3.06)	.28	18.9 (10.4-34.1)	<.001
Receiving mental health therapy	1.46 (0.69-3.08)	.32	0.65 (0.31-1.38)	.26	0.75 (0.36-1.56)	.45
Tension with caregivers about gender identity or expression	1.93 (0.90-4.14)	.09	1.06 (0.52-2.15)	.87	1.55 (0.88-2.74)	.13
Any substance use	4.38 (2.10-9.16)	<.001	2.07 (1.04-4.11)	.04	2.06 (1.08-3.93)	.03
Resilience at baseline (CD-RISC 10 ≥ 22.5) ^e	0.85 (0.42-1.74)	.67	0.51 (0.26-1.00)	.05	0.74 (0.39-1.44)	.38

Abbreviations: aOR, adjusted odds ratio; CD-RISC 10, Connor-Davidson 10-item Resilience Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; GAH, gender-affirming hormone; NA, not applicable; PB, puberty blocker; PHQ-9, Patient Health Questionnaire 9-item scale.

^a Bivariate models are adjusted for baseline PHQ-9.

^b Bivariate models are adjusted for baseline GAD-7.

^c Bivariate models are adjusted for self-harm or suicidal thoughts reported at baseline.

^d Owing to small sample sizes, this group includes Asian or Pacific Islander; Black or African American; Latinx; and Native American, American Indian, Alaskan Native, or Native Hawaiian youths and youths who reported more than 1 race or ethnicity.

^e The median (range) CD-RISC score for the cohort was 22.5 (1-38).

Table 3. Temporal Trends in Mental Health Outcomes in Multivariable Model 1^a

Factor	Moderate or severe depression (PHQ-9 ≥ 10)		Moderate or severe anxiety (GAD-7 ≥ 10)		Any self-harm or suicidal thoughts	
	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Time, mo						
0 (baseline)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
3	2.12 (0.98-4.60)	.06	1.50 (0.71-3.15)	.29	0.99 (0.48-2.06)	.98
6	0.99 (0.42-2.35)	.98	0.78 (0.38-1.59)	.49	1.22 (0.63-2.36)	.56
12	1.27 (0.44-3.67)	.66	0.96 (0.43-2.11)	.91	0.98 (0.39-2.48)	.97
Mental health and substance use at baseline						
Moderate or severe depression (PHQ-9 ≥ 10)	18.5 (8.44-40.5)	<.001	NA	NA	NA	NA
Moderate or severe anxiety (GAD-7 ≥ 10)	3.63 (1.83-7.19)	<.001	12.4 (6.25-24.7)	<.001	NA	NA
Self-harm or suicidal thoughts	NA	NA	NA	NA	19.9 (10.9-36.1)	<.001
Any substance use	3.35 (1.56-7.18)	.002	2.21 (1.09-4.49)	.03	2.07 (1.09-3.93)	.03
Resilience at Baseline (CD-RISC 10 ≥ 22.5) ^b	NA	NA	0.48 (0.24-0.95)	.04	NA	NA

Abbreviations: aOR, adjusted odds ratio; CD-RISC 10, Connor-Davidson 10-item Resilience Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; NA, not applicable; PHQ-9, Patient Health Questionnaire 9-item scale.

^a Model 1 includes categorical temporal variables (ie, months 3, 6, and 12 relative to baseline) and covariates that were statistically significant in bivariate models (such that

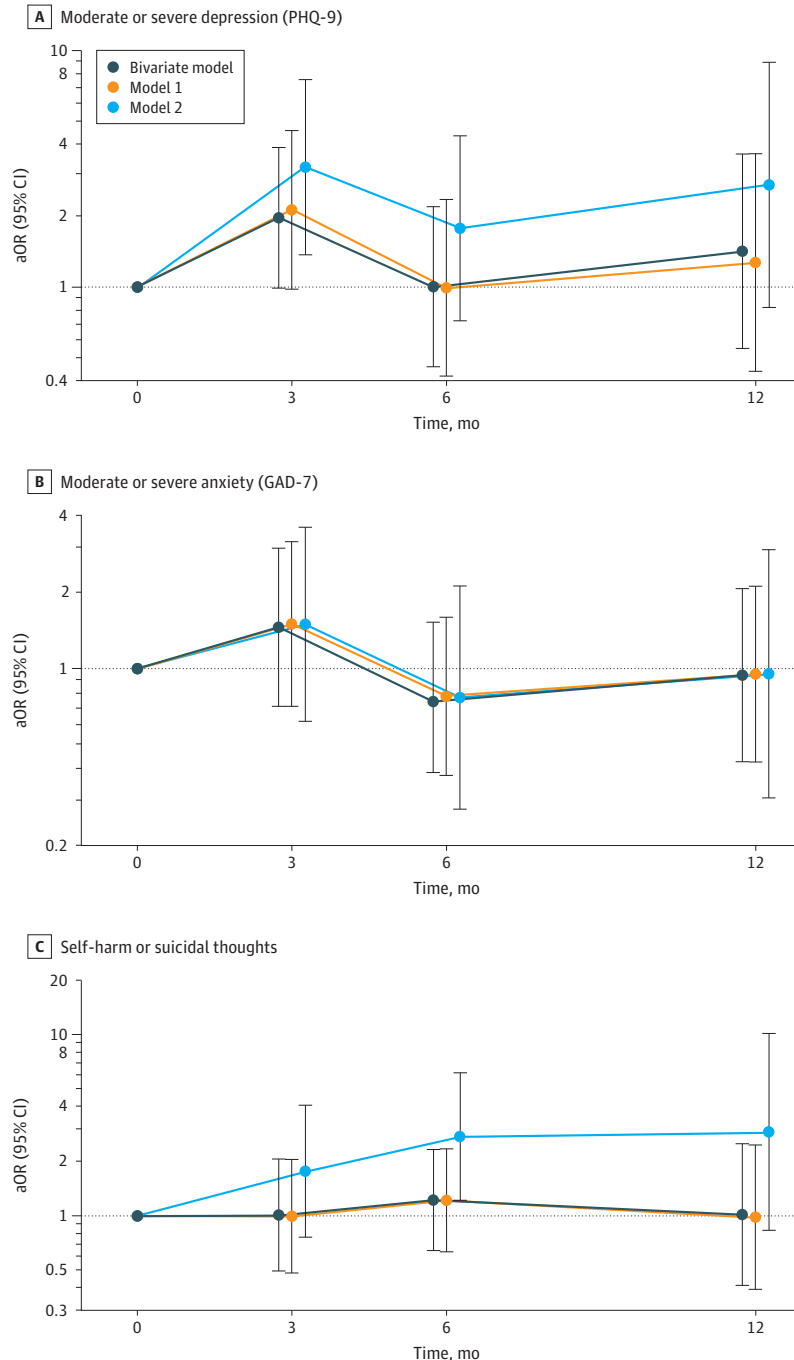
95% CIs did not contain 1.00) (see Table 2). Covariates that were not significant in bivariate models are marked NA.

^b The median (range) CD-RISC score for the cohort is 22.5 (1-38).

Discussion

In this prospective clinical cohort study of TNB youths, we observed high rates of moderate to severe depression and anxiety, as well as suicidal thoughts. Receipt of gender-affirming interventions, specifically PBs or GAHs, was associated with 60% lower odds of moderate to severe depressive symptoms and 73% lower odds of self-harm or suicidal thoughts during the first year of multidisciplinary gender care. Among youths who did not initiate PBs or GAHs, we observed that depressive symptoms and suicidality were 2-fold to 3-fold higher than baseline levels at 3 and 6 months of follow-up, respectively. Our study results suggest that risks of depression and suicidality

Figure. Temporal Trends in Mental Health Outcomes



Outcomes are estimated from bivariate and multivariable generalized estimating equation models. aOR, indicates adjusted odds ratio; GAD-7, Generalized Anxiety Disorder 7-item scale; PHQ-9, Patient Health Questionnaire 9-item scale; whiskers, 95% CIs.

may be mitigated with receipt of gender-affirming medications in the context of a multidisciplinary care clinic over the relatively short time frame of 1 year.

Our findings are consistent with those of prior studies finding that TNB adolescents are at increased risk of depression, anxiety, and suicidality^{1,11,32} and studies finding long-term and short-term improvements in mental health outcomes among TNB individuals who receive gender-affirming medical interventions.^{14,21-24,33,34} Surprisingly, we observed no association with anxiety scores. A recent cohort study of TNB youths in Dallas, Texas, found that total anxiety symptoms improved over a longer follow-up of 11 to 18 months; however, similar to our study, the authors did not observe statistically significant improvements in generalized anxiety.²² This suggests that anxiety symptoms may take longer to improve after the initiation of gender-affirming care. In addition, Olson et al³⁵ found that prepubertal TNB children who socially transitioned did not have increased rates of depression symptoms but did have increased rates of anxiety symptoms compared with children who were cisgender. Although social transition and access to gender-affirming medical care do not always go hand in hand, it is noteworthy that access to gender-affirming medical care and supported social transition appear to be associated with decreased depression and suicidality more than anxiety symptoms.

Time trends were not significant in our study; however, it is important to note that we observed a transient and nonsignificant worsening in mental health outcomes in the first several months of care among all participants and that these outcomes subsequently returned to baseline by 12 months. This is consistent with findings from a 2020 study³⁶ in an academic medical center in the northwestern US that observed no change in TNB adolescents' GAD-7 or PHQ-9 scores from intake to first follow-up appointment, which occurred a mean of 4.7 months apart. Given that receipt of PBs or GAHs was associated with protection against depression and suicidality in our study, it could be that delays in receipt of medications is associated with initially exacerbated mental health symptoms that subsequently improve. It is also possible that mental health improvements associated with receiving these interventions may have a delayed onset, given the delay in physical changes after starting GAHs.

Few of our hypothesized confounders were associated with mental health outcomes in this sample, most notably receipt of ongoing mental health therapy and caregiver support; however, this

Table 4. Association Between GAHs or PBs and Mental Health Outcomes in Multivariable Model 2^a

Factor	Moderate or severe depression (PHQ-9 ≥10)		Moderate or severe anxiety (GAD-7 ≥10)		Any self-harm or suicidal thoughts	
	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
PBs or GAHs	0.40 (0.17-0.95)	.04	1.01 (0.41-2.51)	.98	0.27 (0.11-0.65)	.003
Time, mo						
0 (baseline)	1 [Reference]	NA	1 [Reference]	NA	1 [Reference]	NA
3 mo	3.22 (1.37-7.56)	.007	1.49 (0.62-3.59)	.37	1.77 (0.76-4.13)	.19
6 mo	1.77 (0.72-4.37)	.21	0.77 (0.28-2.11)	.61	2.76 (1.22-6.26)	.02
12 mo	2.71 (0.82-8.95)	.10	0.95 (0.31-2.93)	.93	2.93 (0.83-10.4)	.10
Mental health & substance use at baseline						
Moderate or severe depression (PHQ-9 ≥10)	19.4 (8.64-43.4)	<.001	NA	NA	NA	NA
Moderate or severe anxiety (GAD-7 ≥10)	3.82 (1.87-7.82)	<.001	12.4 (6.25-24.7)	<.001	NA	NA
Self-harm or suicidal thoughts	NA	NA	NA	NA	23.9 (12.9-44.5)	<.001
Any substance use	3.20 (1.49-6.84)	.003	2.21 (1.09-4.50)	.03	2.00 (1.08-3.73)	.03
Resilience at baseline (CD-RISC 10 ≥22.5) ^b	NA	NA	0.48 (0.24-0.95)	.04	NA	NA

Abbreviations: aOR, adjusted odds ratio; CD-RISC 10, Connor-Davidson 10-item Resilience Scale; GAD-7, Generalized Anxiety Disorder 7-item scale; GAH, gender-affirming hormone; NA, not applicable; PB, puberty blocker; PHQ-9, Patient Health Questionnaire 9-item scale.

^a Model 2 includes a time-varying exposure variable measuring the receipt of PBs or GAHs adjusted for temporal trend (ie, categorical variable for months 3, 6, and 12

relative to baseline) and covariates that were statistically significant in the bivariate models (such that 95% CIs did not contain 1.00) (see Table 2). The unadjusted bivariate associations between PBs or GAHs and mental health outcomes are reported in Table 2. Covariates that were not significant in bivariate models are marked NA.

^b The median (range) CD-RISC score for the cohort is 22.5 (1-38).

is not surprising given that these variables were colinear with baseline mental health, which we adjusted for in all models. Substance use was the only variable associated with all mental health outcomes. In addition, youths with high baseline resilience scores were half as likely to experience moderate to severe anxiety as those with low scores. This finding suggests that substance use and resilience may be additional modifiable factors that could be addressed through multidisciplinary gender-affirming care. We recommend more granular assessment of substance use and resilience to better understand support needs (for substance use) and effective support strategies (for resilience) for TNB youths in future research.

This study has a number of strengths. This is one of the first studies to quantify a short-term transient increase in depressive symptoms experienced by TNB youths after initiating gender-affirming care, a phenomenon observed clinically by some of the authors and described in qualitative research.³⁷ Although we are unable to make causal statements owing to the observational design of the study, the strength of associations between gender-affirming medications and depression and suicidality, with large aOR values, and sensitivity analyses that suggest that these findings are robust to moderate levels of unmeasured confounding. Specifically, E-values calculated for this study suggest that the observed associations could be explained away only by an unmeasured confounder that was associated with both PBs and GAHs and the outcomes of interest by a risk ratio of 2-fold to 3-fold each, above and beyond the measured confounders, but that weaker confounding could not do so.³¹

Limitations

Our findings should be interpreted in light of the following limitations. This was a clinical sample of TNB youths, and there was likely selection bias toward youths with supportive caregivers who had resources to access a gender-affirming care clinic. Family support and access to care are associated with protection against poor mental health outcomes, and thus actual rates of depression, anxiety, and suicidality in nonclinical samples of TNB youths may differ. Youths who are unable to access gender-affirming care owing to a lack of family support or resources require particular emphasis in future research and advocacy. Our sample also primarily included White and transmasculine youths, limiting the generalizability of our findings. In addition, the need to reapproach participants for consent and assent for the 12-month survey likely contributed to attrition at this time point. There may also be residual confounding because we were unable to include a variable reflecting receipt of psychotropic medications that could be associated with depression, anxiety, and self-harm and suicidal thought outcomes. Additionally, we used symptom-based measures of depression, anxiety, and suicidality; further studies should include diagnostic evaluations by mental health practitioners to track depression, anxiety, gender dysphoria, suicidal ideation, and suicide attempts during gender care.²

Conclusions

Our study provides quantitative evidence that access to PBs or GAHs in a multidisciplinary gender-affirming setting was associated with mental health improvements among TNB youths over a relatively short time frame of 1 year. The associations with the highest aORs were with decreased suicidality, which is important given the mental health disparities experienced by this population, particularly the high levels of self-harm and suicide. Our findings have important policy implications, suggesting that the recent wave of legislation restricting access to gender-affirming care¹⁹ may have significant negative outcomes in the well-being of TNB youths.²⁰ Beyond the need to address antitransgender legislation, there is an additional need for medical systems and insurance providers to decrease barriers and expand access to gender-affirming care.

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Tordoff, Wanta, Collin, Stepney, Inwards-Breland.

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SUPPLEMENT.

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Supplemental Online Content

Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental health outcomes in transgender and nonbinary youths receiving gender-affirming care. *JAMA Netw Open*. 2022;5(2):e220978. doi:10.1001/jamanetworkopen.2022.0978

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eReferences

This supplemental material has been provided by the authors to give readers additional information about their work.

I. Measures and Survey Instruments

Below we include the exact survey instruments used to ascertain gender, exposure variables, mental health outcome variables, and covariates from youth on the baseline, 3, 6, and 12 month follow-up surveys.

eTable 1. Survey Instruments	
<i>Demographics</i>	
<i>Two-step Gender Identity Question</i>	- What is your gender identity? - Transgender male (female to male) - Transgender female (male to female) - Male - Female - Non-binary or gender fluid - Other: [open text box] - I don't know - What sex were you assigned at birth? - Male - Female
<i>Exposure Measures</i>	
<i>Puberty Blockers</i>	Puberty blockers are a medication that put a young person's puberty development on pause. Have you taken puberty blockers? - Yes - No - I don't know
<i>Gender-affirming Hormones</i>	Have you taken cross-sex hormones (testosterone or estrogen)? - Yes - No - I don't know
<i>Mental Health Outcome Measures</i>	
<i>Generalized Anxiety Disorder 7-item scale (GAD-7)</i>	Over the last 2 weeks, how often have you been bothered by the following problems? - Feeling nervous, anxious, or on edge - Not being able to stop or control worrying - Worrying too much about different things - Trouble relaxing - Being so restless that it's hard to sit still - Becoming easily annoyed or irritable - Feeling afraid as if something awful might happen <u>With response options:</u> not at all, several days, over half of days, nearly every day, and I don't know. - If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with people? - Not difficult at all - Somewhat difficult - Very difficult - Extremely difficult
<i>Patient Health Questionnaire 9-item scale (PHQ-9) for Depression</i>	Over the past 2 weeks, how often have you been bothered by any of the following problems? - Little interest or pleasure in doing things - Feeling down, depressed or hopeless - Trouble falling asleep, staying asleep, or sleeping too much - Feeling tired or having little energy - Poor appetite or overeating - Feeling bad about yourself – or that you're a failure or have let yourself or your family down

	7. Trouble concentrating on things, such as reading the newspaper or watching television 8. Moving or speaking so slowly that other people could have noticed. Or, the opposite – being so fidgety or restless that you have been moving around a lot more than usual. 9. Thoughts that you would be better off dead or of hurting yourself in some way <u>With response options:</u> not at all, several days, over half of days, nearly everyone day, and I don't know. 10. If you checked off any problems, how difficult have those problems made it for you to do your work, take care of things at home, or get along with other people? ○ Not difficult at all ○ Somewhat difficult ○ Very difficult ○ Extremely difficult
<i>Self-harm or Suicidal Thoughts</i>	"Over the past 2 weeks, how often have you been bothered by thoughts that you would be better off dead or of hurting yourself in some way?" (Item-9 from the PHQ-9)
Covariates	
<i>Mental Health Therapy</i>	A readiness assessment is when the patient and their family meet with a mental health professional before starting any medical treatment. Other than having an assessment, are you receiving ongoing mental health therapy? • Yes • No
<i>Tension with Caregivers</i>	There is tension around my gender identity or gender expression... (check all that apply) • ...between my parents or guardians • ...between me and one or more of my parents or guardians • ...between me and my extended family • Other: [open text box] • None of the above
<i>Substance Use (CRAFFT Screening Tool¹ Part A)</i>	During the past 12 months, did you: 1. Drink any alcohol (more than a few sips)? (Do not count sips of alcohol taken during family or religious events) 2. Smoke any marijuana or hashish? 3. Use anything else to get high? ("Anything else" includes illegal drugs, over the counter and prescription drugs, and things that you sniff or "huff") <u>With response options:</u> yes, no, and I don't know
<i>Connor-Davidson 10-item Resilience Scale (CD-RISC 10)</i>	1. I am able to adapt when changes occur. 2. I can deal with whatever comes my way. 3. I can see the humorous side of things when I am faced with problems. 4. Having to cope with stress can make me stronger. 5. I tend to bounce back after illness, injury, or other hardships. 6. I believe I can achieve my goals, even if there are obstacles 7. Under pressure, I can focused and think clearly 8. I am not easily discouraged by failure 9. I think of myself as a strong person when dealing with life's challenges and difficulties. 10. I am able to handle unpleasant or painful feelings like sadness, fear and anger. <u>With response options:</u> not true at all, rarely true, sometimes true, often true, true nearly all the time, and I don't know.

II. Generalized Estimating Equation (GEE) Model Specification

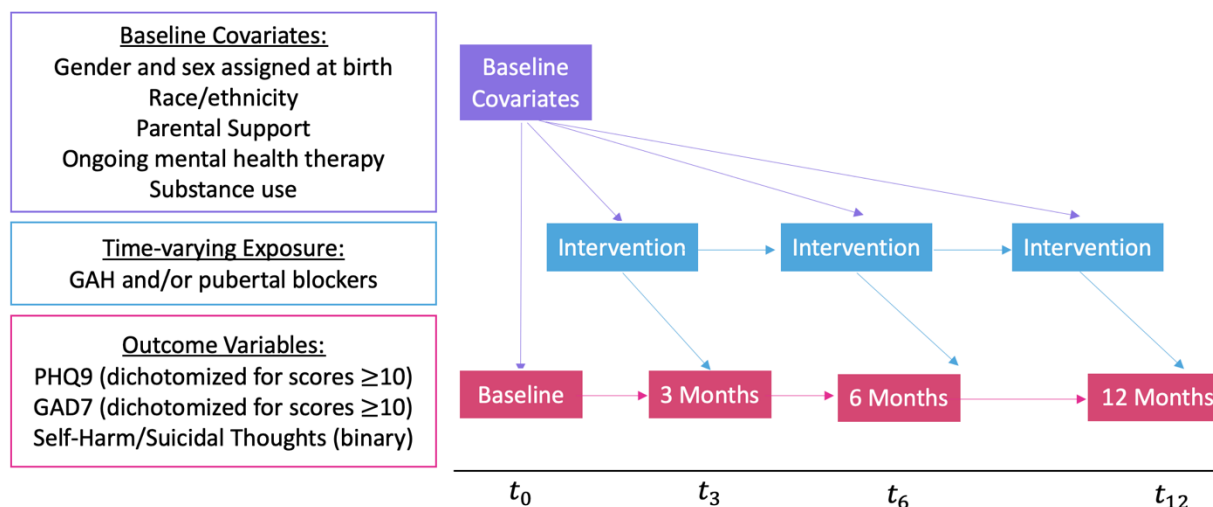
GEE is a marginal model and models population averages (compared to mixed-effect models which are conditional and can model subject-specific effects). We specified the following GEE models to estimate the average change in the outcome variable (Y_i) at each time point (T) relative to baseline (Y_0) (Model 1) and the association between the exposure (E_i) and outcome (Model 2) adjusted for k -many baseline covariates (X_{k0}).

Model 1: $\text{logit}(Y_i) = \beta_0 + \beta_2 T_i + \beta_3 Y_0 + \sum \alpha_k X_{k0}$

Model 2: $\text{logit}(Y_i) = \beta_0 + \beta_1 E_i + \beta_2 T_i + \beta_3 Y_0 + \sum \alpha_k X_{k0}$

We allow the exposure (receipt of PB/GAH) to vary over time, where i indicates the month, and thus use an independent working correlation structure. This model assumes there are no time-varying covariates associated with the exposures and that the exposure is exogenous. A visual schematic of this model is included below in eFigure 1, the counts and percentages of participants in the exposure group at each timepoint is included in eTable 2, and the prevalence of the outcome variables over time stratified by exposure group is included in eTable 3.

eFigure 1. Schematic of Generalized Estimating Equation Model



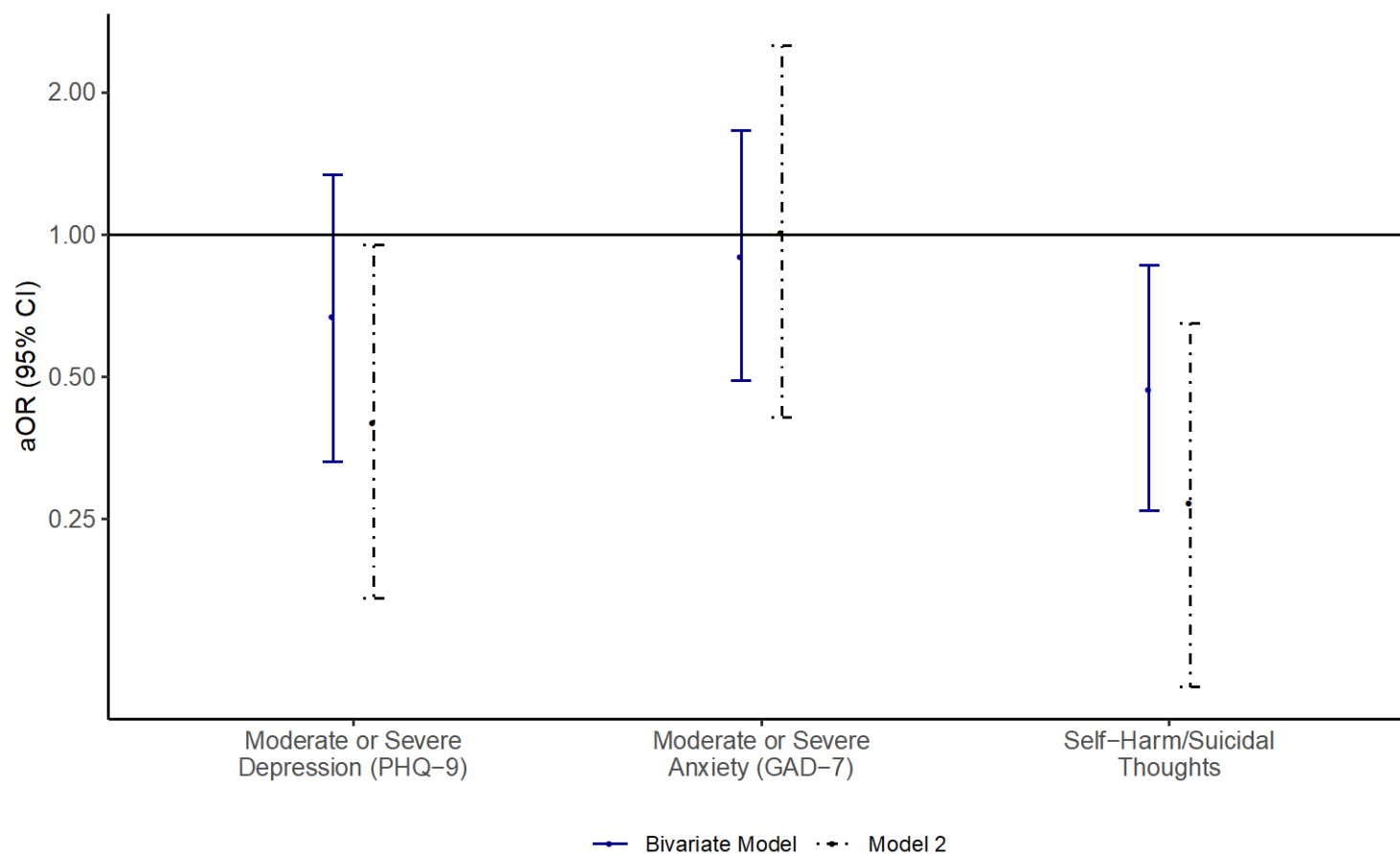
eTable 2. Prevalence of Exposure Over Time				
	Baseline	3 months	6 months	12 months
N	104	84	84	65
Exposure (no.,%)				
PB/GAH	7 (7%)	44 (52%)	59 (71%)	57 (89%)
None	97(93%)	41 (48%)	24 (29%)	7 (11%)

eTable 3. Prevalence of Outcomes Over Time by Exposure Group								
Time Point:	Baseline		3 Months		6 Months		12 Month	
Exposure:	<i>PB/GAH</i>	<i>None</i>	<i>PB/GAH</i>	<i>None</i>	<i>PB/GAH</i>	<i>None</i>	<i>PB/GAH</i>	<i>None</i>
N	7	92	44	38	59	24	57	6
Outcomes (no.,%)								
Moderate to Severe Depression	4 (57%)	54 (59%)	24 (55%)	29 (76%)	33 (56%)	13 (54%)	32 (56%)	5 (83%)
Moderate to Severe Anxiety	4 (57%)	47 (51%)	23 (52%)	23 (61%)	28 (48%)	10 (42%)	29 (51%)	4 (67%)
Self-harm or Suicidal Thoughts	3 (43%)	41 (45%)	13 (30%)	21 (55%)	25 (42%)	11 (46%)	21 (37%)	5 (83%)

There were a small number of youth who did not complete the PHQ-9 or GAD-7 on each survey: 4 youth at baseline, 3 youth at 3 months, and 1 youth at 12 months.

eFigure 2. Association Between Receipt of Gender-Affirming Hormones or Puberty Blockers and Mental Health Outcomes

Associations with moderate or severe depression, anxiety, and self-harm/suicidal thoughts are estimated from bivariate and multivariable GEE models



III. E-Values

A. Calculation

The E-value is a relatively new measure related to the evidence for causality that can be used to assess the robustness of observational study results to unmeasured confounding.² It is defined as the “minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome to explain away a treatment– outcome association.”³ Based on the work of VanderWeele et al.³ the following equations can be used to estimate the E-value for an odds ratio (OR) when the outcome is common (i.e., 15% at the end of follow-up) and when the estimated OR is less than one:

$$\text{Letting } RR^* = 1/\sqrt{OR} \\ E\text{-value} = RR^* + \sqrt{RR^* \times (RR^* - 1)}$$

Applying these equations, we obtain the following E-values:

eTable 4. E-Value Calculation for Association Between Puberty Blockers or Gender-Affirming Hormones and Mental Health Outcomes			
Model	Outcome	Effect Estimate (OR [95%CI])	E-value
Model 2	Moderate to Severe Depression	0.40 (0.17, 0.95)	2.56 (1.19, 4.28)
Model 2	Suicidality	0.27 (0.11, 0.65)	3.25 (1.79, 5.48)

B. Interpretation

We can interpret these findings to suggest that (1) the observed OR of 0.40 could be explained away by an unmeasured confounder that was associated with both the PB/GAH and the moderate to severe depression by a risk ratio of 2.56-fold each, above and beyond the measured confounders, but weaker confounding could not do so, and (2) the observed OR of 0.27 could be explained away by an unmeasured confounder that was associated with both the PB/GAH and the moderate to severe depression by a risk ratio of 3.25-fold each, above and beyond the measured confounders, but weaker confounding could not do so. This is evidence that our findings are robust to a moderate to high degree of unmeasured confounding, since “In the context of biomedical and social sciences research, effect sizes ≥ 2 or 3-fold occasionally occur but are not particularly common; a variable that affects both treatment *and* outcome each by 2- or 3-fold would likely be even less common.”³

In observational studies, unmeasured confounding and lack of exchangeability pose the greatest barrier to drawing causal inferences from observational cohort studies. In addition, there are notable pitfalls in overly relying on p-values for the interpreting the significance of results. For instance, studies with a large sample size often have the statistical power to precisely estimate associations and obtain very small p-values; the p-value may be made arbitrarily small by increasing the sample size, even for small effect sizes. In contrast, the E-value depends on the magnitude of the association; it cannot be made arbitrarily large simply by increasing the sample size. Thus, bias adjustments, such as calculating the E-value, assess robustness of study findings to unmeasured confounding, thereby offering an important supplement to p-values.

IV. Sensitivity Analyses

A. Disaggregated Exposure Variable

We separately examined the association of PB and GAH with the outcomes of interest, although we *a priori* did not anticipate being powered to detect statistically significant associations due to our small sample size and the relatively low proportion of youth who accessed PB (n=19).

eTable 5. Examining Association Between Puberty Blockers or Gender-Affirming Hormones and Mental Health Outcomes Separately							
A. Bivariate Models							
	Moderate or Severe Depression (PHQ-9 $\geq$ 10)			Moderate or Severe Anxiety (GAD-7 $\geq$ 10)			Any Self-harm/Suicidal Thoughts
	aOR (95% CI)	P		aOR (95% CI)	P		aOR (95% CI) P
Gender-affirming hormones	0.75 (0.36, 1.59)	0.459		0.93 (0.49, 1.78)	0.823		0.64 (0.35, 1.14) 0.131
Puberty blockers	0.52 (0.17, 1.59)	0.250		0.76 (0.29, 1.98)	0.568		0.47 (0.13, 1.69) 0.249
B. Multivariable Models (i.e. Model 2)							
	Moderate or Severe Depression (PHQ-9 $\geq$ 10)			Moderate or Severe Anxiety (GAD-7 $\geq$ 10)			Any Self-harm/Suicidal Thoughts
	aOR (95% CI)	P		aOR (95% CI)	P		aOR (95% CI) P
GAH	0.40 (0.16, 1.01)	0.053		1.02 (0.44, 2.37)	0.963		0.43 (0.18, 1.01) 0.052
Puberty blockers	0.52 (0.17, 1.58)	0.248		0.72 (0.26, 2.05)	0.543		0.44 (0.11, 1.74) 0.242
Time (month)							
Baseline	ref			ref			ref
3 months	3.34 (1.47, 7.62)	0.004		1.55 (0.65, 3.67)	0.324		1.52 (0.65, 3.57) 0.333
6 months	1.89 (0.77, 4.64)	0.166		0.81 (0.31, 2.12)	0.665		2.30 (1.00, 5.27) 0.049
12 months	2.93 (0.93, 9.23)	0.067		0.99 (0.35, 2.78)	0.983		2.25 (0.64, 7.99) 0.208
Mental Health & Substance Use at Baseline							
Moderate or Severe Depression (PHQ-9 $\geq$ 10)	18.2 (8.26, 39.9)	<0.001		NA			NA
Moderate or Severe Anxiety (GAD-7 $\geq$ 10)	4.17 (1.97, 8.84)	<0.001		12.3 (6.16, 24.5)	<0.001		NA
Self-Harm/Suicidal Thoughts	NA			NA			22.6 (11.6, 44.3) <0.001
Any substance use	3.21 (1.47, 7.01)	0.003		2.19 (1.08, 4.45)	0.031		1.95 (0.99, 3.83) 0.053
Resilience at Baseline (CD-RISC $\geq$ 22.5) ¹	NA			0.47 (0.23, 0.94)	0.033		NA

B. Restricting Analysis to Youth Age 13-17 Years Old

We restricted our analysis to minor youth age 13-17 (n=90), since they were subject to different laws related to consent and pre-requisite mental health assessments.

eTable 6. Bivariate Model Restricted to Youths Ages 13 to 17 Years							
		Moderate or Severe Depression (PHQ-9 ≥ 10) ¹		Moderate or Severe Anxiety (GAD-7 ≥ 10) ²		Any Self-harm/Suicidal Thoughts ³	
		aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P
GAH/Puberty blockers		0.75 (0.35, 1.63)	0.473	0.79 (0.41, 1.53)	0.486	0.47 (0.24, 0.94)	0.033
Time							
	Baseline	ref		ref		ref	
	3 months	2.55 (1.26, 5.17)	0.010	1.19 (0.54, 2.62)	0.659	1.22 (0.56, 2.68)	0.615
	6 months	1.15 (0.48, 2.75)	0.758	0.82 (0.39, 1.71)	0.596	1.29 (0.61, 2.73)	0.499
	12 months	1.37 (0.48, 3.94)	0.557	0.84 (0.37, 1.90)	0.680	0.81 (0.33, 2.00)	0.649
Gender							
	Transgender male or male	ref		ref		ref	
	Transgender female or female	1.11 (0.48, 2.55)	0.803	1.30 (0.60, 2.82)	0.499	1.37 (0.54, 3.46)	0.511
	Non-binary or genderfluid	3.12 (1.01, 9.58)	0.047	2.29 (0.55, 9.56)	0.256	3.86 (1.11, 13.4)	0.033
Race and ethnicity							
	White	ref		ref		ref	
	Black, Indigenous, and Persons of Color	1.19 (0.51, 2.75)	0.691	0.77 (0.38, 1.56)	0.468	0.82 (0.44, 1.54)	0.541
Age							
	13-15	ref		ref		ref	
	16-17	1.19 (0.51, 2.75)	0.691	0.63 (0.29, 1.39)	0.252	0.86 (0.44, 1.68)	0.657
Mental Health & Substance Use at Baseline							
	Moderate or Severe Depression (PHQ-9 ≥ 10)	31.0 (14.1, 68.3)	<0.001	2.18 (0.96, 4.94)	0.063	1.23 (0.57, 2.67)	0.593
	Moderate or Severe Anxiety (GAD-7 ≥ 10)	4.97 (2.17, 11.36)	<0.001	14.0 (6.76, 29.1)	<0.001	1.57 (0.80, 3.1)	0.193
	Self-Harm/Suicidal Thoughts	1.26 (0.57, 2.78)	0.572	1.61 (0.76, 3.40)	0.215	18.7 (9.72, 35.9)	<0.001
	Receiving mental health therapy	1.70 (0.72, 4.05)	0.228	0.72 (0.32, 1.59)	0.411	0.70 (0.30, 1.63)	0.412
	Any substance use	4.51 (1.94, 10.49)	<0.001	1.83 (0.86, 3.88)	0.114	2.47 (1.21, 5.03)	0.013
Tension with Caregivers		2.59 (1.08, 6.22)	0.032	1.33 (0.62, 2.86)	0.469	1.53 (0.81, 2.89)	0.193
Resilience at Baseline (CD-RISC ≥ 22.5) ⁴		0.88 (0.40, 1.89)	0.734	0.42 (0.21, 0.87)	0.019	0.70 (0.34, 1.43)	0.329

eTable 7. Multivariable Model Restricted to 90 Youths Ages 13 to 17 Years							
A. Model 1 measuring temporal trends in mental health outcomes							
	Moderate or Severe Depression (PHQ-9 $\geq$ 10)			Moderate or Severe Anxiety (GAD-7 $\geq$ 10)			Any Self-harm/Suicidal Thoughts
	aOR (95% CI)	P		aOR (95% CI)	P		aOR (95% CI) P
Time (month)							
Baseline	ref			ref			ref
3 months	2.83 (1.25, 6.44)	0.013		1.22 (0.54, 2.78)	0.634		1.19 (0.53, 2.66) 0.672
6 months	1.12 (0.42, 3.00)	0.822		0.83 (0.38, 1.80)	0.638		1.27 (0.59, 2.75) 0.538
12 months	1.19 (0.37, 3.87)	0.767		0.85 (0.37, 1.93)	0.692		0.76 (0.30, 1.93) 0.558
Mental Health & Substance Use at Baseline							
Moderate or Severe Depression (PHQ-9 $\geq$ 10)	24.1 (9.96, 58.2)	<0.001		NA			NA
Moderate or Severe Anxiety (GAD-7 $\geq$ 10)	3.80 (1.82, 7.96)	<0.001		12.7 (6.11, 26.3)	<0.001		NA
Self-Harm/Suicidal Thoughts	NA			NA			20.9 (10.7, 40.9) <0.001
Any substance use	3.41 (1.41, 8.25)	0.006		2.01 (0.93, 4.37)	0.077		2.50 (1.23, 5.10) 0.012
Resilience at Baseline (CD-RISC $\geq$ 22.5) ¹	NA			0.40 (0.19, 0.83)	0.015		NA
B. Model 2 measuring the association between GAH/puberty blockers and mental health outcomes							
	Moderate or Severe Depression (PHQ-9 $\geq$ 10)			Moderate or Severe Anxiety (GAD-7 $\geq$ 10)			Any Self-harm/Suicidal Thoughts
	aOR (95% CI)	P		aOR (95% CI)	P		aOR (95% CI) P
GAH/Puberty blockers	0.51 (0.19, 1.37)	0.182		0.84 (0.29, 2.40)	0.745		0.32 (0.12, 0.88) 0.027
Time (month)							
Baseline	ref			ref			ref
3 months	3.79 (1.47, 9.78)	0.006		1.32 (0.49, 3.53)	0.581		1.93 (0.76, 4.88) 0.165
6 months	1.73 (0.59, 5.06)	0.315		0.93 (0.30, 2.91)	0.905		2.58 (1.02, 6.57) 0.046
12 months	2.14 (0.53, 8.73)	0.287		0.98 (0.27, 3.58)	0.979		1.99 (0.52, 7.66) 0.317
Mental Health & Substance Use at Baseline							
Moderate or Severe Depression (PHQ-9 $\geq$ 10)	24.3 (9.92, 59.3)	<0.001		NA			NA
Moderate or Severe Anxiety (GAD-7 $\geq$ 10)	4.01 (1.85, 8.69)	<0.001		12.7 (6.11, 26.5)	<0.001		NA
Self-Harm/Suicidal Thoughts	NA			NA			24.3 (12.2, 48.2) <0.001
Any substance use	3.18 (1.34, 7.55)	0.009		1.98 (0.91, 4.32)	0.085		2.33 (1.15, 4.73) 0.019
Resilience at Baseline (CD-RISC $\geq$ 22.5) ¹	NA			0.40 (0.19, 0.83)	0.015		NA

C. Dichotomous Outcome for Depression Based on the PHQ-8

We conducted sensitivity analyses using the PHQ-8 score,⁴ which is equivalent to the PHQ-9 with item-9 regarding self-harm/suicidal thoughts removed. We conducted these analyses in order to determine whether item-9 was driving any associations between moderate to severe depression since we analyzed self-harm/suicidal thoughts as a separate outcome. For these analyses we define moderate or severe depression as a PHQ-8 score ≥ 10 .

eTable 8. Sensitivity Analyses Using Patient Health Questionnaire 8-item Scale Score of 10 or Greater for Moderate to Severe Depression				
		Model 1		Model 2
		aOR (95% CI)	P	aOR (95% CI) P
Puberty blockers or Gender-affirming hormones		0	0.039	0.38 (0.15, 0.98) 0.044
Time (month)				
Baseline		ref		ref
3 months		2.56 (1.07, 6.09)	0.034	3.95 (1.52, 10.3) 0.005
6 months		0.63 (0.27, 1.44)	0.269	1.16 (0.45, 2.99) 0.753
12 months		0.99 (0.31, 3.16)	0.990	2.23 (0.65, 7.68) 0.205
Mental Health & Substance Use at Baseline				
Moderate or Severe Depression (PHQ-9 ≥ 10)		22.5 (8.93, 56.6)	<0.001	23.3 (9.07, 59.7) <0.001
Moderate or Severe Anxiety (GAD-7 ≥ 10)		4.31 (2.15, 8.67)	<0.001	4.57 (2.22, 9.4) <0.001
Self-Harm/Suicidal Thoughts		NA		NA
Any substance use		4.3 (1.79, 10.29)	0.001	4.08 (1.7, 9.81) 0.002
Resilience at Baseline (CD-RISC ≥ 22.5) ¹		NA		NA

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Well-Being and Suicidality Among Transgender Youth After Gender-Affirming Hormones

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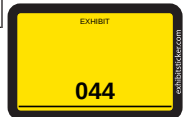
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Objective: This study is a longitudinal evaluation of the effectiveness of gender-affirming hormones for improving psychological well-being and decreasing suicidality among transgender youth referred to a transgender health specialty clinic at a large Midwest children's hospital. **Method:** Forty-seven youth (13.73–19.04 years; $M = 16.59$, $SD = 1.19$) who received gender-affirming hormones were assessed at least 2 times: before the start of treatment and at least 3 months after treatment. **Results:** After gender-affirming hormones, a significant increase in levels of general well-being and a significant decrease in levels of suicidality were observed. **Conclusion:** These findings suggest that gender-affirming hormones are a valuable medical intervention with promising psychosocial outcomes for transgender youth.

Implications for Impact Statement

This study suggests that gender-affirming hormones are a helpful medical intervention for transgender youth. Gender-affirming hormones were found to be associated with decreases in suicidality and improvements in general well-being.

Keywords: transgender, gender-affirming hormones, suicidality, well-being, youth



Over the past few decades, the number of young people presenting to specialty clinics for gender dysphoria (GD) treatment has increased worldwide (Chen, Fuqua, & Eugster, 2016; Olson-Kennedy et al., 2016). GD refers to the distress a person may experience when an incongruence exists between one's sex assigned at

birth and one's experienced gender identity. Transgender people have varying degrees of GD; some have none at all. For peripubertal children and adolescents with GD, clinical practice guidelines recommend the administration of puberty suppression medication (gonadotropin-releasing hormone agonists [GnRHa]). Later, gender-affirming hormones (GAH; estrogen or testosterone) are administered to help alleviate the distress associated with GD (Coleman et al., 2012; Hembree et al., 2017).

Overall, the evidence suggests that youth who received GAH and gender confirmation surgery (GCS) for gender dysphoria experience a corresponding alleviation of the dysphoria and overall improved well-being and mental health outcomes (Hembree et al., 2017; Olson-Kennedy, Warus, Okonta, Belzer, & Clark, 2018). However, further research is needed to develop and refine best practices for serving transgender youth and alleviate GD and associated co-occurring conditions (e.g., anxiety, depression,

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Results of this study were presented at the 2018 World Professional Association for Transgender Health Biennial Symposium in Buenos Aires, Argentina.

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suicidality). De Vries et al. (2014) examined psychological outcomes in youth while on Gn-RHa and then again at least 1 year after GCS. The authors found that psychological functioning had improved over time, gender dysphoria resolved, body image difficulties remitted, and quality of life, life satisfaction, and subjective happiness were comparable with those of same-age peers. Among adults, receiving gender-affirming medical interventions is associated with lower body-related uneasiness (Davis & Meier, 2014; Fisher et al., 2014), improved psychological functioning (Keo-Meier et al., 2015), reduction in anxiety, depression, and anger (Davis et al., 2014), and better quality of life (Ainsworth & Spiegel, 2010).

Emerging evidence suggests that transgender youth might exhibit differential responses to GAH, directly and indirectly, across several domains depending upon sex assigned at birth. Some research suggests there may be differences in emotionality in response to testosterone versus estrogen. One study of transgender adults demonstrated that testosterone treatment was associated with increased mood stability, whereas estrogen treatment was associated with increased mood lability (Slabbekoorn, Van Goozen, Gooren, & Cohen-Kettenis, 2001). Mood instability, in turn, is associated with suicidal ideation (Bowen, Balbuena, Peters, Leuschen-Mewis, & Baetz, 2015) as well as decreased perceptions of well-being (Houben, Van Den Noortgate, & Kuppens, 2015). There may also be sex differences related to the social aspect of medical transition. For instance, compared with transgender girls/women, it may be easier for transgender boys/men to integrate socially because of clear vocal changes (i.e., voice deepening) and facial hair growth, which are traditionally seen as indicators of one's gender. Conversely, the physical changes of a testosterone-mediated puberty may make it harder for transgender girls and women who start estrogen after their endogenous puberty to pass in their affirmed gender, putting them at risk for increased minority stress, which may result in increased suicidal ideation (Testa et al., 2017). In one study, de Vries et al. (2014) compared functioning prior to starting GAH and after GCS and found that transgender men reported greater reduction in anger, anxiety, and externalizing symptoms (e.g., rule-breaking or aggressive behavior) than transgender women,

who had demonstrated either stability or a slight increase in these symptoms.

Research examining mental health outcomes among transgender youth is a priority (Chew, Anderson, Williams, May, & Pang, 2018; Olson-Kennedy et al., 2016). At this time, there is limited research supporting the use of GAH in transgender adolescents (Hembree et al., 2017). Of the studies that do exist, the majority of outcome research has been from European clinical samples, and these studies did not utilize measures of suicidality and well-being. This is a gap because there has been a call to focus on positive aspects of functioning (such as well-being), and low levels of perceived well-being has been linked to suicidality (Lopez et al., 2006; Smith et al., 2018).

The primary aim of this study was to examine suicidality and general well-being following administration of GAH. Specifically, we hypothesized that (a) suicidality will decrease between pretest and final assessment with the administration of GAH and (b) general well-being will improve between pretest and final assessment with the administration of GAH. A secondary aim of the study was to examine whether the effects of GAH on suicidality and well-being differed based on birth-assigned sex. Specifically, we hypothesized that (c) individuals assigned female at birth will experience greater increases in general well-being and larger decreases in suicidality at final assessment compared with those assigned male at birth.

Method

Participants

Participants included adolescents and young adults (age range 13–20 years) who received services for GD at Children's Mercy Hospital Gender Pathway Services (GPS) clinic. Participants were included if they had pretest and final assessment data points and were treated with GAH for at least 3 months. A power analysis was conducted to determine the sample size needed to answer the research questions. The α for the mixed repeated-measures analysis of covariance (ANCOVA) was set at .05. To achieve power of .80 and a medium effect size ($f^2 = .25$), a total sample size of 34 was required for each ANCOVA to detect a significant model, $F(1, 33) = 4.15$. A total of 47 eligible

participants had pretest and final assessment data. The pretest for 23 participants occurred at their first contact with the clinic (the other participants’ pretest assessment was completed at a subsequent visits to clinic but prior to starting GAH). At pretest (Time 0 [T_0]; i.e., before administration of GAH), the age of participants ranged from 13.73 to 19.04 years ($M = 16.59$, $SD = 1.19$). The range of treatment length was 113–1016 days ($M = 349$, $SD = 193$). For most of the sample (90%), duration of treatment was at, or under, 600 days. Thirteen of the participants first presented to our clinic in 2015; 19 in 2016; 14 in 2017; and one in 2018. Of the 47 participants, eight were administered GnRHa in our clinic prior to beginning GAH (we refer to these eight participants elsewhere in the article as the GnRHa + GAH subgroup). See Table 1 for additional participant characteristics.

Procedure

The institutional review board (IRB) of the University of Missouri–Kansas City ceded IRB review and continuing oversight duties to the Children’s Mercy Hospital IRB, which approved the study. Data collection occurred as part of ongoing standard clinical care at GPS

clinic. GPS clinic follows the World Professional Association for Transgender Health Standards of Care, Version 7 (Coleman et al., 2012) and the Endocrine Society’s Clinical Practice Guidelines for the treatment of gender-dysphoric/gender-incongruent people (Hembree et al., 2017). The services provided in GPS clinic are similar to those provided in other specialty gender clinics (e.g., Chen et al., 2016; Edwards-Leeper & Spack, 2012). A multidisciplinary team, including nursing, endocrinology, psychology, and social work professionals, work collaboratively to develop a treatment plan that may include GnRHa and/or GAH. A diagnosis of GD and referral for medical treatment by a mental health professional is required. To avoid unnecessary delays in medical care, our clinic does not require patients to be seen by one of our clinic’s mental health professionals if they have an established GD diagnosis and referral from a community mental health professional. Patients with a referral from a community mental health professional and an established GD diagnosis may be referred directly to endocrinology or multidisciplinary team meetings to begin GnRHa or GAH. Because our team’s mental health professionals administer the clin-

Table 1
Demographic Characteristics for Participants for the Entire Cohort (N = 47) and Each Subgroup: GAH With Previous GnRHa (n = 8) and GAH Only (n = 39)

Demographic characteristics	Entire cohort N (%)	GAH-only subgroup n (%)	GAH + GnRHa subgroup n (%)
Mean age at administration	16.50 years	16.72 years	15.43 years
Mean duration of treatment	349 days	366 days	328 days
Birth assignment			
Assigned female at birth	33 (70.2)	27 (69.2)	6 (75)
Assigned male at birth	14 (29.8)	12 (30.8)	2 (25)
Race/ethnicity			
White	39 (83)	33 (84.6)	6 (75)
Biracial or multiracial	2 (4.3)	2 (5.1)	0 (0)
Latinx/Hispanic	3 (6.4)	3 (7.7)	0 (0)
Black/African American	1 (2.1)	0 (0)	1 (12.5)
American Indian/Alaska Native	1 (2.1)	1 (2.6)	0 (0)
Asian	1 (2.1)	1 (2.1)	1 (12.5)
ZIP code median income	\$57,355	\$61,168	\$53,520
Insurance type			
Self-pay	1 (2.1)	1 (2.6)	0 (0)
Private	36 (76.6)	32 (82.1)	4 (50)
Medicaid	10 (21.3)	6 (15.4)	4 (50)

Note. GAH-only refers to participant who did not received gonadotropin-releasing hormone agonists (GnRHa) prior to being administered gender-affirming hormones (GAH). GnRHa + GAH refers to participants who had received GnRHa prior to being administered GAH.

ic's questionnaires and screeners themselves (rather than our nurses or endocrinologists), roughly half of the youth who would have been eligible to be included this study did not have a pretest data point and therefore could not be included in the final sample. Patients are administered questionnaires and screeners at the beginning of their clinic visit, either at the time of the diagnostic evaluation or during a follow-up appointment with the multidisciplinary team. Responses are reviewed by the mental health professional prior to meeting with the patient. For participants already on GnRHa, new baseline assessments were taken before progressing to GAH. For 10 participants in the study, the pretest data point occurred days before actual administration of GAH (range: 7–74 days; $M = 38$ days). Some causes of the delays included, but were not limited to, waiting for laboratory results, fertility preservation procedures, and insurance-related delays. Between multidisciplinary appointments, patients may see clinic endocrinologists and nurses individually for follow-up care.

Measures

Suicidality. The Ask Suicide-Screening Questions (ASQ) instrument is a four-item dichotomous (yes, no) response measure with high sensitivity (i.e., ability to identify true positives), designed to identify risk of suicide (Horowitz et al., 2012). A patient is considered to have screened positive if they answered yes to any item. A sample item of the ASQ includes, “In the past few weeks, have you felt that you or your family would be better off if you were dead?” In our clinic's survey, we have altered the fourth item of the ASQ (“Have you ever tried to kill yourself?”) and prefaced it with “In the past few weeks . . .” such that we no longer ask about lifetime suicidality. For the purposes of this study, a response of *no* was scored as 0 and a response of *yes* was scored as 1; each item was summed, generating an overall score for suicidality on a scale ranging from 0 to 4, with higher scores indicating greater levels of suicidal ideation. The ASQ has a sensitivity of 97.6% and a specificity of 65.6%. The Cronbach's alpha for the current study was .81 at pretest and at final assessment, after rounding. Prior to March 2017, only three items of the ASQ were administered. No additional data

were missing. As opposed to data that may be missing in nonrandom patterns for unknown reasons possibly related to bias in the variable being measured or sampling bias, the reason for the missing data in this study is known (the item was not asked by providers prior to March 2017). Thus, for purposes of statistical analyses, the data for the ASQ item that was missing these data are considered to be missing at random because they do not likely introduce unknown bias (McKnight, McKnight, Sidani, & Figuero, 2007), and values were imputed with expectation maximization ($N = 28$ imputations at T_0 ; $N = 10$ imputations at Time 1 [T_1] after administration of GAH).

Well-being. The General Well-Being Scale (GWBS) of the Pediatric Quality of Life Inventory (Varni, Seid, & Kurtin, 1999) uses a 5-point response scale, contains seven items, and measures two dimensions (general well-being and general health). The general well-being subscale includes six items. Example items include “I feel happy” and “I think my health will be good in the future.” Participants are asked to consider each item and rate how often they have felt that way over the past month from 0 (*never*) to 4 (*almost always*). The general health subscale contains one item (“In general, how is your health?”), with response options ranging from 0 (*bad*) to 4 (*excellent*). All items are scored and linearly transformed to a 0–100 scale (initial score of 0 = 0, 1 = 25, 2 = 50, 3 = 75, and 4 = 100) for standardized interpretation. High scores reflect fewer perceived problems and greater well-being. The measure has adequate to good internal consistency (ranging from .70 to .92) and clinical validity (Varni et al., 1999). The Cronbach's alpha for the current study was .81 at pretest and .82 at final assessment.

Results

Two mixed repeated-measures ANCOVAs were used to ascertain within-subject differences between pretest (T_0) and final assessment (T_1) suicidality and general well-being scores, with sex assigned at birth as the between-subjects variable. Because there is variability between duration of treatment among participants, the period of time (i.e., duration of treatment) between T_0 and T_1 functioned as a covariate. Schneider, Avivi-Reich, and Mozuraitis

(2015) point out that when the between-groups are not randomly assigned in an ANCOVA, the assumption that the covariate is the same for all participants is not valid (as it is for experimental designs). Thus, the covariate should be centered to account for differences. Accordingly, scores on the covariate were centered by subtracting the sample mean.

The first mixed ANCOVA was conducted to ascertain within-subject differences between baseline suicidality scores (T_0) and suicidality after GAH (T_1). All statistical assumptions required to conduct the mixed ANCOVA were met. Duration of treatment was not significantly related to participants' ASQ scores, $F(1, 44) = .09, p = .77$, partial $\eta^2 = .002$. The main effect was significant, meaning suicidality scores were significantly lower at T_1 after GAH treatment, $F(1, 44) = 15.09, p < .001$, partial $\eta^2 = .26$, demonstrating a large effect size (see Figure 1 and Table 2). Thus, hypothesis 1 was supported. The estimated adjusted mean for suicidality scores decreased by .84 from 1.11 at T_0 to .27 at T_1 . Omitting the item for which we had missing data, an ad hoc comparison revealed that at T_0 , 21 of the 47 participants endorsed at least one of the ASQ screener items (seven participants endorsed only one item, 10 participants endorsed two items, and four participants endorsed three items). At T_1 , only six of the 47 participants had

endorsed at least one of the ASQ screener items (three participants endorsed one item and three participants endorsed two items).

A second mixed ANCOVA was conducted to ascertain within-subject differences between baseline general well-being scores (T_0) and general well-being after administration of GAH (T_1). All statistical assumptions required to conduct the mixed ANCOVA were met. Duration of treatment was not significantly related to participants' general well-being scores, $F(1, 44) = .37, p = .54$, partial $\eta^2 = .01$, showing a small effect size. The main effect was significant, meaning general well-being scores were significantly higher at T_1 after GAH, $F(1, 44) = 11.39, p < .002$, partial $\eta^2 = .21$, demonstrating a large effect size (see Figure 1 and Table 2). Thus, hypothesis 2 was supported. The estimated adjusted mean for general well-being scores increased by 8.53 from 61.7 at T_0 to 70.23 at T_1 . An additional ad hoc comparison of pretest and final assessment scores was made to identify potential differences among the two subgroups (GAH-only and GnRHa + GAH; see Table 3). Whereas each group appears to have equivalent outcomes with regard to general well-being scores and similar baseline suicidality scores, notably no one in the GnRHa + GAH cohort endorsed any items assessing for suicidality at T_1 .

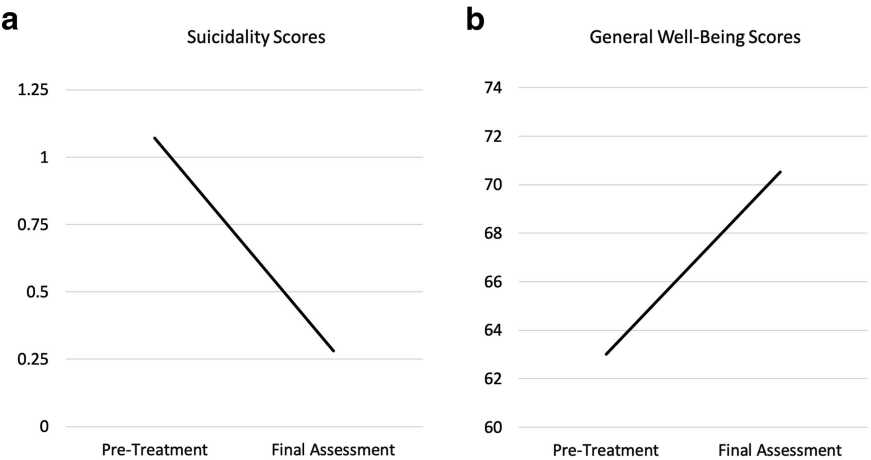


Figure 1. Estimated marginal means of suicidality (ASQ) scores adjusted for the covariate, duration of treatment, at pretest and final assessment (a). Estimated marginal means of general well-being scores (GWBS) adjusted for the covariate, duration of treatment, at pretest and final assessment (b). ASQ = Ask Suicide-Screening Questions; GWBS = General Well-Being Scale.

Table 2
Estimated Marginal Means and Standard Errors of the Analysis of Covariance for Each Dependent Variable

Scale	T ₀			T ₁		
	All	AFAB	AMAB	All	AFAB	AMAB
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>
ASQ	1.11 (.22)	1.01 (.23)	1.21 (.36)	.27 (.12)	.29 (.13)	.24 (.19)
GWBS	61.7 (2.43)	64.95 (2.66)	58.44 (4.09)	70.23 (2.15)	70.94 (2.35)	69.52 (3.62)

Note. Results from each ANCOVA are shown. The assessment point is the repeated measure, covarying duration of treatment. *N* = 47. GWBS = General Well-Being Scale; ASQ = Ask Suicide-Screening Questions; AFAB = assigned female at birth; AMAB = assigned male at birth.

In the first mixed ANCOVA, a significant effect was not observed for sex assigned at birth with regard to suicidality scores, after controlling for duration of treatment, $F(1, 44) = .08$, $p = .79$, partial $\eta^2 = .002$ (see Table 2). In the second mixed ANCOVA, the predicted interaction effect of sex assigned at birth with regard to well-being scores was also nonsignificant, $F(1, 44) = 1.00$, $p = .32$, partial $\eta^2 = .02$, demonstrating a small effect size (see Table 2). Thus, hypothesis 3 was not supported (i.e., the observed differences in suicidality and well-being scores after GAH treatment did not differ based on birth-assigned sex).

Discussion

Results of the analyses confirmed our primary hypotheses. We found that at final assessment, participants’ suicidality scores had signif-

icantly decreased following administration of GAH, confirming hypothesis 1. Prior to receiving GAH patients, on average, endorsed at least one item of suicidality. At final assessment after receiving GAH, however, participants endorsed almost no symptoms of suicidality. In addition, we found that at final assessment, participants’ general well-being scores significantly increased, supporting hypothesis 2. Despite having roughly equivalent pretest suicidality scores, an ad hoc comparison revealed that, in contrast to the GAH cohort with a T₁ mean ASQ score of .33, the GnRH_a + GAH cohort endorsed no suicidality after treatment. The disparity in suicidality outcomes may be due to the initiation of GAH at younger ages among the GnRH_a + GAH cohort, contributing to improved psychological and physical outcomes (de Vries et al., 2014). It may also be that participants who had been administered GnRH_a

Table 3
Suicidality and General Well-Being Score Means and Standard Deviations for the GAH-Only (n = 39) and GAH + GnRH_a (n = 8) Subgroups at T₀ and T₁

Scale	T ₀		T ₁	
	GAH-only	GnRH _a + GAH	GAH-only	GnRH _a + GAH
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
ASQ	1.06 (1.3)	1.08 (1.49)	.33 (.77)*	.01 (.02) ^{a,*}
GWBS	62.75 (16.43)	64.29 (8.32)	70.79 (13.46)	69.2 (12.8)

Note. GAH-only refers to participant who did not received gonadotropin-releasing hormone agonists (GnRH_a) prior to being administered gender-affirming hormones (GAH). GnRH_a + GAH refers to participants who had received GnRH_a prior to being administered GAH. ASQ = Ask Suicide-Screening Questions; GWBS = General Well-Being Scale.

^a The mean value of .01 is an artifact of the imputations conducted for the item omitted from the ASQ prior to March 2017. Participants in the GnRH_a + GAH subgroup did not endorse any suicidality items at T₁.

* Statistically significant difference between GAH-only and GnRH_a + GAH mean values at T₁ ($p < .05$).

prior to GAH have more, or earlier, parental support.

Hypothesis 3 (i.e., those assigned female at birth will experience greater improvements in general well-being and larger decreases in suicidality) was not supported. Although hypothesis 3 was not supported, this finding may have been due to insufficient power because we did observe a small effect size for general well-being scores. Ultimately, we may infer from our findings that GAH is associated with less suicidality and greater well-being for all youth, regardless of assigned sex at birth.

Our findings demonstrate that levels of suicidality decrease, whereas general well-being increases, among adolescents diagnosed with GD after receiving GAH. The findings contribute to a growing literature supporting the hypothesis that transgender adolescents and adults benefit from GAH in terms of quality of life and psychological functioning (de Vries et al., 2014; Keo-Meier et al., 2015). Clinicians and advocates working with transgender youth and their families can cite these data as support that GAH is associated with improved psychological outcomes among transgender youth. Our study, specifically, speaks to reduced risk for suicidality and improved well-being, both of which are prominent worries of parents. Parents often struggle with the decision about whether to provide permission for irreversible steps in medical transition, such as initiation of GAH. Their fears may be alleviated to some extent as the emerging evidence supports use GAH among transgender youth.

Concordant with existing guidelines (American Psychological Association, 2015, Guideline 11), our findings also support the notion that transgender people tend to have more positive life experiences when they receive gender-affirming care. Affirmative care may help to counteract the wide range of societal, personal, and environmental discrimination that transgender youth often encounter. However, the pathway through which beneficial outcomes arise following affirming care is not entirely clear. GAH facilitate secondary sex characteristics consistent with one's experienced gender. Access to this treatment may reduce GD and lower body-related uneasiness (Fisher et al., 2014), resulting in increased well-being and decreased suicidality. It may also be that the sense of affirmation that comes with receiving care by affirming professionals and a potential increase

in parental acceptance lessens distal minority stress factors (i.e., nonaffirmation; see Testa, Habarth, Peta, Balsam, & Bockting, 2015), thereby resulting in improved mental health.

Limitations and Directions for Future Research

Confounding variables of this study may include level of familial support, whether a patient is actively receiving psychotherapy, or differences in the specifics of gender-affirming medications (e.g., dosage). Given the protective role of parental support in health and well-being among transgender youth (Simons, Schrager, Clark, Belzer, & Olson, 2013), it could be argued that such support affected the improvements in well-being and decreases in suicidality observed in this study. However, it should be noted that at baseline, a relatively high level of parental support was required among all participants (compared with youth, e.g., who do not have access to gender-affirming medical care because of lack of parental support) because the parents at our clinic must provide permission for their child to receive gender-affirming medical interventions. That is, most participants in this study had some degree of parental support. Consequently, these findings may not be generalizable to transgender youth with unsupportive parents. It may be that GAH, combined with parental support or other types of support (e.g., individual counseling, support groups), are active ingredients in producing beneficial outcomes, but our study did not assess these factors. Future research may want to examine the concomitant roles of parental support and gender-affirming medications on psychological outcomes among transgender youth. Moreover, GD is a clinical diagnosis, and often it is difficult to ascertain the degree of GD an individual is experiencing. Future studies may benefit from assessing the severity of gender dysphoria before and after undergoing gender-affirming medical intervention as a means of evaluating the impact of the intervention on GD itself.

As noted by others (Costa et al., 2015), it may be the case that by virtue of scheduling an appointment with a gender-affirming multidisciplinary treatment team, adolescents have an immediate reduction in distress, knowing they are one step closer to receiving gender-affirming treatment. In this case, the pretest

scores would not have captured any immediate relief resulting from the knowledge that an initial appointment was scheduled. Additionally, it is also unclear whether the beneficial outcomes associated with GAH take effect immediately after administration of the medication, come about after physical changes begin to manifest, or vary over time. Future studies might examine change over time (e.g., using a time-series design) and age of initiation of treatment while also accounting for level of parental support and outward physical appearance because these factors may explain or alter the intervention's effect on suicidality and well-being. Future studies would further benefit from including measures that specifically assess symptoms of anxiety and depression to further evaluate the potential role of GAH on emotional functioning. In addition, our longitudinal study lacked a control group, so we cannot infer that GAH are causally responsible for the beneficial outcomes observed. Because withholding potentially life-saving treatment from youth seeking medical care would be unethical, future studies should address this limitation by including data with appropriate comparison groups to strengthen findings. For example, future researchers might compare transgender youth who have received GAH with age- and demographic-matched peers seeking therapy for issues that are also thought to be influenced by gender dysphoria (e.g., depression, anxiety).

In addition, the total sample was primarily White (83%) and thus unrepresentative of the diverse overall population of transgender youth. For transgender youth of color, who experience additional discrimination and societal barriers (James et al., 2016), such discrimination could attenuate the beneficial outcomes observed with gender-affirming medical interventions. Research from other regions of the United States with more racially diverse clinical populations can help answer such a research question. Furthermore, our study did not make any distinction among participants for nonbinary gender identities and classified participants based on sex assigned at birth. To date, no studies have outlined GAH regimens for nonbinary individuals (Chen, Edwards-Leeper, Stancin, & Tishelman, 2018). Future studies should explore the trajectory of nonbinary and genderqueer identities over time and describe outcomes associated with affirming medical interventions, given that

nonbinary youth report higher rates of attempted suicide compared to transgender adolescents assigned male at birth and their cisgender peers (Toomey, Syvertsen, & Shramko, 2018).

In addition, youth served in our clinic receive comprehensive care by an experienced multidisciplinary team. Thus, these findings may not generalize to all transgender youth prescribed GAH regimens (and not all transgender youth desire medical treatment). However, our findings likely generalize well to other patients in clinics with similar treatment models.

Conclusion

GAH appears to be associated with improvements in general well-being and decreasing suicidality among transgender youth. To our knowledge, this is the first study to demonstrate that levels of suicidality decrease, and general well-being increases, among adolescents diagnosed with GD after receiving GAH. The findings contribute to a growing literature showing that transgender adolescents and adults benefit from GAH in terms of improved quality of life and psychological functioning (e.g., Keo-Meier et al., 2015).

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CERTIFICATE OF SERVICE

I certify that on August 12, 2022, I electronically filed the foregoing APPELLEES' SUPPLEMENTAL APPENDIX with the Clerk of the Court for the United States Court of Appeals for the Eleventh Circuit by using the appellate CM/ECF system.

I certify that all participants in this case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

s/ Barbara Schwabauer
BARBARA SCHWABAUER
Attorney