TABLE 3 Summary of effects on bone development by puberty-blocking treatment (GnRHa) followed by CSHT in children with gender dysphoria.[20–25]

Outcome measures	Number of study participants, description of studies	Main Result	"Certainty of Evidence"	Deduction in GRADE[a]
Bone density during puberty-blocking hormonal treatment (g/cm^2, g/cm^3)	*n* on hormones = 363 *n* evaluated = 297 Five observational cohort studies (four retrospective and one prospective)[20–24]	Unchanged bone density (DXA measurement)	⊕⊕◯◯ Low certainty	–1 risk of overall bias[b] –1 precision
Bone density during puberty blocking hormonal treatment in relation to reference data in the literature (z-score)	*n* on hormones = 408 *n* evaluated = 292 Five observational cohort studies (four retrospective, and one prospective)[21–25]	Decreased increase in bone density over time	⊕⊕◯◯ Low certainty	–1 risk of overall bias[b] –1 precision
Bone density after 1–3 years (up to 22 years of age) of CSHT, which had been preceded by puberty-blocking hormonal treatment in relation to reference data in the literature	*n* on hormones = 268 *n* evaluated = 165 Three observational cohort studies (two retrospective and one prospective)[21,24,25]	After group median five years with CSHT, bone density recovered in hip but not in lumbar spine compared to data at start of treatment (z-score)	⊕⊕◯◯ Low certainty	–1 risk of overall bias[b] –1 precision

Abbreviations: CSHT, Cross-sex hormone treatment; DXA, Dual-Energy X-ray Absorptiometry.

[a]Starting at 4 for optimal studies in each study type.

[b]Analysis not based on stage in puberty development.

treatment and after at least two years on CSHT and compared with reference values of the general population: the bone geometry resembled the reference curve for the experienced sex only when GnRHa was started during early puberty. Bone geometry estimates in those who started GnRHa treatment during mid and late puberty remained within the reference curve of the biological sex.[26]

3.6 | Body composition and metabolic markers

GnRHa treatment effectively reduced endogenous sex hormone serum levels (Table 4). DXA scans after 1 year of GnRHa treatment revealed increased fat mass and reduced lean body mass.[28] Longitudinal growth depends on bone maturity (bone age) of those in the study group. Ongoing pubertal growth spurt will be arrested when GnRHa therapy is started, reducing the growth velocity to the prepubertal rate.[29]

Nokoff et al studied body composition and insulin sensitivity during 1 year of GnRHa therapy.[30] In addition to body composition, metabolic effects as insulin sensitivity during CSHT, and changes in blood pressure during testosterone therapy were examined.[31–33] Of these studies, three originated from Amsterdam.[29,32,33] The Amsterdam studies included observations during GnRHa therapy,[28] 1 year after starting CSHT,[32] as well as after a group median >5 years with CSHT in a cohort of 22-year-old adolescents.[31,33] The studies from Amsterdam were generally larger than the other studies. CSHT changed body composition towards the affirmed sex.[31,32] Obesity (defined as BMI >30 at age 22 years) was more prevalent in the transgender population[33] (Table 4).

3.7 | CSHT in children without prior GnRHa treatment

We were able to identify three studies of low-to-moderate bias examining CSHT in children without prior GnRHa treatment.[13,34,35] All were retrospective longitudinal studies. Because the number of study participants was small, studies were deemed to have low external validity, and because the studies examined different outcomes (e.g., lipid serum levels, Hb, blood pressure, metrorrhagia), it was not possible to draw any overall conclusions from these studies. Although the Mullins et al. paper[13] included several individuals at elevated risk of arterial or venous thrombosis, no cases of thrombosis were reported.

4 | DISCUSSION

We performed an extensive literature search to examine psychosocial and cognitive outcomes as well as metabolic and bone health in children with gender dysphoria taking hormone therapy. No randomised controlled trials were found, but we could identify 24 relevant observational studies. However, these were limited by

TABLE 4 Summary of findings of puberty-blocking (GnRHa) hormone treatment on anthropometric measures, body composition, and metabolism in children with gender dysphoria.[28–33]

Outcome measures	Number of study participants, description of studies	Main result	"Certainty of Evidence"	Deduction in GRADE[a]
Anthropometric measures	*n* on hormones = 192 *n* evaluated = 192 One retrospective observational cohort study[31]	Increased weight and body mass index	Cannot be assessed	−2 risk for overall bias[b] −1 precision[c] −1 indirectness[d]
Body composition	*n* on hormones = 325 *n* evaluated = 286 Two prospective observational cohort studies and one controlled cross-sectional study[28,30,31]	Decreased lean body mass	Cannot be assessed	−2 risk for overall bias[b] −1 precision[c] −1 indirectness[d]
Metabolic measures	*n* on hormones = 209 *n* evaluated = 209 One retrospective observational cohort study and one controlled cross-sectional study[30,32]	No change in serum lipids or blood pressure Increased insulin level in MtF Decreased insulin sensitivity	Cannot be assessed	−2 risk for overall bias[b] −1 precision[c] −1 indirectness[d]
Blood pressure	*n* on hormones = 15 *n* evaluated =15 One retrospective observational cohort study[33]	Change in blood pressure	Cannot be assessed	−2 risk for overall bias[b] −1 precision[c] −1 indirectness[d]
Growth (cm/year)	*n* on hormones = 55 *n* evaluated = 55 One prospective multicentre observational GnRHa treatment cohort study[29]	Reduced growth velocity	Cannot be assessed	−2 risk for overall bias[b] −1 precision[c] −1 indirectness[d]

[a]Starting at 4 for optimal studies in each study type.

[b]Selection of study participants is difficult to assess. Analysis not based on stage in puberty development.

[c]Few study subjects in each study, hence there is heterogeneity in outcome and analyses.

[d]Single study. In this context, 'indirectness' is similar to 'external validity'.

methodological weaknesses, for instance lack of or inappropriate control group, lack of intra-individual analyses, high attrition rates that precluded conclusion to be drawn. The exception being that children with gender dysphoria often had lower group mean values for BMD already prior to GnRHa treatment, and that GnRHa treatment delays the physiologically occurring BMD gain during pubertal sex hormone stimulation. However, this GnRHa-induced delay in BMD gain is almost fully compensated for by later ensuing CSHT. Although study participants were followed up to 22 years of age, the observed remaining deficit may depend on the limited study group size or on too short observation time.[21]

Our review highlights several specific knowledge gaps in gender dysphoria that are important to bridge not least given the recent increased incidence in many countries.[6,7] First, randomised controlled trials are lacking in gender dysphoria research. We call for such studies, which may be the only way to address biases that we have noted in the field. Given the current lack of evidence for hormonal therapy improving gender dysphoria, another ethically feasible option would be to randomise individuals to hormone therapy with all study participants, independent of intervention status, receiving psychological and psychosocial support. However, controlled trials do not necessarily require placebo treatment, but could for example build on the date or time of starting hormonal therapy to generate comparison groups. However, it should also be noted that this is a highly vulnerable population.

A second limitation concerns the statistical management of data. In the reviewed studies, observational data have frequently been analysed at a group level where intra-individual changes would have been more appropriate. Intra-individual analyses would allow for a better understanding of how subgroups of individuals respond (both positively and negatively) to hormone therapy. Group-level analyses are sensitive to selection bias because of high drop-out rates: The group studied at the end of the study is a selection of the group studied at baseline, which increases indirectness (reduces external validity). Moreover, it is important to analyse the distribution of individual data to be able to identify outliers who may be at risk for severe consequences of treatment.

Third, many studies only present data on chronological age but fail to account for puberty stage and biological age. This is a concern because the main purpose of GnRHa treatment is to suppress puberty and, with that, biological ageing.

Fourth, long-term studies are lacking. The duration of GnRHa treatment and CSHT was rarely >4 years. The absence of long-term studies is worrying because many individuals start treatment as minors (<18 years) and CSHT is lifelong. Fifth, individuals who stop GnRHa treatment before the start of CSHT need to be described and followed up. Sixth, some of the findings underlying this review are old, and studies reflecting the changing demographics of individuals seeking care for gender dysphoria are warranted.

TABLE 5 The GEnder Dysphoria HORmone treatment (GENDHOR) checklist.

	Recommendations
Aim	Describe the aim of the study
Study participants:	
Cases/exposed	Define gender dysphoria in your study, including the assessment tools used. Define eligibility criteria for your study (including chronological age, bone age or puberty stage, according to Tanner or Prader (when study concerns adolescents), biological sex, perceived gender identity, psychiatric and somatic comorbidities, medications at baseline). List exclusion criteria (diagnoses). List ages of participants at the start of each treatment (including absolute age ranges).
Comparators/ unexposed	Clarify how controls were selected (were controls recruited from the general population?) or whether national/ regional reference data (for instance, Z-scores) were used instead of individual controls.
Study design	Describe the study design: Cross-sectional, retrospective, prospective; case–control (and if nested), cohort study, randomised clinical trial.
Setting	Describe the setting of the study. Were study participants included at a tertiary centre or from the general population? Describe the catchment area/population of participating centres.
Intervention	Hormone treatment Describe whether GnRHa, anti-androgens, CSHT, or a combination was used. List generic names, mode of administration, and dosages of all treatments. Specify the treatment duration of each treatment. If hormone serum concentrations are studied, include the standard procedure for the timing of blood samples to hormone intake. If patients undergo surgery, clarify the type of surgery and number of participants undergoing each surgical procedure (gonadectomy, mastectomy, laryngeal surgery, vaginoplasty/phalloplasty, etc.). Clarify if any participant received psychiatric counselling before, or during the study, including total duration and frequency of counselling.
Variables	Define each variable (including co-variates) and its source. If possible, mention any effort to validate the variables.
Data measurement	Clarify who collected the data on study participants. Present time between first and second measurements if your study is longitudinal and includes "before-after" measurements in relation to the intervention. Mention if study participants had previously been included in other studies with a different aim or examining other outcomes.
Blinding	Describe if the data collectors were blinded to participant status/treatment or not.
Loss to follow-up	Indicate the number of participants discontinuing GnRHa/ CSHT and the reason(s) for discontinuation, including no longer wish to pursue gender reassignment treatment. Describe loss to follow-up/missing data
Statistical methods	Describe statistics according to a relevant checklist. Consider when applicable: Intra-individual changes (mean, SD, median, range) vs. between-group differences.
Descriptive data	In addition to usual demographic, clinical, social/socioeconomic information, report body mass index (BMI), smoking, use of oral contraceptives (type) or other hormonal treatment, puberty stage. Report any psychiatric illness at baseline, as well as the use of psychotropic medication. Describe other comorbidities, including disorders that could be considered contraindications for either hormone treatment or surgery. Specify follow-up time (median, mean) since the start of the intervention and since start of hormone treatment (define intervention start).
Outcome data	Specify main outcome of the study. Indicate all secondary outcomes, including adverse events.
Adverse events/ complications	Describe all adverse events.
Main results	Present absolute numbers. Calculate absolute and relative risks/Intraindividual effects/change and group mean/ median. Present incidence data. Describe any adjustment for potential confounders.
Limitations	Discuss limitations of your study, including limitations of the measurements used (e.g., DXA) and sources of potential bias or imprecision.
Generalisability/ external validity	Can data be generalised to individuals with gender dysphoria outside your study centre and the study country?
Conflict of interest	Report any conflict of interest.

Note: Based on our literature review, we created a *GEnder Dysphoria HORmone treatment checklist* (GENDHOR).

This list consists of recommendations that researchers may consider when planning a study of gender dysphoria, whether observational or interventional.

Abbreviations: CSHT, Cross-sex hormone treatment; DXA, Dual-Energy X-ray Absorptiometry; GnRHa, Gonadotropin-releasing hormone agonist (analogues).

Finally, we could not evaluate the frequency of individuals who drop out from GnRHa treatment and no longer wish to continue with gender transition. However, a follow up study was published after our literature search.[36] Of 720 children (31% born male and 69% born female) who started GnRHa treatment in adolescence, 98% continued to use hormone treatment into adulthood, which suggests that children generally continue with gender transition once they have started GnRHa treatment. We know from internet-based surveys that detransitioning exists,[37] but such studies cannot provide reliable estimates of detransitioning frequency because of selection bias. Studies that closely follow individuals who start GnRHa therapy and/or CSHT until at least age 30 are urgently needed. We also acknowledge there are other potential side effects from GnRHa therapy or CSHT that were not included in our review such as alopecia and abscesses from injections.[38]

Due to limitations in reporting of data, previous published studies in this field repeatedly contain insufficient details on drug administration and dosages, treatment duration, and the type of surgery performed. Some of these limitations will be partly remedied by the introduction of the new ICD version 11, and the Utrecht criteria,[39] but the field also urgently needs high quality longitudinal studies that not only assess medical outcomes but also those outcomes that matter most for affected individuals. Building on the identified limitations in previous research, we compiled a checklist to improve gender dysphoria research ("GENDHOR", Table 5). The aim of this checklist is not to replace existing research guidelines, but using it together with existing guidelines might support researchers and peer reviewers, and ultimately benefit patients and their families.

Last, there have been studies in this field published after the date of our literature search (9 November 2021). These have not been added to this study in order to not depart from the systematic approach. We nevertheless wish to comment on some of the publications. First, the National Institute for Health and Care Excellence in England (NICE) conducted evidence reviews of GnRHa[40] as well as CSHT[41] for children with gender dysphoria, which were independent from our work. The conclusions generally align with our findings. Second, Chien et al.[42] recently published a prospective study of psychosocial functioning during 2 years after initiation of CSHT in youths (12–20 years of age) with gender dysphoria. Of 315 participants, 162 completed that study. Life satisfaction increased, and depression and anxiety scores decreased, among biological females but not biological males. The strongest finding was a moderately improved appearance congruence. No information on concomitant psychological or psychopharmacological therapy was provided.

5 | CONCLUSION

This systematic review of almost 10 000 screened abstracts suggests that long-term effects of hormone therapy on psychosocial and somatic health are unknown, except that GnRHa treatment seems to delay bone maturation and gain in bone mineral density.

AUTHOR CONTRIBUTIONS

Study concept and design: All authors. Acquisition of data: Malin Höistad, Jan Adolfsson. Drafting of the manuscript: All authors. Interpretation of data and critical revision of the manuscript for important intellectual content: All authors. Administrative, technical, or material support: Jan Adolfsson, Malin Höistad. Funding acquisition: the Swedish agency for technology assessment and assessment for social services.

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CONFLICT OF INTEREST STATEMENT

JFL coordinated an unrelated study on behalf of the Swedish inflammatory bowel disease quality register (SWIBREG) that received funding from the Janssen Corporation. JFL has also received financial support from Merck Sharp & Dohme developing a paper reviewing national healthcare registers in China. JFL is currently discussing potential research collaboration with Takeda. ML has received lecture honoraria for Lundbeck pharmaceuticals and served as consultant for AstraZeneca. The other authors report no conflict of interest.

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SURGERY

Age Is Just a Number: WPATH-Affiliated Surgeons' Experiences and Attitudes Toward Vaginoplasty in Transgender Females Under 18 Years of Age in the United States

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ABSTRACT

Background: A rising number of female-affirmed transgender adolescents are being treated with gonadotropin-releasing hormone analogues and subsequently cross-sex hormones at early or mid-puberty, with vaginoplasty as the presumed final step in their physical transition. But, despite the minimum age of 18 years defining eligibility to undergo this irreversible procedure, anecdotal reports have shown that vaginoplasties are being performed on minors by surgeons in the United States, thereby contravening the World Professional Association for Transgender Health (WPATH) standards of care (SOC).

Aim: To explore surgeons' attitudes toward ethical guidelines in the SOC; any professional experiences of performing vaginoplasty on transgender minors; views of surgical risks, benefits, and harm reduction measures; and perceptions of future challenges and concerns in this area of surgical practice.

Methods: A qualitative semistructured interview approach was used to collect data from 13 male and 7 female surgeons who perform transgender vaginoplasty in the United States.

Outcomes: Professional experiences and attitudes toward vaginoplasty in transgender minors were analyzed using the constant comparative method applied to 20 individual interview transcripts.

Results: While there was close agreement concerning surgical techniques, proper patient selection, and predictive elements of postoperative success, attitudes toward the SOC and the reliance on the guidelines varied. The sole practitioner model is gradually giving way to a more holistic team approach, with patient responsibility dispersed among different professionals. Different approaches to surgical training, professional standards, and fellowship programs were suggested. Several participants expressed a need for centralized data collection, patient tracking, and increased involvement of the WPATH as a sponsor of studies in this emergent population.

Clinical Implications: Drawing on surgeons' attitudes and experiences is essential for the development of standards and practices. A more precise and transparent view of this surgical procedure will be essential in contributing to the updated version 8 of the WPATH SOC.

Strengths and Limitations: The abundant data elicited from the interviews address several meaningful research questions, most importantly patient selection criteria, surgical methods, and issues critical to the future of the profession. Nevertheless, the limited sample might not be representative of the surgical cadre at large, particularly when exploring experiences and attitudes toward vaginoplasty in minors. A larger participant pool representing WPATH-affiliated surgeons outside the United States would improve the generalizability of the study.

Conclusion: Taken together, the study and its findings make a significant contribution to the planned revision of the WPATH SOC. **Milrod C, Karasic DH. Age Is Just a Number: WPATH-Affiliated Surgeons' Experiences and Attitudes Toward Vaginoplasty in Transgender Females Under 18 Years of Age in the United States. J Sex Med 2017;14:624–634.**

Key Words: Adolescent; Gender Confirming Surgery; Surgeon; Transgender; Vaginoplasty; World Professional Association for Transgender Health

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INTRODUCTION

During the past 5 years, treatment of gender dysphoric adolescents presenting for medical interventions in the United States has received increased attention and visibility in the clinical literature and the mainstream media.[1–5] Supported by parents and referred by psychiatrists, psychologists, and other mental health professionals, transgender youths are seeking gender-affirmative treatment in private practice settings, public health centers, and hospitals with specialized services dedicated to transgender health care.[6–8] Major American insurance exchanges and health maintenance organization networks also are beginning to cover medical care designed to alleviate gender dysphoria in teens, ranging from fully reversible interventions such as puberty-suppressing gonadotropin-releasing hormone analogues and partly reversible gonadal steroid treatment to irreversible procedures such as bilateral mastectomy with chest reconstruction for male-affirmed late teens and genital surgeries such as orchiectomy and/or vulvovaginoplasty in female-affirmed older adolescents.[9] Medical providers of transgender care generally adhere to the most recent (version 7) World Professional Association for Transgender Health (WPATH) Standards of Care (SOC), in which eligibility and readiness criteria for irreversible interventions can be applied when the adolescent has reached the legal age of majority in a given country.[10] The document specifies that the age criterion should not be seen as an indication for "active intervention," only as an age threshold, with the understanding that the legal age of majority varies from nation to nation. The current SOC provide some flexibility in the minimum age requirement for chest reconstruction in male-affirmed adolescents, although it could be argued that this procedure is practically irreversible. Conversely, female-affirmed teenagers must defer orchiectomy and/or vaginoplasty until 18 years of age to stay compliant with the SOC and the legal age of majority in the United States. This position also is supported by the Endocrine Society, a worldwide organization dedicated to the education and practice advancement of endocrinology.[11] The society has issued recommendations concerning the treatment of trans youth, in which it is suggested that genital surgery be deferred until the individual has reached 18 years of age. The Endocrine Society does acknowledge that 16-year-olds are legal adults in many countries and are mature enough to make medical decisions of some cognitive complexity; nevertheless, because data are not available on outcome studies concerning genital surgery in minors, the shared recommendation by the two organizations still stands.

In the Netherlands, where adolescents from 16 years of age are legally competent to make treatment choices independent of parental consent,[12] the policy of Dutch clinics treating transgender teens is that genital surgery should not be performed before 18 years of age. A review of the available literature concerning the Dutch protocol shows that although clinicians agree that emotional maturity represents a better criterion than minimum age, there is acknowledgment that objective criteria do not exist in assessing readiness for genital surgery in adolescents.[13] In addition, although puberty suppressants are available to gender dysphoric adolescents at 12 years of age and cross-sex hormones are permitted at the minimum age of 16 years,[14–16] a recommended candidate for genital surgery is at least 18 years old and has been living in the affirmed gender for a minimum of 2 years after initiating hormone treatment. Dutch outcome studies of late adolescents and young adults who have undergone irreversible procedures 1 to 4 years before follow-up have reported psychologically normative functioning and a high satisfaction rate with no regrets by transsexuals after surgery.[17–19] Moreover, anecdotal reports and at least one news media release have reported that vaginoplasties in patients younger than 18 years have been performed by surgeons in the United States, who thereby contravene or sidestep the SOC.[20,21] Contrary to the concise criteria guiding decisions for postadolescent surgical treatment [p. 54], there are no guidelines in the WPATH SOC that support the surgeon in the decision to perform vaginoplasty on transgender women younger than 18 years. The surgeon must rely on evaluations by other professionals, careful patient selection, and the personal conviction that proceeding with surgery is the right decision, with the added legal burden of obtaining consent from parents in lieu of the minor and assuming principal responsibility for the physical risk to the young patient who might not always be compliant with or fully understand postoperative care. The surgeons who perform the procedure on transgender minors have, without exception, refrained from publishing any peer-reviewed outcome data or technical articles on this small but increasingly important population. In addition, although only a few teaching programs offer endocrinology fellowships that include transgender health care,[22] no American educational institutions currently provide fellowships or standardized training in genital surgery for female-affirmed transgender adolescents. These factors have contributed to a dearth of specific medical information, a lack of shared surgical expertise, and inadequate guidance that would otherwise be widely available to all practitioners of transgender medicine and to the general public. To go beyond anecdotal evidence and explore the collective experiential knowledge of surgeons who specialize in performing vaginoplasty as part of gender-confirming surgery (GCS), the authors report the findings of their qualitative research study investigating WPATH-affiliated surgeons' views, experiences, and attitudes toward performing vaginoplasty on transgender minors in the United States.

AIMS

The aim of the study was to explore any professional experiences of performing vaginoplasty on transgender minors in the United States; views of surgical risks, benefits, harm reduction measures, beliefs, and attitudes related to the ethical guidelines on adolescents in the SOC; and perceptions of future challenges and concerns in this area of surgical specialty. The proximate goals of the study were to elucidate experiences and attitudes

toward the growing surgical practice of vaginoplasty in transgender minors and to provide foundational knowledge in an under-researched area, with the long-term objective of using the study findings in the future development of criteria for irreversible surgical procedures in the eighth version of the WPATH SOC.

METHODS

Because of the anticipated small number of potential participants active in a highly specialized surgical field, a qualitative study format was preferred. A modified analytic induction approach was chosen because of the specifically targeted research questions.[23] Purposive sampling was initiated; a search under the *Medicine: Surgery* and *Medicine: Gynecology/Urology* tabs inside the optional provider directory located on the WPATH website[24] yielded the names of 21 affiliated plastic surgeons and 20 gynecology or urology specialists practicing in the United States. Additional names of member surgeons whose names were not in the directory were found after performing multiple Google searches using key words pertaining to vaginoplasty or GCS. After verifying that the procedure was offered by telephoning each surgical practice and by viewing proprietary websites when available, 22 surgeons nationwide were identified as providers of vaginoplasty to the transgender female patient population. An invitation e-mail was sent to each surgeon, followed by telephone calls to the corresponding surgical practice, in which potential participants were informed in detail about the study objectives and its parameters. Twenty surgeons chose to participate, and two declined. A semistructured interview sheet consisting of 30 items related to the study goals and supplemented by additional prompt questions, when applicable, were used to elicit responses in the following main areas:

1. Demographic information and professional GCS experience of participant
2. Any concerns regarding performing vaginoplasty in minors
3. Negotiating consent or assent and risk management
4. Training, professionalism, and the WPATH SOC

All interviews were conducted by the first author, a licensed psychotherapist, during a 45-day period by telephone, with exception of one face-to-face interview. Average interviewing time was 25 minutes. All interviews were audio-recorded with the participant providing verbal consent at the beginning of each recording. Interviews were transcribed by the first author, de-identified, and checked multiple times against the master recording files to ensure accuracy. Transcripts were saved in rich text format (.rtf) files and processed using HyperRESEARCH qualitative data analysis software (Researchware Inc, Randolph, MA, USA). Analysis was implemented using line-by-line coding of the transcribed material and by performing the constant comparison procedure to identify repeated patterns in the available data. Codes were refined into categories that were used to structure the analysis further into major thematic areas according to standard grounded theory.[25] Coding checks were performed by the 2 authors to ensure intercoder reliability.[26] Data gathering procedures were reviewed and approved to ensure their consistency with the ethical principles required by the institutional review board of the second author's affiliated institution.

RESULTS

Demographic and general participant data are presented in Table 1. The vast majority of participants operated at in-patient hospitals; however, one surgeon reported performing the procedure at an out-patient surgery center, with multiple visitations at the patient's home or hotel after surgery. The preferred method of vaginoplasty was a one-stage penile inversion, most often augmented by a full-thickness scrotal skin graft. Nine surgeons had never performed vaginoplasty on a transgender female minor, and the remaining 11 participants reported 1 to 20 cases per surgeon. Of the 11 surgeons who had performed vaginoplasty on a transgender female minor, 10 were in private practice. Reported ages of minors undergoing surgery ranged from 15 to "a day before 18" years (surgeon 7). Most participants had noticed a definite increase in the number of minors requesting information about the procedure on their own or being referred for vaginoplasty by their mental health providers.

Table 1. Basic participant demographics (N = 20)

Participants	n
Sex	
Men	13
Women	7
Surgical specialty or board certification	
General plastic surgery	13
Urology	4
OBG	2
Plastic surgery + urology (double board certification)	1
Primary practice setting	
Private practice	16
University hospital or teaching institution	4
Insurance network contracted provider	
Yes	14
No	6
Years in practice	
Minimum–maximum	4–43
Average	19
Years performing GCS	
Minimum–maximum	< 1–26
Average	10
Performed vaginoplasty on transgender minor	
Yes	11
No	9

GCS = gender-confirming surgery; OBG = obstetrics and gynecology.

Surgeon 16 quantified a shift in the general age group of patients: "When I first started my practice, I would estimate that 85% of patients were older than 25. Now, I would say that only 40% of my patients are older than 25 in the last nine years." In addition, although there was no unanimous recall of the youngest patient ever reported in the media to undergo the procedure, a few participants believed that they were responsible for having operated on "the youngest," with surgeon 16 stating that "… the patient was a 15-year-old who was just on the cusp of turning 16."

Anatomic and Physiologic Issues

There was little concern over the younger adolescent and her ability to physically withstand the invasive procedure compared with a middle-age or elderly patient; however, almost all surgeons remarked on the penoscrotal hypoplasia or limited penile shaft size that would ensue after the use of puberty-suppressing gonadotropin-releasing hormone analogues, sometimes for as long as 3 years. Two surgeons who reported operating on minors commented, "… they are coming in after being put on blockers, so they have 11-year-old genitalia" (surgeon 9) and "… you are really doing vaginoplasty on a micropenis" (surgeon 16). Most participants emphasized that the surgical techniques were the same for all patients no matter the age; of those who had performed the procedure on several minors, the use of flank skin grafts most commonly resolved the problem of inadequate tissue availability. In other reported measures, surgeon 2 implanted a scrotal tissue expander that required periodic infusion during 2 months, and surgeon 14 used donor tissue matrix (LifeCell, Branchburg, NJ, USA), deeming it "nicely successful" and thereby avoiding patient exposure to external flank scarring. The alternative procedure of using sigmoid- or ileum-derived grafts to create the neovagina was seen as a last resort by a few participants who stated diversion colitis, excessive secretion, persistent odors, and potential leakage of stool into the peritoneum as some of the concomitant morbidities.

Psychological and Contextual Concerns

An overwhelming majority of surgeons cited psychological maturity as the main criterion for adolescent patient selection, stating "Age is arbitrary. The true measures of how well a patient will do are based on maturity, discipline and support" (surgeon 11). Most participants emphasized that mental maturity was related to the ability to understand the stressors of undergoing surgery and expectations of postoperative self-care, particularly the commitment to a consistent dilatation schedule to maintain patency of the neovagina:

> The biggest concern is, will they be mature enough to be able to take care of themselves after surgery. Not just having the surgery done. Will they do what they need to do after surgery maintain the vaginal depth involved? In actuality, I don't think it is age dependent, it is the maturity of the patient. An 18-year-old goes off to college and leaves the parents. They leave that protective environment and everything becomes less important to them in terms of the dilatation and care. Some of my biggest struggles have not been with the 16-year-old group because they are still at the parents' house—it is the 18-year-olds who disappear and go to college within a few months after their surgery. Those are the patients who are most likely to lapse in their aftercare. (Surgeon 9)

The confluence of undergoing vaginoplasty and leaving home to become a college student in the same year was seen by many as problematic:

> Oftentimes, a child in the United States comes in after or during their senior year in high school; they want surgery over the summer and they want to go off to a dormitory in September, in their first year of college, which is a disaster. And that is a more important situation than just the age of the patient. What is going on socially with the patient is more important than the age. (Surgeon 16)

> I have found that it is very difficult when the patients have to transition once they are in college. … Plus with their busy schedules and their busy lifestyles, it is very difficult for them to adhere to their dilation schedule. So the reason why I decided to operate on people younger than 18, is that I would prefer that they have their gender reassignment surgery done while they are still at home and their parents can help them adhere to their schedule until a significant period of time has passed so they will not compromise their results. I base it on very strong family support, very strong letters from their psychologist and their behavioral health therapist and that is really how I make the decision. You also need to take into account the maturity of the individual and whether they are at a point where they are mature enough to understand the seriousness of the surgery and the seriousness of adhering to all of the post-op instructions so that they maximize their results. (Surgeon 15)

Some surgeons viewed timing the procedure before college attendance as a harm reduction measure:

> Younger patients who have the support of their families, support of their parents, and can have the operation while they are still at home, as opposed to being alone at school or at work, anecdotally tend to do much better than someone who is alone and doesn't have appropriate support. (Surgeon 5)

> There could be benefits that could outweigh the risks when you look at the demographics of women who are in their late teens wanting to have GCS prior to going to college, or prior to entering into very sensitive social roles. (Surgeon 17)

Participants also pointed to the importance of a safe and affirmative environment in which to recuperate (ie, being cared for by supportive parents at home who monitor the recovery process):

> The added issue with the under 18 patient is parental involvement, and I personally would want to have the parents on board. Particularly if the child is still living at home with the parents. The place people go back to after surgery is critically important for the result. And that's not just for GCS—if someone is going back to a hostile place and the place is not supportive of the surgery, it is often likely that the person has a less than optimal result. (Surgeon 18)

Opinions were sometimes divided as to the adolescent undergoing the procedure for mainly social or sexual purposes:

> The benefit is not because they want to have sex, but because they can fully socially transition with their peers before they go off to college—assuming they want to go to college. (Surgeon 14)

> I personally know of two young women who are trying to transition. They are seeing mental health providers and endocrinologists. They are 16 and there is a real struggle there because there is a sense of urgency on their part and they are being held back. I get that, they need to go through some steps. But I know that they do not want to do a full transition later in their life; they want to do this so that they can be intimate in college. (Surgeon 17)

In addition, a few participants urged caution, suggesting that some adolescents engage in gender exploration as part of a developmental phase and as part of the current zeitgeist:

> I think it goes along the lines of a young person's mind still being in the developmental stage. Things may happen and they may reorient their thinking, not just whether they are trans or not, but they may reorient their thinking about which surgery will serve their transgender needs. It is not a binary or tertiary model where they are just gay, straight, bisexual, or trans; there are a whole host of colors in-between. Many trans patients do not want GCS—it could be that at 15 they do, and at 25 they do not. (Surgeon 18)

> Depending on how old they are, there are a lot of classes that adolescents, even preadolescents in elementary schools, are getting these days. And they are trying to figure out if they are doing it because it is a new norm, versus what they really want. I have seen some of my patients' children go through phases of in and out, of thinking transgender. So that would be my concern—is it because it is popular now? (Surgeon 19)

Consent and Risk Management

While participants had a clear understanding of the legal constraints in obtaining informed consent specifically from the adolescent, there were a few different approaches to securing consent from the family unit. Parents or legal guardians were invariably signators; however, Surgeon 2 also added the requirement of the young patient writing an essay about the reasons for wanting to undergo the procedure and "describe what her feelings are in her identity as a person." Surgeon 16 explicitly required the parents to become active participants in the post-operative dilatation process, or else the patient would not be deemed "a good candidate for surgery." Other participants requested multiple or longer office visits when going over the various written consent forms, ranging from 5 to 40 pages, and always in the presence of parents or legal guardians. The parents' marital status was often a concern, because most surgeons were aware of divorce creating a change in guardianship or custody of the minor. Comparatively few participants addressed the issue of postsurgical infertility in the interviews; among those who reported having discussions with the patient and her family, there was the recognition that the topic had been explored beforehand with other practitioners or "not often something that is at the forefront of people" (Surgeon 4).

All participants adhered strictly to the SOC by requiring separate evaluation letters from two mental health professionals clearing the minor for surgery. Many emphasized that a recommendation from an unfamiliar psychotherapist was not acceptable; in addition, a third letter from an independent psychiatrist or the patient's pediatric endocrinologist was occasionally required to bolster the surgeon's confidence that the minor had been thoroughly vetted. The professional quality of each letter also was very important and should demonstrate the writer's qualifications as an expert in transgender issues. Surgeon 12 clarified:

> We ask for two letters. One of them has to be from someone who has an established relationship with the patient. I don't remember exactly what the wording is, but they can't just go to one session and say, "Hey, I'm transgender, I want surgery." We do read the letters and we also do confirm that the letters are real. You can imagine (laughs). We call the therapist's office and make sure that our patient is a patient of theirs. We just get confirmation that the letters are real and that it's not something they just typed up on their own, you know. The letter has a certain verbiage and anybody who is experienced with treating gender issues should know the language of the final letter of recommendation. Not just, "there were three monthly sessions." No!

Nearly all participants reported an overwhelming reliance on mental health practitioners to assess the minor's psychological readiness for surgery. Statements including "completely" (Surgeon 9) or "extremely" (Surgeon 10) were used to emphasize

trust in the diagnostic expertise of mental health providers. Surgeon 3 concurred:

> I rely on them entirely. I need to make sure that the patients have realistic expectations, that they are not … I need to judge their maturity level and that they can handle pretty significant stress of any surgical procedure. But I don't pretend to be a psychologist or have any expertise in the diagnosis of gender dysphoria, that's a decision that needs experts.

However, a few pointed out that they were sometimes just as attuned to potential concerns as mental health professionals and would assume some responsibility for evaluating the patient's psychological condition:

> I scrutinize the letters that the mental health providers forward to me. If they are negative, I rely a lot on them because that has a lot of value. But since they are almost never negative, I may rely a lot less on them! Then I rely on my own experience. I cover everything that I believe should have been covered in the letter, and then I go through that list of capacity, development, all those issues in my check-off list. I do this because any other way is a disservice to the patient; I'm responsible for all that. (Surgeon 20)

Despite the legal impossibility to obtain informed consent from the underage patient, the vast majority of participants were not concerned with malpractice lawsuits from parents or even from the patients as adults in the future. Engaging in best practices, maintaining open communication with the patient and her parents, and above all providing good results were seen as protective measures against any legal action. Nevertheless, opinions were evenly split as to the surgeon's assumption of physical risk to the adolescent patient. Some asserted that this was uniquely the surgeon's domain:

> It should be the surgeon, not the hormone prescriber. There is a lot of misinformation that the hormone prescribers give, in my opinion. They have no business talking about surgical issues, unless they have training. We could train the hormone providers, but too often they have never set foot in an operating room, and say things from a surgical standpoint that in my opinion simply is not true. And I don't think that the hormone providers understand that when there is a micropenis, it's a different surgery. When you all you have is a hammer, everything looks like a nail! (Surgeon 16)

Others advocated for a dispersion of responsibility:

> I think it should be everybody. And I think it should be me, the endocrinologist, the mental health provider. It has to be multidisciplinary to make sure they are sexually mature in terms of development, and that from an endocrine standpoint they are able to be on the hormones successfully and manage them appropriately. One of the concerns for me would be if they haven't been on the hormones long enough or they haven't had adequate endocrine care—how will that change the tissue postoperatively? I know it's a concern for top surgery and it would also be for bottom surgery. It has to be both. (Surgeon 17)

Training, Professionalism, and the WPATH SOC

When asked about the lack of published data on surgery in minors, most participants asserted that GCS in all age groups had been a very small part of surgical medicine until very recently and that data on large volumes of procedures were not yet available. Some also cited the perceived "taboo" or outright stigma in performing the surgery and therefore a certain reluctance to share results or specific techniques. One surgeon pointed to the closure of US-based academic gender services programs in the 1970s, resulting in fewer publications, no tracking data, and privatization of the procedure. But while, none of the participants reported currently tracking patients, a multidisciplinary team approach with elaborate data collection was unanimously favored by those who practiced in academic settings. A vision of close collaboration with non-surgical professionals also emerged among the private practitioners, particularly when there were added concerns of operating on pediatric patients:

> My thought is that with patients like this, there should be a group formed. It should have regularly scheduled meetings. The meetings should include a surgeon, mental health professionals, and endocrinologist and/or interested parties and they should all sit at the same table to specifically assess the patient's case. So someone comes into the TG clinic and they are age 11. By the time they are 14 or 15, they may have had multiple discussions about this, they've been tracked for three or four years, there is a history there and the question becomes much clearer than someone just showing up at your office with two letters. In younger patients, it's much more important to be tracked for a few years and to not just get a snapshot of what they are at any given point in time on the temporal graph. (Surgeon 18)

A few participants described attempts to contribute their surgical expertise to the creation of post-residency programs or accredited GCS fellowships in various academic settings. For those in private practice, the complexity in shaping a transgender surgical excellence center appeared daunting and the difficulties and frustrations in coordinating private practice with teaching responsibilities were echoed by several solo practitioners. Anger and resentment at the perceived lack of established training centers in teaching hospitals sometimes spilled over in complaints that indicated a polarization of long-term practitioners against newcomers to the field who were seen as motivated by profit, often at the expense of the transgender population:

> I believe that anyone who is performing vulvoplasty should have a fellowship training that is at least one year. It is going to be a rough period figuring that out, but I think we will get there eventually. I have seen horrific unethical practices by surgeons who lie about their experience and horrific results surgically as a result of that. We are using transgender people as guinea pigs and the medical profession allows this to happen. WPATH has the ability to have some teeth and regulate this more. But we don't. And while there is a concern that there are not enough surgeons and there is a 41% suicide attempt rate thrown around a lot, I don't feel that there is any emergency regarding the provision of substandard care. There have been no major changes in surgery since the 1970s or 1980s. And there has been plenty of time to establish a fellowship. And now all of a sudden because it's in the media, and really, the biggest reason for why everyone is doing it now, is the money is flowing. Because now insurance is paying. And now all these institutions have to have a program yesterday. And they are not doing it correctly, in my opinion. Seeing a week's worth of surgery—maybe for a mastectomy, or maybe for an orchiectomy, or some of these other surgeries that are closely related, but this surgery is very advanced. The complications have severe consequences on patients' lives and you can't learn it in a week. And that is what's happening; someone is going to see someone with a reputable name; they learn for a week, and they start doing them. And that is completely unethical! (Surgeon 14)

The term *Wild West* also was used by a few highly experienced surgeons who were alarmed at the absence of surgical standards and the ease of entering the subspecialty without any documented training. To remedy the potential influx of "a bunch of solo practitioners, basically cowboys or cowgirls who kind of build their little house, advertise, and suck people in" (surgeon 13), several participants called on the WPATH to assume a larger role in demanding more stringent professional requirements and contribute toward sponsoring fellowships and surgical trainings across the country. However, despite the desire for the WPATH to create mechanisms for data tracking and providing greater oversight, a plurality of participants perceived the SOC as purposely "vague" and more as "inherently flexible guidelines" when the question of lowering or keeping the minimum age requirement was brought to the forefront. In fact, approximately one third of participants agreed that the SOC were appropriate in maintaining 18 years as the minimum age criterion for vaginoplasty; the remaining surgeons favored a case-by-case approach or endorsed a shift toward accepting patients younger than 18, although none were certain when any such changes would officially occur. Surgeon 17, a urologist, encapsulated the major points of concern:

> I believe in time they will probably lower it. But I don't know if it should be a number or a developmental stage. Physiologically, it would make more sense if it were a multi-disciplinary guideline in terms of sexual maturity and emotional maturity. The problem is that it is up to interpretation, and that's where the dangers lie. But it's needed. Just because someone has reached the age of 18 doesn't mean that they are a better candidate than someone who is 16. That's the complexity and the difficulty in having a stringent age number guideline. I think it will change in time. My experience of these women is that no one just wakes up and says, "oh yeah, I think I'm a woman" at 17. This is a lifelong realization and a process of transition that's gradual. And I think that they need to consider care for the younger female patient. Mostly just because of the social implications, her happiness and her mental health—and let's not forget about the intimacy and the sexual health. To me, it would make sense to lower it and assess each patient individually. I don't know if it can be a number. To me, there might be a minimum age but I don't know what that should be. I will see a 16- or 17-year-old that I will agree to do surgery on, and then there could be another one I won't agree to, based on sexual and physical maturity.

DISCUSSION

The present study of 20 US-based, WPATH-affiliated surgeons provides novel information on how surgeons interpret the current SOC and thus shape their subjective criteria when deciding to perform vaginoplasty on female transgender minors and their overall attitudes toward best surgical practices in transgender medicine. The vast majority of surgeons agreed on a variety of methodologic and treatment issues, including patient selection and surgical techniques. In particular, plastic surgeons were biased toward penile inversion augmented by scrotal grafts, sometimes adding flank grafts, tissue expanders, or donor matrix tissue,[27–29] and decisively rejecting intestinal vaginoplasty that would require no such additional measures and eliminate the need for lifelong dilatation. However, although diversion colitis, excess mucus, or malodor were cited by the American surgeons as negative sequelae, a meta-review of 21 studies using data on cisgender women with vaginal agenesis and transgender women reported no occurrence of diversion colitis; in addition, odor occurrence in the ileal neovagina was not observed and transient excessive discharge decreased to acceptable levels within 6 months in sigmoid-derived and ileal vaginoplasty.[30] Bowel vaginoplasty in transgender women is performed to a greater extent in Europe, where genitourinary surgery maintains a presence in public health-funded transgender care and acceptable patient satisfaction rates have been documented on a relatively consistent basis, most recently in a sample of postadolescent transgender women.[31,32] The authors surmise that as rates of GCS in adolescent minors treated with gonadal steroids begin to increase, colon vaginoplasty in the

United States could become a more commonly available alternative to penile inversion, particularly as more urologic surgeons obtain training in the procedure and additional outcome studies are published in the future.

Among nearly all surgeons, the term *maturity* rather than specific chronological age defined the desired mental readiness criterion for undergoing vaginoplasty and participating in crucial postsurgical dilatation. Oberman[33] remarked that "maturity operates as a code word, invoked to permit minors access to treatments that society deems desirable, and to limit their access to treatments that carry the possibility of long-term negative consequences" [p. 127]. If the dedication to consistent dilatation represented a positive marker of mental maturity to the participants, the most significant psychological detractor was not being underage; rather, it was the looming problem of turning 18 and leaving home for college, becoming distracted by new experiences, and losing parental supervision of the long-term aftercare necessary for a final successful outcome. In fact, the penultimate senior high school year was considered the most ideal to undergo surgery, largely seen as a measure of harm reduction by the surgeons who had performed vaginoplasty on minors. Decreasing harm as a justification for transgender adolescent treatment has been previously acknowledged among different practitioners, with the vast majority endorsing earlier medical intervention to prevent psychological suffering and potentially more invasive treatments in later adulthood.[1,34,35] Moreover, the American College of Obstetricians and Gynecologists issued a position paper noting that cisgender female teenagers seeking corrective plastic surgery procedures in the United States were motivated by a desire to "fit in" rather than stand out.[36] This is in sharp contrast to a recent Dutch qualitative study of gender dysphoric adolescents who unexpectedly found it difficult to define an appropriate minimum age concerning the initiation of gonadotropin-releasing hormone analogues.[16] The surgeons in the present sample might be pursuing a conventional harm-decreasing strategy in balancing the putative suffering of the adolescent with the necessary elements of maturity and universally developmental milestones to secure a good surgical outcome.

Participants were almost in lockstep reliance on mental health professionals to provide two separate, detailed patient recommendation letters for surgery in accordance with the WPATH SOC. The surgeons had a clear understanding that the burden of differentiating between gender-variant children who grow up to request gender transition and those who retain their assigned gender identity falls first and foremost on behavioral clinicians, although a few participants were willing to share the ultimate responsibility for assessing the minor's mental readiness. Milrod[35] described "a genuine expression of fear among clinicians in making the wrong diagnosis, based on the fact that young people often experiment with gender role behavior as a consequence of normative identity development, and perhaps more so when the adolescent is gender variant" [p. 341]. Any such trepidation was not present among the participants who mostly denied concerns about lawsuits or fears of postsurgical regret among their adolescent patients. It appears that the preference for a team approach and dispersion of responsibility among several professionals were expressed partly as added safeguards before preoperative consultations, among them the discussion of fertility preservation. From an ethics perspective this presents a dilemma, because surgical castration is often the last link in a chain of transitioning related medical interventions. Even if the surgeon deems the teenager to be mature and expressing a definite intent to undergo the procedure, there simply might not be sufficient recognition of its finality. Recommendations in this area are to create a fertility preservation team in which the surgeon's and hormone prescriber's roles overlap when communicating facts, and that obtaining assent from the minor should be viewed as a continuing process rather than a singular event.[37-39]

Two areas of considerable divergence, if not contention, were training and professionalism in the field. Long-time private practitioners pitted their expertise against more newly practicing surgeons who allegedly operate without sufficient training and are motivated by insurance payments plus a rapidly increasing patient flow. Hafferty and Light[40] normalized these professional skirmishes as "turf battles," indicative of an emerging area of medicine in which the "exclusive right" to perform certain procedures gradually erodes as provider organizations and hospitals begin to establish their own centers dedicated to comprehensive care for a specific population. Insurance companies also have begun to create their own standards, presumably to control costs, and have become the new gatekeepers, particularly vis-à-vis lower- and middle-income patients who benefit from procedures performed by surgeons employed in public and non-profit health care settings.[41] In addition, plastic surgery residents from more than 20 accredited plastic surgery programs across North America recently expressed a critical need for more education related to transgender surgery[42]; whether nascent fellowships and residency programs will devote a portion of their instruction to vaginoplasty in minors will probably depend on any changes to the minimum age requirement in future versions of the WPATH SOC.

Participants espoused conflicting opinions of the WPATH. On one hand, there were complaints that the organization lacked interest in promoting surgical standards or deeper engagement in sponsoring educational activities or fellowships; on the other, there was often a neutral stance toward the current age requirement and favoring the SOC as sufficiently vague, thereby not interfering with the surgeon's selection of the appropriate surgical candidate. Paradoxical attitudes to the WPATH and its standards are not unique to this particular group of affiliated members; a study including 36 psychologists, psychiatrists, and endocrinologists in 10 countries showed that the WPATH SOC were considered "too liberal and too conservative."[43] The WPATH has recently taken

action in a number of educational areas, primarily in its Global Education Initiative, to provide certification of mental health professionals and to offer surgical courses encompassing didactic sessions and cadaver laboratories.[24] As the field matures, it is certain that the WPATH will play a more prominent role in contributing to, if not setting, the surgical standards, particularly for genital surgeries in adolescents. The current absence of directives does not appear to stop vaginoplasties in female-affirmed minors; in fact, the rate of such procedures will likely continue to increase as surgeons refine their techniques and expand their patient population in tandem with earlier social transition and gonadal treatment of gender dysphoric adolescents in the United States.

LIMITATIONS

There are several limitations to the study. Despite attempts to include every surgeon performing transgender vaginoplasty in the United States, it was not always possible to locate surgeons who were not listed in the WPATH directory or on proprietary websites. The limited sample might not be representative of the surgical cadre at large, particularly when exploring experiences and attitudes toward vaginoplasty in minors. A larger participant pool representing WPATH-affiliated surgeons outside the United States would improve the generalizability of the study. An international surgeon study also would address the cultural differences between the United States and other regions, in which adolescent life transitions such as college attendance might be negotiated differently and potentially influence the results. The authors also are aware of age, gender, and generational cohort of participants potentially influencing the responses; for this study, however, these variables were not the focus and therefore are not presented in the results. Another consideration is the collegial relationship between the study authors and some of the participants; the surgeons might not have been entirely forthcoming in their responses because of impression management or concerns of losing anonymity in a professional community limited to a few hundred members. Future studies dealing with genital surgery in minors would benefit from the added participation of gender professionals from other disciplines in a more inclusive approach.

CONCLUSIONS

The available research literature contains no data on vaginoplasty in transgender minors. The findings of this study represent the experiences and attitudes of surgeons who until now have declined open discussion and disclosure of results that could further advance surgical treatment in transgender adolescents. The abundant data elicited from the interviews address several meaningful research questions, most importantly patient selection criteria, surgical methods, and issues critical to the future of the profession. Taken together, the study and its findings make a significant contribution to the planned revision of the WPATH SOC.

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LETTER TO THE EDITOR

Suicide by Clinic-Referred Transgender Adolescents in the United Kingdom

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Introduction

Surveys show that adolescents who identify as transgender are vulnerable to suicidal thoughts and self-harming behaviors (dickey & Budge, 2020; Hatchel et al., 2021; Mann et al., 2019). Little is known about death by suicide. This Letter presents data from the Gender Identity Development Service (GIDS), the publicly funded clinic for children and adolescents aged under 18 from England, Wales, and Northern Ireland. From 2010 to 2020, four patients were known or suspected to have died by suicide, out of about 15,000 patients (including those on the waiting list). To calculate the annual suicide rate, the total number of years spent by patients under the clinic's care is estimated at about 30,000. This yields an annual suicide rate of 13 per 100,000 (95% confidence interval: 4–34). Compared to the United Kingdom population of similar age and sexual composition, the suicide rate for patients at the GIDS was 5.5 times higher. The proportion of patients dying by suicide was far lower than in the only pediatric gender clinic which has published data, in Belgium (Van Cauwenberg et al., 2021).

Suicidality in Transgender Adolescents

"About half of young trans people…attempt suicide," declared the United Kingdom Parliament's Women and Equalities Committee (2015). Similar figures are cited by news media and campaigning organizations. The *Guardian* reported Stonewall's statistic that "almost half" of transgender young people "have attempted to kill themselves" (Weale, 2017). "Fifty percent of transgender youth attempt suicide before they are at age 21" stated the mother of the most famous transgender youth in the English-speaking world (Jennings & Jennings, 2016). As a transgender theologian has observed, "the statistic about suicide attempts has, in essence, developed a life of its own" (Tanis, 2016).

Representative surveys of students in high schools provide one source of evidence for this statistic. In New Zealand, 20% of transgender students reported attempting suicide in the past 12 months, compared to 4% of all students (Clark et al., 2014). In the United States, 15% of transgender students reported a suicide attempt requiring medical treatment in the last 12 months, compared to 3% of all students (Centers for Disease Control & Prevention, 2018; Jackman et al., 2021; Johns et al., 2019). In another American survey, 41% of transgender students reported having attempted suicide during their lifetime, compared to 14% of all students (Toomey et al., 2018).

To what extent are self-reported suicide attempts reflected in fatalities? The connection is not straightforward. Respondents who report suicide attempts are not necessarily indicating an intent to die. One survey of the American population found that almost half the respondents who reported attempting suicide subsequently stated that their action was a cry for help and not intended to be fatal (Nock & Kessler, 2006). In two small samples of non-heterosexual youth, half the respondents who initially reported attempting suicide subsequently clarified that they went no further than imagining or planning it; for the remainder who did actually attempt suicide, their actions were usually not life-threatening. To an extent, then, "the reports were attempts to communicate the hardships of lives or to identify with a gay community" (Savin-Williams, 2001). Although such elaborate survey methods have not been used to study transgender populations, there is anecdotal evidence for a similar disjuncture. The pediatric endocrinologist who established the first clinic for transgender children in the United States stated that "the majority of self-harmful actions that I see in my clinic are not real suicide attempts and are not usually life threatening" (Spack, 2009).

Suicide mortality has been studied in the transgender population using registry data. The annual suicide rate is calculated by dividing the number of suicides by the total number of years each person was at risk. An individual who was observed for 20 years, for instance, contributes 20 person-years to the denominator. The

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largest study covers over 8,000 patients who visited the gender clinic in Amsterdam from 1972 to 2017 (Wiepjes et al., 2020). The annual suicide rate was 29 per 100,000 for transmen, quadruple the rate for the female population, and 64 for transwomen, quadruple the rate for the male population. A Swedish study of 324 individuals who had undergone genital surgery between 1973 and 2003 found much higher annual suicide rates: 250 per 100,000 for transmen, 43 times the rate for matched female controls, and 285 for transwomen, 16 times the rate for matched male controls (M. Boman, personal communication, 12 April 2021; Dhejne et al., 2011). Only one published study has reported suicide fatalities among transgender adolescents. Belgium's pediatric gender clinic provided counseling to 177 youth aged from 12 to 18 years, who had been referred between 2007 and 2016: five of them (2.8%) committed suicide (Van Cauwenberg et al., 2021). The mean age of referral was 15, implying a mean duration of 3 years before transition to an adult clinic, which translates to an annual suicide rate of 942 per 100,000. This is the highest suicide mortality recorded for any transgender population.

Method

This Letter estimates the suicide rate at the world's largest pediatric gender clinic. Based in London, the GIDS is part of the Tavistock and Portman NHS Foundation Trust, and serves youth under 18 from England, Wales, and Northern Ireland who are "experiencing difficulties with their gender identity development" (Carmichael & Davidson, 2009). Like all such services throughout Western Europe and North America, it has experienced enormous growth; referrals increased from 100 in 2009 to a peak of 2700 in 2019. The waiting list in April 2021 exceeded 5300.

The GIDS patients manifest typically high rates of self-harming behavior. In a sample of 900 adolescents (aged from 13 to 17) admitted to the clinic from 2009 to 2017 and given the Youth Self-Report questionnaire, 44% answered that they sometimes or very often "deliberately try to hurt or kill myself" (de Graaf et al., 2020). Unfortunately, both behaviors are combined in this question. In a different sample of over 700 children and adolescents (aged from 4 to 17) assessed by the GIDS in 2012 and 2015, 10% were flagged by clinicians as having attempted suicide (Morandini et al., 2021).

Suicides

Since the early 2000s, the National Health Service has implemented mandatory reporting of "serious incidents" (Department of Health, 2001, 2010). The death of any patient—including those on the waiting list—suspected to be suicide is reported to the Tavistock's Board of Directors. The Tavistock cooperates with a comprehensive surveillance system for every death classified as suicide or (after an open verdict by the coroner) probable suicide in the United Kingdom (National Confidential Inquiry into Suicide & Homicide by People with Mental Illness, 1999; National Confidential Inquiry into Suicide and Safety in Mental Health, 2019). Papers for the Tavistock's Board meetings are available from April 2007 onwards; those not on the Trust's website were acquired by a Freedom of Information request. The pdf files of the *Agenda and Papers* (through September 2021) were searched for the keyword "suicid"; all 442 instances were inspected. From 2007 to 2020, four patients of the GIDS died by suspected suicide: two on the waiting list, in 2016 and 2017; and two after having been seen, in 2017 and 2020. The last case was described as "likely" to be suicide, because the inquest has not yet been held. These figures were confirmed by Freedom of Information requests to the Tavistock.

Triangulation is possible from two sources. Comprehensive mortality data on all adolescents aged from 10 to 19 who committed suicide in the United Kingdom from 2014 to 2016 include five transgender individuals (Rodway et al., 2020). Due to confidentiality restrictions, it is not possible to disaggregate these further by age or by country. Presumably, one of these is the patient of GIDS who died in 2016. The remaining four might have been 18 or 19—the risk of suicide increases significantly in the late teens—or might have lived in Scotland. Alternatively, they might have been eligible for the GIDS but had not sought a clinical referral (made by the local Child and Adolescent Mental Health Service, the child's general practitioner, social worker, or teacher) or had not obtained it.

Another source is the Transgender Day of Remembrance website, which aims to record all deaths by suicide or violence (Metcalfe, 2021). For the United Kingdom between 2007 and 2020, the website names 3 adolescents under the age of 18 who committed suicide. One was one of the GIDS patients (the match is certain because they were named in the *Agenda and Papers*). The other two had no involvement with the GIDS (or any other gender clinician), as was evident from their inquests, though one was under the psychiatric care of another NHS Trust (BBC News, 2021; Bunyan, 2008). In addition, the website lists suicides by two "young" transgender people, sourced from Twitter, without information on their name or age. In one case, it is not clear whether the person lived in the United Kingdom.

Patients

With suicides as numerator, two denominators are relevant. Because comprehensive data on patient numbers became available from 2010, the period will be the 11 years from 2010 to 2020. (These are financial years; thus, 2020 runs from April 2020 to March 2021.) The first denominator is the total number of individual patients, estimated by summing the annual number of referrals to the GIDS from 2010 to 2020—excluding those aged 18 or over, as they are not accepted. The total number is 15,032. This sum omits patients at the clinic who had been referred before

2010, and so is a slight underestimate. (The Online Supplement provides full details.)

The second denominator is the total number of patient-years: the sum of the number of years spent by each individual as a patient of the GIDS. The number of patients seen by the GIDS each year was available from 2014 to 2020. Before 2014 only the number of patients first seen was available. From 2014 to 2016, the number of patients seen was consistently double the number first seen, and so the former number for 2010 to 2013 was estimated by doubling the latter. All these numbers exclude patients on the waiting list. The number waiting at the beginning of each year from 2016 to 2020 was obtained by Freedom of Information request. Before then the number was not available, and so must be treated as zero. This leads to an underestimate, of course, but the waiting list became appreciable only from 2015. The total number of patient-years over this period is estimated as 30,080. In other words, patients spent on average 2 years at the GIDS (including time on the waiting list). Time on the waiting list contributed 41% of the total patient-years.

Results

From 2010 to 2020, the four suicide deaths equate to 0.03% of the 15,032 patients. Taking the denominator as 30,080 patient-years, the annual suicide rate is calculated as 13 per 100,000 (95% confidence interval: 4 to 34 per 100,000). For comparison, the annual suicide rate in England and Wales between 2010 and 2020 for adolescents aged from 15 to 19 years averaged 4.7 (Office for National Statistics, 2021). This does not quite correspond to the age range of the GIDS patients, however. At referral, the patients ranged in age from 3 to 17 years; only 7% were younger than 10. The mean was 14 years and the median 15. Most patients stay with the GIDS until transitioning to an adult service. Therefore, the average age of patients at any point in time will lie somewhere between 14 and 17. A better comparison is therefore the overall suicide rate for adolescents aged from 14 to 17 (available only for the entire United Kingdom for 2015–2017), which was 2.7 per 100,000 (Office for National Statistics, 2018; Rodway et al., 2020). Comparison should also account for the difference between the sexes, because males are more likely to commit suicide than females. Of the GIDS patients, 69% were female. Adjusting for sex, the GIDS patients were 5.5 times more likely to commit suicide than the overall population of adolescents aged 14 to 17.

Discussion

How reliable are these estimates? The chief uncertainty about the numerator is whether the fourth death will be ruled as suicide when the inquest is eventually held. It could be speculated that there were further suicides unknown to the Tavistock and to the National Confidential Inquiry into Suicide and Safety in Mental Health. All that can be said is that the single suicide by a GIDS patient from 2014 to 2016 is not out of line with comprehensive mortality data on suicides by transgender adolescents in the United Kingdom which counted five suicides in a longer age range and wider geographical area. The denominator for the annual suicide rate, however, is pieced together from various series and so is inevitably approximate. Statistics from the early 2010s are less reliable, though they make only a small contribution to the grand total; the last three years contribute more than half of the total number of patient-years. The most significant limitation is the lack of information on the age and sex of all the patients who committed suicide.

Direct comparison can be made with the Belgian pediatric gender clinic (Van Cauwenberg et al., 2021). Its annual suicide rate was about 70 times greater than the rate at the GIDS. This is especially puzzling because patients at the Belgian clinic scored better, on average, than those at the GIDS on tests of psychological functioning (de Graaf et al., 2018). The explanation for the huge disparity in suicide is not clear. The Amsterdam's clinic annual suicide rate was four times greater than the rate at the GIDS. The higher rate is not surprising, however, because the Dutch clinical population was dominated by older adults: the median age at first visit was 25 (Wiepjes et al., 2020). Suicide rates peak in middle age, and so a population of older adults would be at higher risk than a population of adolescents.

The suicide rate of the GIDS patients is not necessarily indicative of the rate among all adolescents who identify as transgender. On the one hand, individuals with more serious problems (and their families) would be particularly motivated to seek referral and more likely to obtain it, and so the clinical subset would be more prone to suicide. One study suggests that a child who frequently attempted suicide was more readily referred to the GIDS (Carlile et al., 2021). On the other hand, young people facing hostility from their families would be less able to seek referral, and this hostility could make them especially vulnerable to suicide.

Taking into account these limitations, the estimated suicide rate at the GIDS provides the strongest evidence yet published that transgender adolescents are more likely to commit suicide than the overall adolescent population. The higher risk could have various causes: gender dysphoria, accompanying psychological conditions, and ensuing social disadvantages such as bullying. Studies of young people referred to the GIDS in 2012 and 2015 found a high prevalence of eating disorders, depression, and autism spectrum conditions (ASC) (Holt et al., 2016; Morandini et al., 2021)—all known to increase the probability of suicide (Simon & VonKorff, 1998; Smith et al., 2018). Eating disorders and depression could be consequences of transgender identity and its ensuing social repercussions, but this is implausible for ASC insofar as it originates in genes or the prenatal environment. From a sample of over 700 referrals to the GIDS in 2012 and 2015, 14–15% were diagnosed with ASC (Morandini

et al., 2021). This compared to 0.8–1.1% of students in England (Department for Education, 2012, 2015). The association between autism and gender dysphoria is found in many populations (Socialstyrelsen, 2020; Warrier et al., 2020). Autism is known to increase the risk of suicide mortality, especially in females (Hirvikoski et al., 2016; Kirby et al., 2019; Socialstyrelsen, 2020). To some extent, therefore, the elevated suicide rate for transgender youth compared to their peers reflects the higher incidence of ASC. The same holds for other psychiatric disorders associated with gender dysphoria (Dhejne et al., 2016). Ideally, the suicide rate for patients of the GIDS would be compared to the suicide rate for patients in contact with other NHS mental health services, but the latter rate is not available.

One final caveat is that these data shed no light on the question of whether counseling or endocrinological interventions—gonadotropin-releasing hormone agonist or cross-sex hormones—affect the risk of suicide (Biggs, 2020; Turban et al., 2020). Although two out of the four suicides were of patients on the waiting list, and thus would not have obtained treatment, this is not disproportionate: the waiting list contributed nearly half of the total patient-years.

Conclusion

Data from the world's largest clinic for transgender youth over 11 years yield an estimated annual suicide rate of 13 per 100,000. This rate was 5.5 times greater than the overall suicide rate of adolescents of similar age, adjusting for sex composition. The estimate demonstrates the elevated risk of suicide among adolescents who identify as transgender, albeit without adjusting for accompanying psychological conditions such as autism. The proportion of individual patients who died by suicide was 0.03%, which is orders of magnitude smaller than the proportion of transgender adolescents who report attempting suicide when surveyed. The fact that deaths were so rare should provide some reassurance to transgender youth and their families, though of course this does not detract from the distress caused by self-harming behaviors that are non-fatal. It is irresponsible to exaggerate the prevalence of suicide. Aside from anything else, this trope might exacerbate the vulnerability of transgender adolescents. As the former lead psychologist at the Tavistock has warned, "when inaccurate data and alarmist opinion are conveyed very authoritatively to families we have to wonder what the impact would be on children's understanding of the kind of person they are…and their likely fate" (Wren, 2015).

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Declarations

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Clinical Research Article

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Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones

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Abbreviations: 1CTP, carboxyterminal cross-linked telopeptide of type I collagen; aBMD, areal bone mineral density; ANOVA, analysis of variance; BMAD, bone mineral apparent density; BMD, bone mineral density; CV, coefficient of variation; DXA, dual-energy x-ray absorptiometry; GnRH, gonadotropin-releasing hormone; GnRHa, gonadotropin-releasing hormone analogue; P1NP, N-terminal propeptide of type-1 collagen; PBM, peak bone mass.

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Abstract

Context: Hormonal interventions in adolescents with gender dysphoria may have adverse effects, such as reduced bone mineral accrual.

Objective: To describe bone mass development in adolescents with gender dysphoria treated with gonadotropin-releasing hormone analogues (GnRHa), subsequently combined with gender-affirming hormones.

Design: Observational prospective study.

Subjects: 51 transgirls and 70 transboys receiving GnRHa and 36 transgirls and 42 transboys receiving GnRHa and gender-affirming hormones, subdivided into early- and late-pubertal groups.

Main Outcome Measures: Bone mineral apparent density (BMAD), age- and sex-specific BMAD z-scores, and serum bone markers.

Results: At the start of GnRHa treatment, mean areal bone mineral density (aBMD) and BMAD values were within the normal range in all groups. In transgirls, the mean z-scores were well below the population mean. During 2 years of GnRHa treatment, BMAD stabilized or showed a small decrease, whereas z-scores decreased in all groups. During 3 years of combined administration of GnRHa and gender-affirming hormones, a significant increase of BMAD was found. Z-scores normalized in transboys but remained below zero in transgirls. In transgirls and early pubertal transboys, all bone markers decreased during GnRHa treatment.

Conclusions: BMAD z-scores decreased during GnRHa treatment and increased during gender-affirming hormone treatment. Transboys had normal z-scores at baseline and at the end of the study. However,

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transgirls had relatively low z-scores, both at baseline and after 3 years of estrogen treatment. It is currently unclear whether this results in adverse outcomes, such as increased fracture risk, in transgirls as they grow older.

Key Words: bone mineral density, bone, GnRH analogue, sex steroids, gender dysphoria, transgender, adolescents

Over the last decades, children diagnosed with gender dysphoria have increasingly come to the attention of the psychomedical care system and clinicians recognize their suffering, aggravated by the somatic changes of puberty (1, 2). The development of secondary sex characteristics can be temporarily halted with gonadotropin-releasing hormone analogue (GnRHa) treatment (3). This offers the adolescent the opportunity to explore their wish to pursue gender-affirming treatment, while no longer experiencing the agonizing development of secondary sex characteristics due to endogenous puberty, which are incongruent with gender identity. Birth-assigned girls must be at least in Tanner breast stage 2 with clear palpable mammary tissue, while birth-assigned boys must have reached Tanner stage G2 before initiating treatment with GnRHa (3, 4). If no contraindications exist, sex steroids consistent with the affirmed gender are added to the GnRHa treatment at an age where adolescents can give informed consent to such treatment, usually at approximately 16 years (3). There is much discussion about this age, since 16 years is considered a late age to induce puberty in adolescents.

In young adults, peak bone mass (PBM) is higher in men than in women (5). Sex steroids play an essential role in the establishment of gender differences in bone mass, both through direct effects and indirect effects, for example, via differences in muscle mass and insulin-like growth factor (6). Puberty is an important period in determining adult bone mineral content (6). Together, these findings strengthen the notion that maximizing bone mineral accrual during adolescence may be important in the prevention of osteoporosis and fractures at older age.

One of the primary concerns when using GnRHa in adolescents for a prolonged period of time is the potential decrease in bone mineral density (BMD) (3, 7). The suppression of the endogenous sex steroids to stop pubertal development, as recommended by current guidelines, may potentially interfere with the normal pubertal bone mass increment and reduce PBM. Therefore, assessment of BMD every 1 to 2 years is recommended (3). Three studies in adolescents diagnosed with gender dysphoria receiving GnRHa and gender-affirming hormone treatment reported decreases in areal BMD (aBMD) and bone mineral apparent density (BMAD) z-scores during GnRHa treatment, although not all significant (8-10). Little difference was noted in change of BMAD z-scores between early- and late-pubertal groups as defined by bone age (8). Catch-up of bone mineral accrual during subsequent gender-affirming hormone treatment may be incomplete (8-10). One study investigated bone markers and showed a decrease of carboxyterminal cross-linked telopeptide of type I collagen (1CTP) and N-terminal propeptide of type-1 collagen (P1NP) during GnRHa and during subsequent gender-affirming hormone treatment which was interpreted as evidence of decreased bone turnover (8). All these studies compared data at the start of GnRHa treatment, at the start of gender-affirming hormones and one endpoint, either 12–24 months after the start of gender-affirming hormone therapy or age 22 years. However, this does not provide information on the course of BMD during treatment. Do BMD z-scores continue to decline with prolonged use of GnRHa? How long do BMD z-scores continue to increase during GAH treatment? These questions remain unanswered. Now that increasing numbers of adolescents undergo this treatment, possibly starting at younger ages, there is a clear need for such data. Therefore we set out to describe the course of BMD during 2 years of GnRHa therapy and during 3 years of subsequent gender-affirming hormone treatment in a large group of adolescents diagnosed with gender dysphoria, with measurements at yearly intervals. We also investigated whether the outcome was influenced by the pubertal stage, as defined by Tanner stage, at which GnRHa treatment was started. In addition, we report data from a small subgroup with more prolonged GnRHa treatment.

Methods

Subjects and protocol

Subjects were adolescents fulfilling *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) criteria for gender identity disorder (the term used at the time) (11) and eligible for treatment according to existing guidelines at that time (4, 12, 13). The design of the study was observational and prospective, and individuals were included from 1998 to 2009. The first phase of treatment consisted of intramuscular injections of GnRHa 3.75 mg (Triptorelin-CR (Ferring Pharmaceuticals, Denmark). The first 2 injections were administered with a 2-week interval followed by injections every 4 weeks to suppress endogenous sex steroid production. To induce female pubertal development in

transgirls, oral estrogens were prescribed in an increasing dosage over a period of 2 years as previously described (4). Male puberty in transboys was induced by administering Sustanon (a mixture of testosterone propionate, -fenylpropionate, -isocaproate and -decanoate) intramuscularly in increasing doses over a period of 2 years (14). In subjects who were 16 years of age or older at the start of pubertal suppression, gender-affirming hormones were started at half the adult dose and increased to the adult dose after 6 months. A dose of 2 mg 17beta-estradiol per day and 125 mg testosterone-esters per 2 weeks was considered an adult dose. From 45 subjects, some data were also included in previous studies by Vlot et al (8) and Klink et al (10), but those studies only reported results at 3 time points: at the start of GnRHa, at the start of gender-affirming hormones, and after 2 years of gender-affirming hormones (8) or age 22 years (10), and they did not describe a detailed course of BMD and bone markers over several years of GnRHa or gender-affirming hormone treatment.

Different effects of treatment might be expected depending on the pubertal stage at baseline. A previous study used a bone age cutoff of 14 and 15 years for transboys and transgirls, respectively, to define early- and late-pubertal groups (8). However, especially for transboys, bone age 14 years signifies the final stages of puberty and near completion of linear growth rather than midpuberty. In the current study, Tanner stage was used to define early- and late-pubertal groups, with the early-pubertal group defined as Tanner stage 2 or 3 at the start of GnRHa treatment, and the late-pubertal group as Tanner stage 4 or 5.

Bone densitometry

Dual-energy x-ray absorptiometry (DXA) was performed before GnRHa administration and then every subsequent year using Hologic QDR 4500 (Hololgic Inc., Waltham, MA, USA). Likewise, at the start of gender-affirming hormone treatment, a DXA scan was performed, with yearly measurements thereafter. Areal BMD (aBMD, g/cm^2) of the lumbar spine, nondominant hip, and whole body, as well as the bone mineral content of the whole body (BMC-WB, g) were measured. To calculate z-scores based on age and sex, the National Health and Nutrition Examination Surveys (NHANES) references values were used. Because changes in aBMD might partly be due to altered growth during treatment, we also studied BMAD (g/cm^3) calculated as described by Ward et al (15). BMAD z-scores were calculated using LMS data from an English reference population (15). To calculate z-scores the reference population of the birth-assigned sex was used. For adolescents older than 17 years no reference values of BMAD are available; therefore, reference values of 17 year-olds were used to calculate the z-score at older ages (15).

Serum bone markers

Markers of bone formation (P1NP, P3NP, and osteocalcin) and of bone resorption (1CTP) were determined in fasting blood samples, drawn before noon on the same days as the DXA scans, and stored at –20 °C.

Osteocalcin was measured by an immunometric assay (Colorimetric, BioSource, Nivelles, Belgium) (lower detection limit of 0.4 nmol/L; inter-assay coefficient of variation (CV) for the whole range <10%). Serum 1CTP, P1NP, and P3NP levels were measured using a radioimmunoassay (Orion Diagnostica, Espoo, Finland). The lower ranges of detection were 1 µg/L for 1CTP, 5 µg/L for P1NP, and 1µg/L for P3NP. The inter-assay CV for the whole range of 1CTP was 7% and for P1NP 8%. The CV for P3NP was 6% at 4.2 µg/L and 8% at 6.2 µg/L.

Statistical analyses

Independent *t* tests were used to ascertain differences between the ages of the transgirls and transboys. To analyze changes in BMAD over time, data were analyzed using a linear mixed model. A full factorial model was chosen as fixed part of the model, ie, a model consisting of time (3 or 4 levels), pubertal stage (early/late), and sex and all possible interactions (ie, three 2-way and one 3-way interactions). An unstructured covariance matrix was used as random part of the model. An advantage of the linear mixed model approach above traditional repeated measurements analysis of variance (ANOVA) is that all acquired data are included in the analyses and no data are lost due to incomplete data sets.

Differences in aBMD during a more prolonged period of GnRHa treatment were calculated using the related samples Wilcoxon Signed Ranked test.

All data on BMAD, and z-scores are presented as estimated marginal means and standard error of the mean. The statistical package was SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

Ethical approval

The study was placed on the International Standard Randomized Controlled Trial Number register and ascribed registration number ISRCTN 81574253 (www.isrctn.com). Approval by the local medical ethical committee was obtained. Informed consent for the study was obtained from all adolescents, and if aged <18 years also from their parents.

Results

A total of 54 transgirls and 73 transboys started treatment according to this protocol. For 51 transgirls and 70 transboys, DXA scans were available at the start of GnRHa administration and these individuals were included in the analyses. There were no significant differences between the ages of the transgirls and the transboys at the start of GnRHa administration (Table 1).

A total of 36 transgirls and 42 transboys received gender-affirming hormone treatment in addition to GnRHa treatment. The transboys were slightly but significantly older at start of gender-affirming hormone treatment than the transgirls (Table 1). The ratio of subjects who were in early and in late puberty was not different in the group evaluated for the effects of gender-affirming hormone treatment compared with the group analyzed during GnRHa treatment alone.

Anthropometric data and data on pubertal development of the subjects at baseline are shown in Table 1. All adolescents had sex characteristics typical of the sex assigned at birth and none had signs of a difference/disorder of sex development. None of the adolescents had a bone fracture during the study.

Changes during 2 years of GnRHa treatment

Bone mineral apparent density. Changes in aBMD and aBMD z-scores are shown in Table 2. BMAD of the lumbar spine did not change during 2 years of GnRHa treatment in the transgirls or the early pubertal transboys ($P = 0.84$, $P = 0.09$, and $P = 0.69$, respectively) (see Fig. 1, Table 2). In the late-pubertal transboys, a small but significant decrease in BMAD of the lumbar spine was found.

BMAD of the femoral neck showed a significant decrease in the late-pubertal transgirls and in both groups of transboys ($P = 0.007$, $P = 0.015$, and $P < 0.001$, respectively) (see Fig. 1, Table 2). The small decrease in the early pubertal transgirls was not significant ($P = 0.31$).

Bone mineral apparent density z-scores. At the start, z-scores of the BMAD at both locations were higher in the transboys than in the transgirls. The BMAD z-score of the lumbar spine significantly decreased in all 4 groups ($P \leq 0.001$) (see Fig. 1, Table 2). The BMAD z-scores of the femoral neck significantly decreased in all groups ($P = 0.006$, $P = 0.002$, and $P < 0.001$) except for the early-pubertal transgirls ($P = 0.25$). Four transgirls had a z-score of the hip below −2 after 2 years of GnRHa treatment and 3 individuals had a z-score of the lumbar spine below −2. Two transboys had a z-score of the hip below −2 whereas none of the transboys had a z-score of the lumbar spine below −2 after 2 years of GnRHa treatment.

Bone mineral density during prolonged GnRHa treatment. Because the average age at the start of GnRHa treatment was more than 14 years, most individuals were not treated with GnRHa for more than 2 years

Table 1. Characteristics at the Start of GnRHa Treatment and at the Start of Gender-Affirming Hormone Treatment

Start GnRHa		Transgirls (n = 51)	Transboys (n = 70)	*P* value
	Age in years, mean ± SD	14.1 ± 1.7	14.5 ± 2.0	n.s.
	Pubertal group: Early/late	15/36	14/56	n.s.
	Height in cm, mean ± SD	169.0 ± 8.9	162.2 ± 8.8	<0.001
	Weight in kg, mean ± SD	57.9 ± 12.9	56.2 ± 14.7	n.s.
	BMI in kg/m^2, mean ± SD	20.1 ± 3.3	21.3 ± 4.2	n.s.
	Serum estradiol in pmol/L, median [IQR]		Early: 113.5 [63.5–129.3] Late: 121 [83.5–231.5]	
	Serum testosterone in nmol/L, median [IQR]	Early: 3.8 [2.15–6.15] Late: 13 [10.3–17.8]		
Start gender-affirming hormones		Transgirls (n = 36)	Transboys (n = 42)	
	Age in years, mean ± SD	16.2 ± 1.2	16.9 ± 1.1	0.005
	Pubertal group: Early/late	10/26	5/37	n.s.
	Duration of GnRHa use before start GAH, years	2.0 ± (0.94)	1.8 ± (1.11)	n.s.
	Height in cm, mean ± SD	176.5 ± 7.3	167.1 ± 7.4	0.005
	Weight in kg, mean ± SD	66.7 ± 11.9	63.5 ± 11.5	n.s.
	BMI in kg/m^2, mean ± SD	21.1 ± 3.2	22.8 ± 4.0	n.s.

Abbreviations: BMI, body mass index; GAH, gender-affirming hormones; GnRHa, gonadotropin-releasing hormone analogue; IQR, interquartile range; n.s., not significant; SD, standard deviation.

Table 2. aBMD and BMAD During 2 Years of GnRHa Treatment

	Transgirls					
	Early Pubertal		Late-Pubertal			
	0 mo	24 mo	0 mo	24 mo	*p*1	*p*2
aBMD_LS g/cm^2	0.73 (0.03)	0.75(0.03)	0.79 (0.02)	0.82 (0.02)	<0.05	<0.05
Z-score	−0.67 (0.26)	−1.26 (0.24)	−0.33 (0.17)	−0.92 (0.17)	<0.05	<0.05
aBMD_hip g/cm^2	0.81 (0.03)	0.86 (0.03)	0.87 (0.02)	0.89 (0.02)	<0.05	n.s.
Z-score	−0.49 (0.24)	−0.93 (0.21)	−0.43 (0.16)	−1.01 (0.15)	<0.05	<0.05
Whole body BMD g/cm^2	0.90 (0.02)	0.92 (0.02)	0.95 (0.01)	0.95 (0.01)	<0.05	n.s.
Z-score	−0.56 (0.24)	−1.51 (0.20)	−0.51 (0.16)	−1.62 (0.15)	<0.05	<0.05
BMAD_LS g/cm^3	0.20 (0.01)	0.20 (0.01)	0.20 (0.01)	0.21 (0.0!)	n.s.	n.s.
Z-score	−0.33 (0.33)	−1.19 (0.34)	−0.65 (0.20)	−1.21 (0.22)	<0.05	<0.05
BMAD_hip g/cm^3	0.28 (0.01)	0.27 (0.01)	0.28 (0.01)	0.26 (0.01)	n.s.	<0.05
Z-score	−0.94 (0.27)	−1.23 (0.35)	−1.01 (0.17)	−1.56 (0.25)	n.s.	<0.05
	Transboys					
	Early-pubertal		Late-pubertal			
	0 mo	24 mo	0 mo	24 mo	*p*1	*p*2
aBMD_LS g/cm^2	0.75 (0.03)	0.80 (0.03)	0.95 (0.01)	0.92 (0.01)	<0.05	<0.05
Z-score	−0.28 (0.27)	−1.04 (0.26)	0.38 (0.14)	−0.71 (0.14)	<0.05	<0.05
aBMD_hip g/cm^2	0.79 (0.03)	0.83 (0.03)	0.93 (0.01)	0.89 (0.02)	<0.05	<0.05
Z-score	0.09 (0.26)	−0.50 (0.24)	0.46 (0.13)	−0.56 (0.13)	<0.05	<0.05
Whole body BMD g/cm^2	0.88 (0.02)	0.92 (0.02)	1.03 (0.01)	1.01 (0.01)	<0.05	<0.05
Z-score	−0.28 (0.27)	−0.82 (0.24)	0.66 (0.13)	−0.40 (0.13)	<0.05	<0.05
BMAD_LS g/cm^3	0.22 (0.01)	0.22 (0.01)	0.25 (0.01)	0.24(0.01)	n.s.	<0.05
Z-score	−0.15 (0.29)	−0.86 (0.30)	0.33 (0.14)	−0.56 (0.17)	<0.05	<0.05
BMAD_hip g/cm^3	0.30 (0.01)	0.28 (0.01)	0.32 (0.01)	0.30 (0.01)	<0.05	<0.05
Z-score	−0.23 (0.25)	−0.94 (0.30)	0.04 (0.12)	−0.54 (0.18)	<0.05	<0.05

aBMD and BMAD during 2 years of GnRHa treatment. Values are presented as estimated marginal means ± standard error. *p1* represents the *P* value between the start and after 2 years of treatment for the early pubertal groups. *p2* represents the *P* value between start and after 2 years of treatment for the late-pubertal groups. For changes per year of treatment see Fig. 1.

Abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMD, bone mineral density; LS, lumbar spine.

before gender-affirming hormone treatment was started. However, a few younger individuals were treated for up to 4 years. The aBMD values of the lumbar spine and hip in 4 transboys and 11 transgirls remained stable during 3 years of GnRHa treatment. The z-scores on the other hand declined (Table 3).

Serum bone markers. At baseline, there were no significant differences in serum levels of any of the 4 bone markers (P1NP, P3NP, osteocalcin, 1CTP) between the early- and late-pubertal groups of transgirls (Fig. 2). In the transboys, baseline serum levels of all 4 bone markers were significantly higher in those in early puberty compared to those in later puberty.

After 2 years of GnRHa treatment serum levels of all 4 bone markers showed a significant decrease in both groups of transgirls and in early-pubertal transboys, which was most marked during the first year of treatment (Fig. 2). Serum levels of P3NP and 1CTP showed a smaller but significant decrease in late-pubertal transboys whereas serum levels of P1NP and osteocalcin did not change in this group.

Changes during 3 years of gender-affirming hormone treatment

After an average of 1.89 years (± 1.03 year) of GnRHa administration, gender-affirming hormones were added to the treatment. Both early-pubertal groups were on GnRHa for a significantly longer time (2.5 years in transgirls (n = 7) and 4.0 years in transboys (n = 3)) when compared with both late-pubertal groups (1.5 years in transgirls and 1.7 years in transboys) ($P < 0.001$).

Bone mineral apparent density. Changes in aBMD and aBMD z-scores are shown in Table 4. A significant increase in BMAD of the lumbar spine was found in all 4 groups

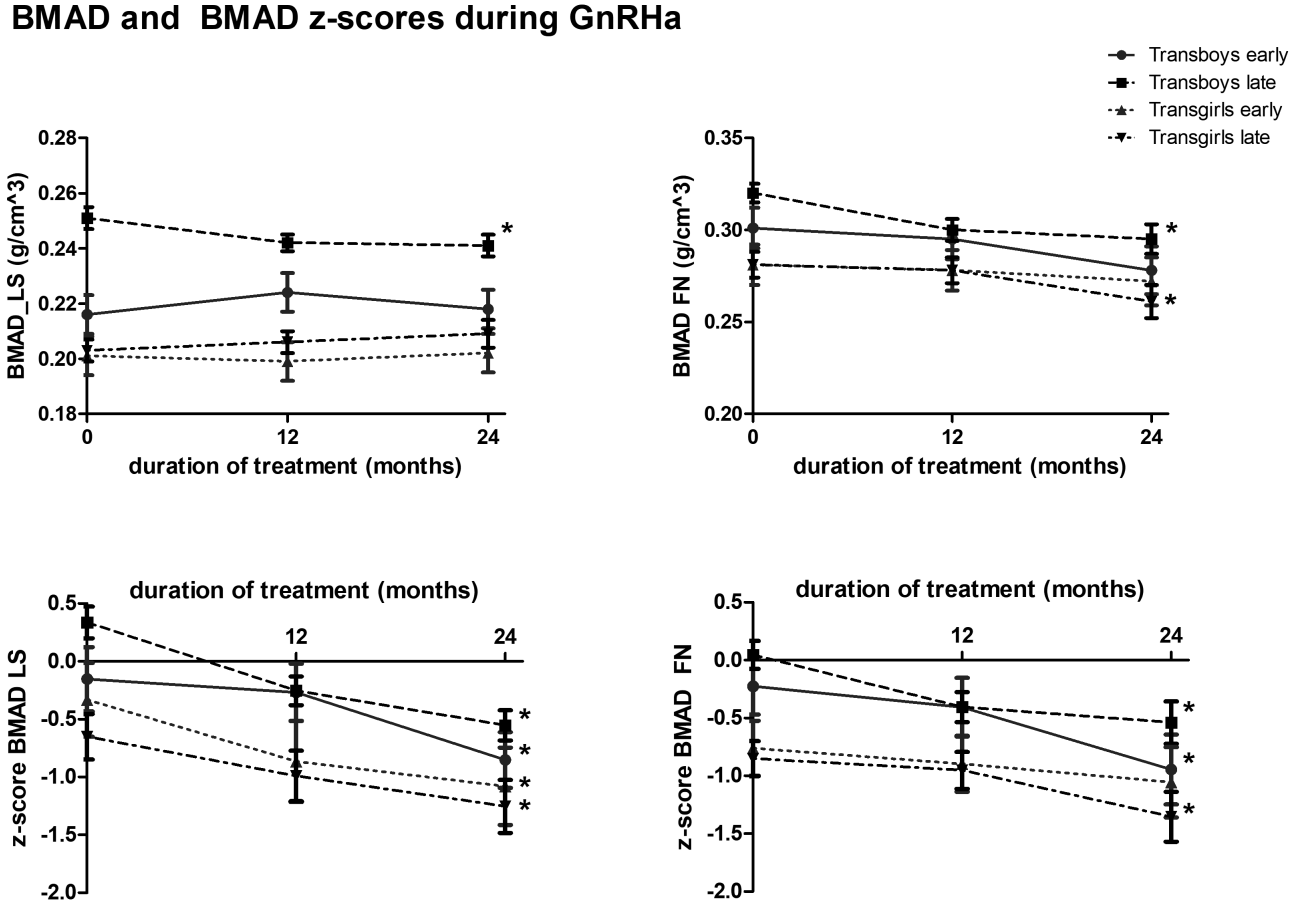

Figure 1. Estimated marginal means and standard error of the mean of BMAD prior to and during 2 years of GnRHa administration in transgirls and transboys. Significant changes during the 2 years of GnRHa administration are indicated by an asterisk. Abbreviations: BMAD: bone mineral apparent density; FM, femoral neck; LS, lumbar spine.

($P < 0.001$) after 3 years of gender-affirming hormone treatment (Fig. 3, Table 4). The BMAD of the femoral neck showed a significant increase in both groups of transgirls and in the early-pubertal transboys ($P < 0.05$). In the late-pubertal transboys the increase was not significant.

Bone mineral apparent density z-scores. The BMAD z-scores of the lumbar spine significantly increased in all 4 groups (Fig. 3, Table 4). Z-scores of the femoral neck showed a significant increase in both groups of transgirls and in the early pubertal transboys. The increase of the z-score in late-pubertal transboys was not significant.

Three transgirls had a z-score of the femoral neck below –2 and 3 individuals had a z-score of the lumbar spine below –2 after 3 years of gender-affirming hormone treatment. None of the transboys had a z-score below –2 after 3 years of gender-affirming hormone treatment.

Serum bone markers. The mean serum levels of the bone markers prior to gender-affirming hormone administration are shown in Fig. 4. Serum levels of P1NP, P3NP, and 1CTP were significantly higher in the early pubertal transgirls than in the late-pubertal transgirls. In the transboys, baseline serum levels of P1NP and P3NP were significantly higher in the early pubertal group compared with the late-pubertal group. Levels of all 4 markers changed little in the late-pubertal transboys, whereas in the early pubertal transboys and late-pubertal transgirls, osteocalcin, P1NP, and P3NP showed a pronounced decrease during the first year of gender-affirming hormone treatment, after which levels stabilized. Remarkably, in the early-pubertal transgirls an initial increase in the P1NP, P3NP, and 1CTP levels was found followed by a decrease. After 3 years of gender-affirming hormone treatment, all 4 bone markers had significantly decreased in both early and late-pubertal transgirls. In transboys, osteocalcin, P1NP, and 1CTP significantly decreased. In both early and late-pubertal transboys, serum levels of P3NP did not significantly change.

Discussion

This study examined the impact of puberty suppression and subsequent addition of gender-affirming hormones

Table 3. aBMD and aBMD Z-Scores During 3 Years ofGnRHa Treatment

Sex	Age at Start (Range)	Duration GnRHa(yrs)		Start	12 Months	24 Months	36 Months	*P*
Transgirls	12.6 (12.1-12.8)	3.45 (0.43)	aBMD LS (g/cm^2) mean(± SD) (n = 4)	0.73 (0.9)	.74 (0.10)	0.77 (0.11)	0.77 (0.11)	0.14
			Z-score LS mean (± SD) (n = 4)	−0.43 (1.41)	−0.92 (1.40)	−1.05 (1.31)	−1.15 (1.00)	0.07
			aBMD Hip (g/cm^2) mean (± SD) (n = 4)	0.80 (0.04)	0.82 (0.4)	0.83 (0.05)	0.85 (0.06)	0.07
			Z-score hip mean (± SD) (n = 4)	−0.18 (0.50)	−0.65 (0.34)	−1.08 (0.42)	−1.08 (0.42)	0.007
Transboys	12.7 (11.9-14.0)	3.30 (0.50)	aBMD LS (g/cm^2) mean (± SD) (n)	0.85 (0.13) (11)	0.88 (0.10) (11)	0.90 (0.11) (11)	0.90 (0.9) (11)	0.29
			Z-score LS mean (± SD) (n)	0.42 (1.01) (9)	−0.52 (0.83) (10)	−0.35 (0.96) (11)	−0.53 (0.78) (11)	0.008
			aBMD Hip (g/cm^2) mean (± SD) (n)	0.88 (0.09) (9)	0.88 (0.71) (11)	0.87 (0.08) (11)	0.88 (0.09) (11)	0.95
			Z-score hip mean (± SD) (n)	0.86 (0.71) (8)	0.40 (0.71) (8)	−0.18 (0.67) (9)	−0.30 (0.67) (10)	0.12

Abbreviations: aBMD, areal bone mineral density; LS, lumbar spine; SD, standard deviation.

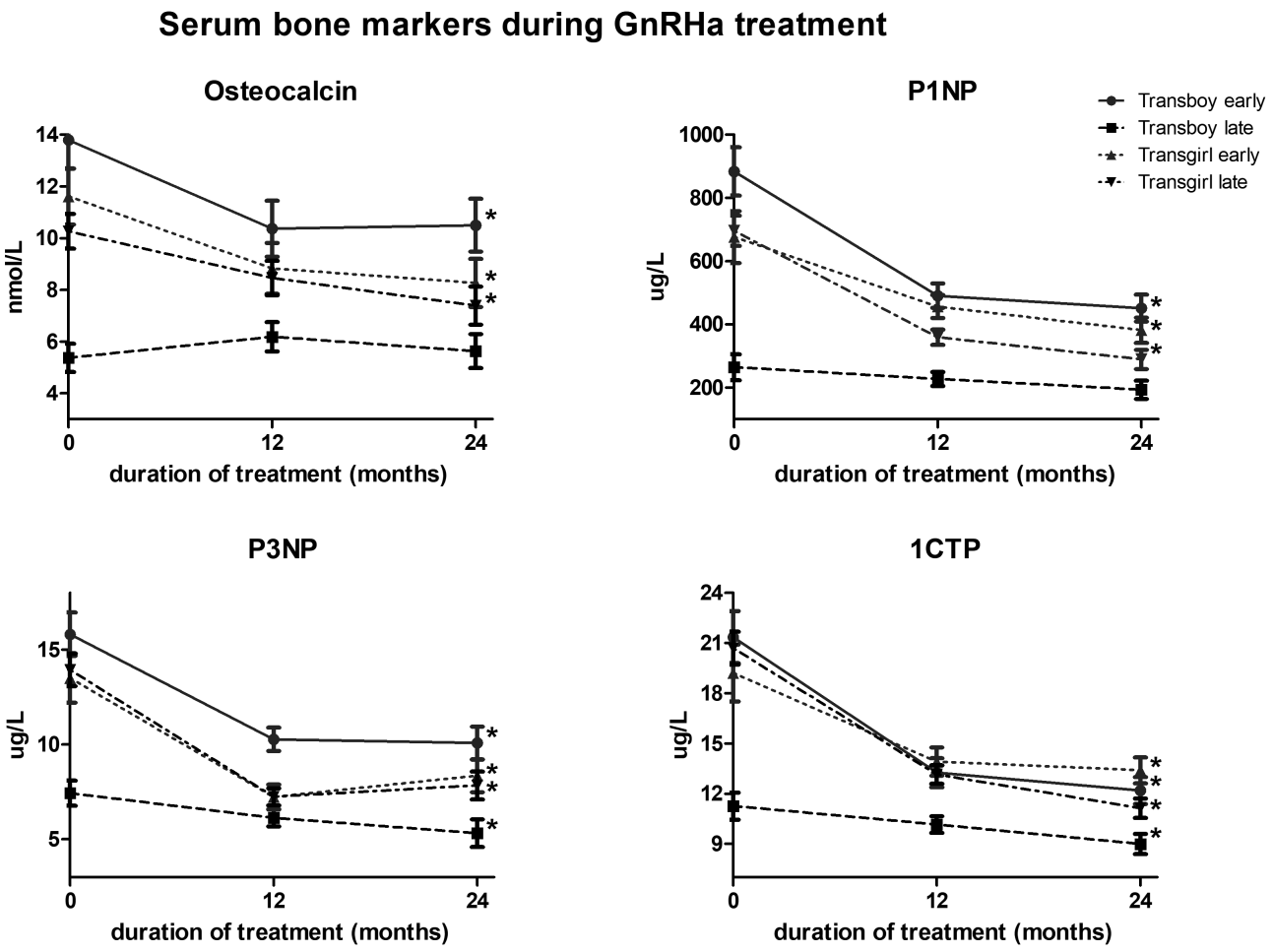

Figure 2. Estimated marginal means and negative standard error of the mean of osteocalcin, P1NP, P3NP, and 1CTP prior to and during 2 years of GnRHa administration in transgirls and transboys. Significant changes during the 2 years of GnRHa administration are indicated by asterisk.

Table 4. aBMD and BMAD During 3 Years of Gender-Affirming Hormone Treatment in Addition to GnRHa Treatment

	Transgirls					
	Early-Pubertal		Late-Pubertal			
	0	36	0	36	*p*1	*p*2
aBMD_LS g/cm^2	0.77 (0.03)	0.95 (0.04)	0.83 (0.02)	0.95 (0.03)	<0.05	<0.05
Z-score	−1.37 (0.30)	−0.82 (0.39)	−0.99 (0.19)	−1.05 (0.25)	<0.05	n.s.
aBMD_hip g/cm^2	0.87 (0.03)	1.02 (0.04)	0.88 (0.02)	0.96 (0.02)	<0.05	<0.05
Z-score	−0.99 (0.23)	−0.09 (0.28)	−0.86 (0.14)	−0.70 (0.18)	<0.05	n.s.
Whole body BMD g/cm^2	0.93 (0.02)	1.06 (0.06)	0.96 (0.01)	0.98 (0.04)	<0.05	n.s.
Z-score	−1.67 (0.23)	−1.22 (0.28)	−1.42 (0.14)	−1.48 (0.18)	<0.05	n.s.
BMAD_LS g/cm^3	0.20 (0.08)	0.24 (0.09)	0.21 (0.05)	0.24 (0.06)	<0.05	<0.05
Z-score	−1.39 (0.36)	−0.49 (0.40)	−1.29 (0.23)	−0.50 (0.25)	<0.05	<0.05
BMAD_hip g/cm^3	0.28 (0.01)	0.31 (0.02)	0.27 (0.01)	0.27 (0.01)	<0.05	<0.05
Z-score	−0.88 (0.23)	−0.35 (0.37)	−1.36 (0.20)	−1.21 (0.24)	<0.05	<0.05
	Transboys					
	Early-pubertal		Late-pubertal			
	0	36	0	36	*p*1	*p*2
aBMD_LS g/cm^2	0.82 (0.04)	1.02 (0.07)	0.90 (0.02)	0.99 (0.02)	<0.05	<0.05
Z-score	−1.30 (0.43)	0.11 (0.58)	−0.68 (0.16)	−0.26 (0.22)	<0.05	<0.05
aBMD_hip g/cm^2	0.83 (0.04)	1.02 (0.06)	0.88 (0.02)	0.96 (0.02)	<0.05	<0.05
Z-score	−0.82 (0.33)	0.59 (0.43)	−0.50 (0.12)	0.12 (0.16)	<0.05	<0.05
Whole body BMD g/cm^2	0.94 (0.03)	1.11 (0.10)	1.02 (0.01)	1.10 (0.03)	n.s.	<0.05
Z-score	−1.06 (0.32)	0.21(0.43)	−0.30 (0.12)	−0.05 (0.16)	<0.05	<0.05
BMAD_LS g/cm^3	0.22(0.01)	0.26 (0.01)	0.24 (0.01)	0.26 (0.01)	<0.05	<0.05
Z-score	−1.01 (0.49)	0.12 (0.51)	−0.61 (0.18)	−0.04 (0.18)	<0.05	<0.05
BMAD_hip g/cm^3	0.28 (0.02)	0.32 (0.02)	0.30 (0.01)	0.32 (0.01)	<0.05	n.s.
Z-score	−0.71 (0.37)	0.01 (0.43)	−0.41 (0.14)	−0.10 (0.16)	<0.05	n.s.

aBMD and BMAD during 3 years of GnRHa plus gender-affirming hormone treatment. Values are presented as estimated marginal means ± standard error. *p1* represents the *P* value between start and after 3 years of treatment for the early-pubertal groups. *p2* represents the *P* value between start and after 3 years of treatment for the late-pubertal groups.

For changes per year of treatment see Fig. 2.

Abbreviations: aBMD, areal bone mineral density; BMAD, bone mineral apparent density; BMD, bone mineral density; LS, lumbar spine.

on bone development in adolescents diagnosed with gender dysphoria. At the start of GnRHa treatment, aBMD and BMAD values were within the normal range. However, transgirls had z-scores well below zero, whereas these were close to zero in transboys. This finding is consistent with previous studies (8, 10, 16-18) and may be explained by differences in lifestyle and exercise intensity between transgirls and transboys. A recent study showed that high-school transgirls have a higher intake of fast-food and are less physically active than transboys (19). In a different cohort of transgender adolescents we found vitamin D levels <50 nmol/L in 74% of transboys and 78% of transgirls starting GnRHa treatment ((9) and unpublished data). However, these findings do not explain why BMD z-scores are lower in transgirls than in transboys. Alternatively, it may be hypothesized that biological factors that act during intrauterine or early development and are involved in the development of gender dysphoria, are also related to bone development programming. For example, a whole-exome sequencing study in transgender individuals found 21 variants in 19 genes associated with estrogen activated pathways of sexually dimorphic brain development (20). These variants in estrogen receptor–activated pathways might also play a role in bone mineral acquisition.

During GnRHa treatment we observed a decline of aBMD and BMAD z-scores in line with previous studies (8-10). In transgirls a decrease of aBMD z-scores was also reported with the use of the anti-androgenic progestin cyproterone acetate (18). In contrast, 1 study showed that in transboys treated with the progestin lynestrenol for an average of 11.6 months aBMD z-scores were stable or increased (18). If these results are confirmed, also with more prolonged treatment duration, the better safety profile with regard to bone health is an important point to discuss with adolescents. In particular, older transboys who have already

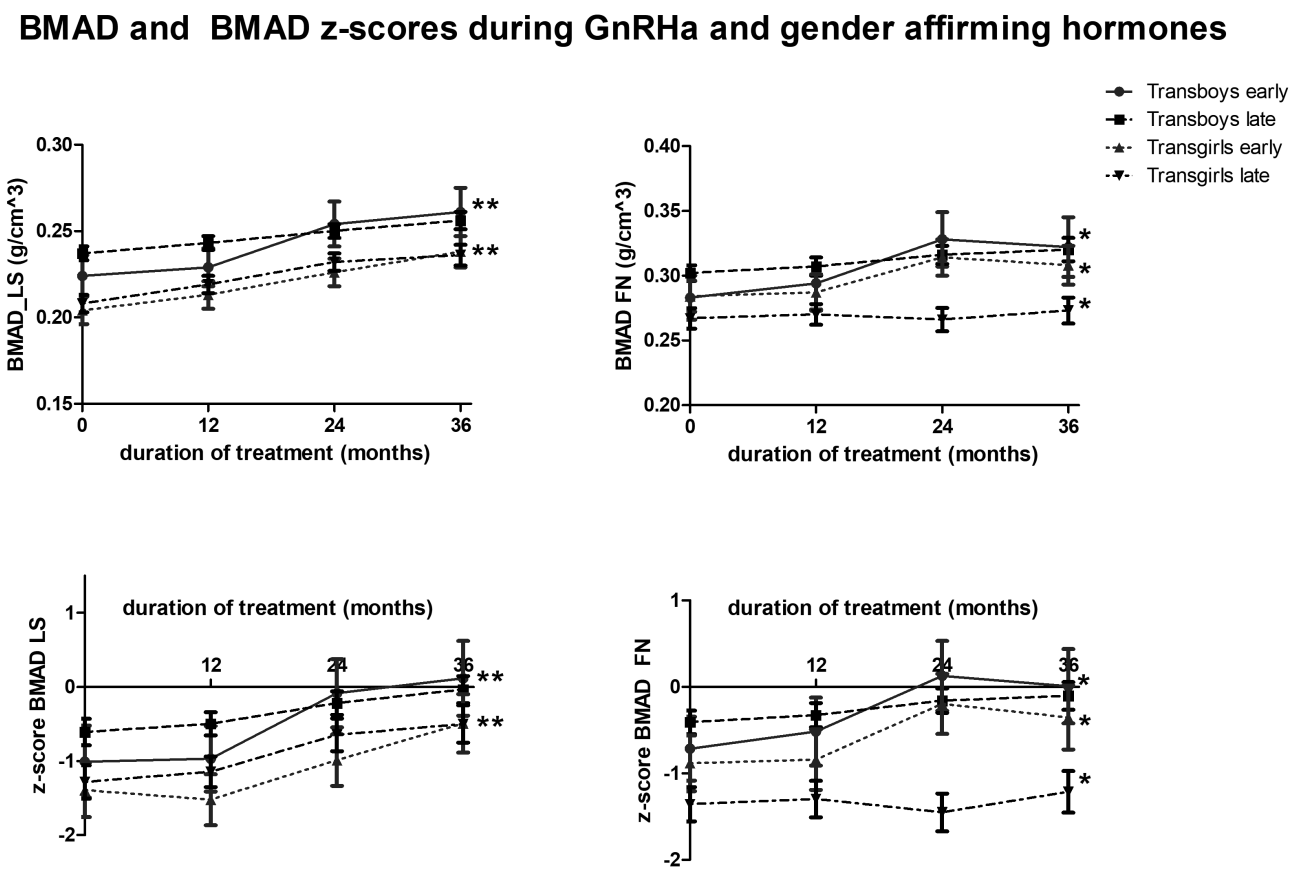

Figure 3. Estimated marginal means and standard error of the mean of BMAD prior to and during 3 years of GnRHa + gender-affirming treatment in transgirls and transboys. Significant changes during the 3 years of GnRHa + gender-affirming treatment are indicated by an asteriks.

completed breast development may prefer lynestrenol to GnRHa treatment.

In most individuals with prolonged (3-4 years) GnRHa treatment, no further decrease in aBMD z-scores was observed in the last year, suggesting that z-scores might stabilize. Data from a larger cohort of adolescents treated with GnRHa for longer periods of time are needed, especially now that adolescents are presenting at younger ages at gender identity clinics and starting treatment at the onset of puberty.

During gender-affirming hormone treatment, a significant increase in the BMAD of the lumbar spine was found in all groups, and of the femoral neck in all but the late-pubertal transboys. In line with previous studies, BMAD z-scores were close to zero in transboys after 3 years of testosterone treatment (8-10). The increase in z-scores was most pronounced in the early pubertal transboys whose z-scores were slightly higher after 3 years of androgen treatment than at the start of GnRHa treatment.

The BMAD z-scores remained well below zero in transgirls in line with previous studies (8, 10). However, BMAD z-scores in early-pubertal transgirls increased more during estrogen treatment and were higher after 36 months than the scores reported by Vlot et al after 24 months (8). This might be due to the extra year of estrogen treatment in the current study, although the z-score of BMAD at the femoral neck no longer seemed to increase between 24 and 36 months. In contrast, the BMAD z-scores of the femoral neck in the late-pubertal transgirls were much lower after 36 months in the current study than previously reported (8). This may be due to the lower z-scores at the start of GnRHa treatment (–1.01 vs –0.44) and at the start of estrogen treatment (–1.36 vs –0.36) in the current study compared with the study by Vlot et al.

An important limitation of this study is the lack of an untreated control group. As discussed above, z-scores in transgirls were already well below 0 at the start of treatment, and these might have further decreased even without treatment, as low BMD was also observed in adult transwomen before the start of any treatment (16, 17).

Another issue is which reference population should be used to calculate BMD or BMAD z-scores. In transgirls who started treatment in early puberty, bone architecture may be more similar to that of cisgender females than to cisgender males. A recent study did not find changes in cortical bone geometry in response to estrogen treatment in adult transwomen, but the authors suggested that this might have been different if they had started treatment during puberty (21).

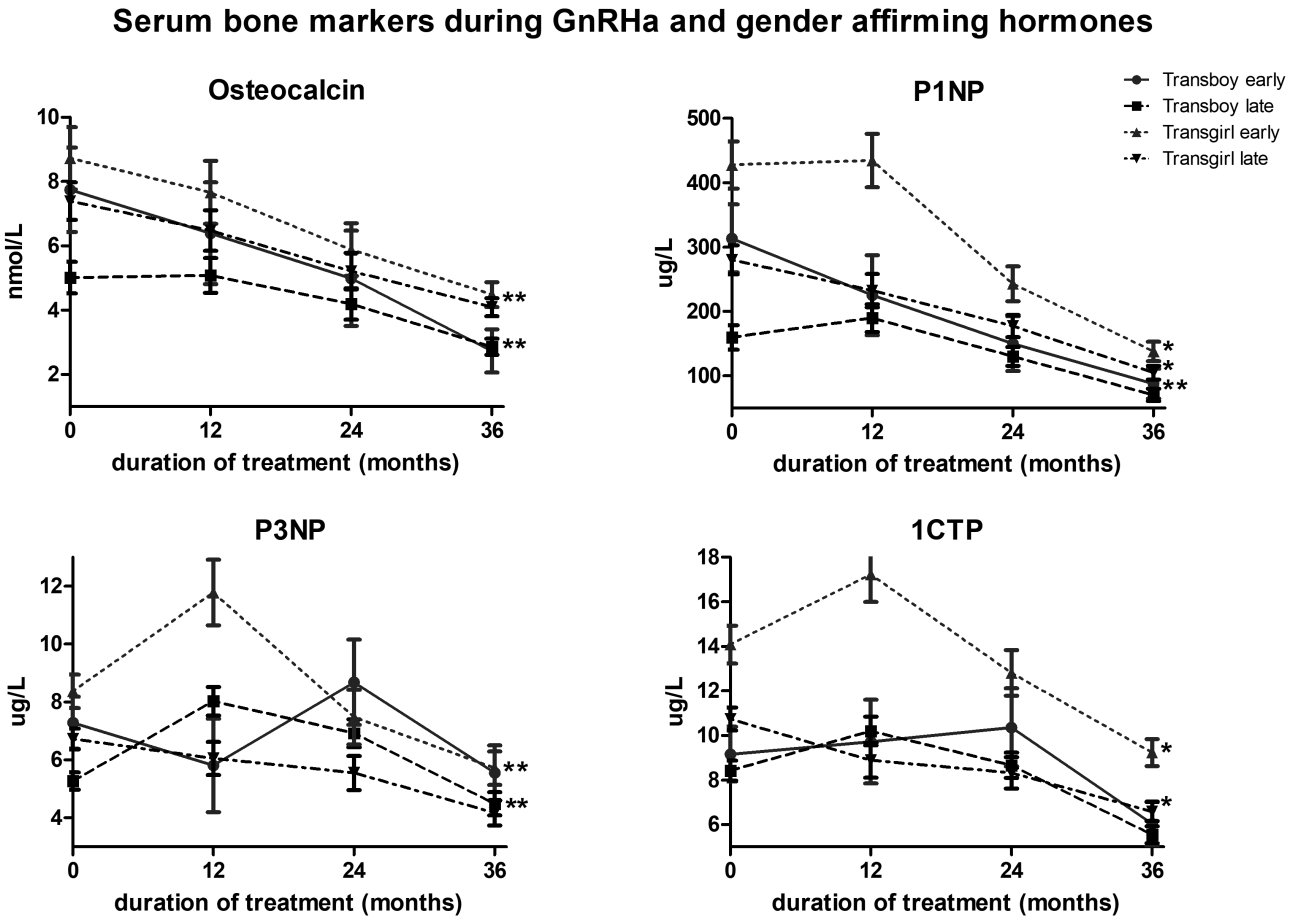

Figure 4. Estimated marginal means and standard error of the mean of osteocalcin, P1NP, P3NP, and 1CTP prior to and during 3 years of GnRHa + gender-affirming treatment in transgirls and transboys. Significant changes during the 3 years of GnRHa + gender-affirming treatment are indicated by an asteriks.

GnRHa are not only used in transgender children, but also in other populations, mainly in children with precocious or early puberty. A recent publication from an international consortium on the use of GnRHa concluded from the available evidence in this group that the treatment was safe with regard to bone mineral density, with attenuated bone mineral accrual reported during treatment but recovery by late adolescence (22). Different findings in children with precocious puberty compared with transgender adolescents may be due to the different timing of GnRHa treatment, the use of gender-affirming hormones, with current estradiol dose possibly insufficient (23), versus endogenous puberty, and due to differences in baseline BMD between the groups.

In transgirls and early-pubertal transboys, all bone markers decreased during the first year of GnRHa treatment while BMD levels remained stable. However, in the late-pubertal transboys bone turnover markers were lower at baseline and did not change. This suggests that the decline of the bone markers during GnRHa treatment may not be due to reduced bone mineral accrual but may rather reflect reduced growth velocity after initiating treatment. The late-pubertal transboys had likely already reached (near) adult height, which could explain the lower and stable levels of bone turnover markers. We previously observed a similar decrease of alkaline phosphatase during GnRHa treatment, but only in those who had not yet completed growth (24). The opposite effect was seen during the first year of treatment with gender-affirming hormones, where bone markers increased in the early pubertal transgirls, who likely had most growth potential. In adults, changes in P1NP were also found to be only weakly correlated to changes in BMD in transwomen and not significantly correlated in transmen (25). A previous study of bone turnover markers in adolescents observed a similar pattern of changes in P1NP and 1CTP to the current study (8). However, changes in osteocalcin were only seen in late-pubertal transboys, possibly due to the small number of subjects in that study with large interindividual differences in the changes of osteocalcin levels (8).

Based on the current study we propose that it is sufficient to perform DXA scans at the start of GnRHa

treatment, every 2 years during GnRHa treatment, at the start of gender-affirming hormone treatment, and then every 2 to 3 years. Adolescents should be counseled on the importance of weight-bearing exercise, an adequate dietary calcium intake, sufficient sunlight exposure to ensure adequate vitamin D levels, or vitamin D supplementation (26). In addition, it is important to ensure an adequate estrogen dose resulting in physiological serum estradiol levels. Routine measurement of bone turnover markers does not seem to be useful for monitoring bone health.

In conclusion, treatment with GnRHa results in a stabilization and maintenance of previously achieved bone mass in the lumbar spine but a small decrease in BMAD of the femoral neck of the nondominant hip. Gender-affirming hormone treatment increases bone accretion and normalizes the age- and sex-specific BMAD z-scores in transboys. Transgirls had lower BMAD z-scores, especially the late-pubertal group, but as z-scores were already lower at baseline, this may be due to other factors than the endocrine treatment, such as lifestyle factors. The consequences of lower BMD for long-term bone health in these individuals remains unclear. Future studies should evaluate peak bone mass in those who started treatment as adolescents and investigate clinically important outcomes such as fracture risk in this population.

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Clinical Trial Information: International Standard Randomized Controlled Trial Number registration no. ISRCTN 81574253 (http://www.controlled-trials.com/isrctn/).

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Disclosure Summary: The authors have nothing to disclose.

Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Continuation of Gender-affirming Hormones Among Transgender Adolescents and Adults

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Abstract

Introduction: Concerns about future regret and treatment discontinuation have led to restricted access to gender-affirming medical treatment for transgender and gender-diverse (TGD) minors in some jurisdictions. However, these concerns are merely speculative because few studies have examined gender-affirming hormone continuation rates among TGD individuals.

Methods: We performed a secondary analysis of 2009 to 2018 medical and pharmacy records from the US Military Healthcare System. We identified TGD patients who were children and spouses of active-duty, retired, or deceased military members using International Classification of Diseases-9/10 codes. We assessed initiation and continuation of gender-affirming hormones using pharmacy records. Kaplan-Meier and Cox proportional hazard analyses estimated continuation rates.

Results: The study sample included 627 transmasculine and 325 transfeminine individuals with an average age of 19.2 ± 5.3 years. The 4-year gender-affirming hormone continuation rate was 70.2% (95% CI, 63.9-76.5). Transfeminine individuals had a higher continuation rate than transmasculine individuals 81.0% (72.0%-90.0%) vs 64.4% (56.0%-72.8%). People who started hormones as minors had higher continuation rate than people who started as adults 74.4% (66.0%-82.8%) vs 64.4% (56.0%-72.8%). Continuation was not associated with household income or family member type. In Cox regression, both transmasculine gender identity (hazard ratio, 2.40; 95% CI, 1.50-3.86) and starting hormones as an adult (hazard ratio, 1.69; 95% CI, 1.14-2.52) were independently associated with increased discontinuation rates.

Discussion: Our results suggest that >70% of TGD individuals who start gender-affirming hormones will continue use beyond 4 years, with higher continuation rates in transfeminine individuals. Patients who start hormones, with their parents' assistance, before age 18 years have higher continuation rates than adults.

Key Words: transgender gender dysphoria, sex-hormones, treatment, adolescent, adult

Abbreviations: ICD, International Classification of Diseases; MHS, Military Healthcare System; TGD, transgender and gender-diverse

Approximately 1 in 250 adults or almost 1 million adults in the United States identify as transgender (1). The frequency of adults, and especially younger adults, reporting a gender-diverse identity has increased over time (1). Some persons who identify as transgender or gender-diverse (TGD) will seek treatment with gender-affirming hormones to align their bodies more closely with their gender identity (2). Medical treatment of people who identify as transgender improves body satisfaction, quality of life, and mental health (2, 3). However, many of these treatments are not entirely reversible (4).

Some adolescents or adults who take gender-affirming hormones subsequently elect to stop treatment (5, 6). Most adults who stop gender-affirming hormones report doing so for reasons unrelated to a change in gender identity, such as pressure from family, difficulty obtaining employment, or discrimination (7). Also, discontinuation of gender-affirming hormones does not necessarily represent a failure in treatment or initial decision-making. Some TGD adolescents and adults who start and then discontinue gender-affirming hormones experience use of hormones as an important part of consolidating their gender identity and experience no regret over the use of hormones despite some permanent effects (5, 7, 8). However, a portion of TGD individuals who pursue gender-affirming medical or surgical affirmation do express regret over the permanent effects of treatment (5, 9, 10). In a

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metanalysis of 7928 TGD individuals who had gender confirmation surgery, 1% expressed regret after surgery (9). The most prevalent reason for regret was psychosocial circumstances, particularly from a lack of social support or negative reactions from family and employers (9). Concerns about future regret after medical or surgical affirmation and the capacity of adolescents to provide informed assent for this treatment, with the assistance of their families, have led legislators and members of the judiciary in some locations to attempt to limit access to these interventions for youths (11-14). For example, in the United States, 16 states do not provide coverage for gender-affirming medical care through public insurance for those with incomes below the federal poverty line (Medicaid). Two states have outlawed gender-affirming care for minors, another state has taken administrative action to classify gender-affirming medical care for minors as child abuse, and 20 state legislatures are considering laws to make some or all aspects of gender-affirming medical care for minors illegal during the 2022 legislative session (13, 14). In the United Kingdom, a court ruled that gonadotropin-releasing hormone analogues could not be administered to transgender patients younger than age 16 years without obtaining a court order and suggested that older TGD adolescents should be required to obtain a court order before starting gender-affirming hormones (12).

Clinical guidelines for medical affirmation of persons who identify as TGD suggest that the rate of "de-transition" among postpubertal adolescents and adults is rare, but few studies have assessed the actual rate of treatment discontinuation (6, 7, 10). In a cross-sectional study of a self-selected sample of 27 715 TGD adults in the United States, 61.9% reported a history of social affirmation (ie, changing name, pronouns, appearance), 44.8% reported medical affirmation with hormones, and 19.5% reported surgical affirmation (7). A history of stopping affirmation and reverting to living in their sex assigned at birth for at least a little while was more common among people who only engaged in social affirmation (30.8%) than among people who had started medical (9.1%) or surgical (6.9%) affirmation (7). Among TGD adults who stopped affirmation, 82.5% reported at least 1 external factor, such as pressure from family and community or difficulty with employers as a reason to stop and 15.9% reported at least 1 internal factor, such as psychological distress and uncertainty or fluctuation in gender identity as a reason to stop. Only 5% of people who stopped affirmation reported stopping because they realized that changing gender was no longer desired. At the time of the survey, 68% of people who had discontinued affirmation had subsequently restarted (7). In a 1-year chart review of 174 adults treated at a national gender clinic in the United Kingdom, 12 (6.9%) patients discontinued medical affirmation during a 1-year period. Of these 12 patients, 4 later reengaged in gender-affirming care (6). At the Center of Expertise on Gender Dysphoria, a specialized gender clinic that provides > 95% of all gender-affirming medical and surgical care in the Netherlands, > 75% of TGD adults who started gender-affirming hormones between 1972 and 2014 had completed 1.5 years of gender-affirming hormones and met criteria for gonadectomy by the end of 2015 (10). However, this study did not assess hormone continuation rates directly.

Prior studies of treatment discontinuation rates among TGD adults undergoing medical affirmation have been limited to small samples of patients from specialized gender clinics who stopped coming in for appointments or a cross-sectional study of self-reported de-transition rates among adults who continue to identify as TGD and obtained hormonal therapy both in and outside the health care system (6, 7, 15). These studies found low levels of treatment discontinuation. The discontinuation that did occur was frequently temporary and unrelated to a change in gender identity. However, none of these studies have examined discontinuation rates among minors or assessed objective measures of medication continuation. Therefore, in the current study, we assessed the rate of treatment discontinuation after starting gender-affirming hormones among TGD adolescents and adults and identified demographic groups at higher risk of discontinuation of gender-affirming hormones. We hypothesized that gender-affirming hormone continuation rates will not differ between individuals who start hormones before or after reaching the age of legal majority.

Methods

This study is a secondary analysis of US Military Healthcare System's (MHS) medical and pharmacy billing records from October 2009 to September 2018 for family members of active-duty service members. Data were extracted from the Military Healthcare Data Repository, which includes insurance billing records of all inpatient and outpatient care and outpatient prescriptions provided to individuals enrolled in the military's health care benefit (TRICARE) both domestically and abroad at military and civilian treatment facilities.

We used the following inclusion criteria for our study:

- The patient was a child or spouse of an active duty, retired, or deceased servicemember at the time of the initial TGD-related diagnosis
- Patient had 2 or more medical encounters for a TGD-related diagnosis on different days (International Classification of Diseases [ICD] codes: ICD-9 302.6, 302.85 302.50, 302.51, 302.52, 302.53, and ICD-10 F64.0, F64.1, F64.2, F64.8, F64.9, Z87.890)
- Patient received an initial prescription for gender-affirming hormones between 30 days before the date of their first TGD-related medical encounter and 90 days after their date of his or her last TGD-related medical encounter
- Patient received at least 2 prescriptions for gender-affirming hormones.

We excluded active-duty servicemembers and military retirees from our analysis because servicemembers are required to obtain permission from the military service to transition while on active duty (16) and follow rules governing gender affirmation and use of gender-affirming hormones. We felt this would make them a distinctly different population from their family members and it would be inappropriate to combine them.

Use of ICD 9/10 codes to identify TGD individuals is a validated methodology. In a previous study, these codes were well-matched with clinical text notes in identification of TGD individuals (17, 18). We required patients to have 2 or more encounters with an associated TGD diagnosis to limit false-positive identifications.

We used medical and pharmacy records to identify TGD individuals who started gender-affirming hormones. We identified a TGD individual's sex assigned at birth using the sex recorded at the first encounter, for any reason, in our dataset. Then, we used pharmacy billing records to identify prescriptions and days supplied of gender-affirming hormones for both initial prescriptions and refills. We defined gender-affirming hormone prescriptions as prescriptions for testosterone issued to individuals coded as female at their first encounter and prescriptions for estrogens issued to individuals coded as male at their first encounter. We attempted to limit our sample to patients using gender-affirming hormones by requiring patients to obtain at least 2 prescriptions for gender-affirming hormones and obtain the initial prescription for gender-affirming hormones between 30 days before the date of their first TGD-related medical encounter and 90 days after their date of their last TGD-related medical encounter.

We collected patient age at the initial TGD-related encounter, age at the time of the first prescription for gender-affirming hormones, family role (spouse vs offspring), determined if the patient started gender-affirming hormones before or after gender-affirming health care became an officially covered military benefit for family members on September 1, 2016, and military rank of the insurance sponsor (16). We used military rank (enlisted vs officer) of the patient's insurance sponsor at the time of the last medical encounter in our dataset as a proxy for family income. Officers are required to have a 4-year college degree before military service, whereas enlisted servicemembers are only required to have a high school degree or equivalent. Officers also have a higher average base pay than enlisted servicemembers. In 2019, the average base salary for servicemembers with 10 years of military service was $48 864 for enlisted servicemembers and $86 832 for officers (19).

We used Kaplan-Meier analyses to estimate the rate of discontinuation of gender-affirming hormones after starting treatment (20). We identified patients as discontinuing their gender-affirming hormones if they failed to obtain another prescription for gender-affirming hormones more than 90 days after completing their most recent prescription. Patients were censored from further analysis if they were no longer obtaining health care in the MHS (reached the date of their most recent medical encounter in the database).

We used the log-rank test to assess the influence of sex assigned at birth, age at initiation of gender-affirming hormones (< 18 years vs 18 years of age and older), family income (officer vs enlisted insurance sponsor), family role (spouse vs offspring), and if the patient started gender-affirming hormones before or after gender-affirming care became an official TRICARE benefit on September 1, 2016 (16). We limited our analysis of the influence of official insurance coverage to the first 22 months after starting gender-affirming hormones because we only had 22 months of data after the change occurred. We also used Cox proportional hazard analysis to determine the independent influence of our demographic factors on discontinuation rates. This study was institutional review board-approved as a secondary analysis of preexisting records. Statistical significance was defined as $P < 0.05$.

Results

Of the 952 individuals in our study, 66% were assigned female at birth, 61% were ≥ 18 years old, 71% had an enlisted insurance sponsor, and 90% were children of active duty, retired, or deceased servicemembers (Table 1, Fig. 1). Patients who discontinued obtaining refills of gender-affirming hormones continued to obtain medical care in the MHS for an average of 324 days (SD, 274; range, 91-1602) after they completed their final prescription for gender-affirming hormones (Table 1). The number of patients initiating gender-affirming hormones increased during the study period, and 58% of patients had their first appointment for transgender-related care during the last 22 months of our study (September 2016-June 2018), after gender-affirming care was included as an officially covered TRICARE benefit for family members (14) (Table 1 and Fig. 2).

In our sample, 70.2% (95% CI, 63.9-76.5) of patients who started medical affirmation continued to fill prescriptions for gender-affirming hormone for at least 4 years (Fig. 1). Transfeminine individuals were more likely to continue obtaining gender-affirming hormones in the MHS than transmasculine individuals. The 4-year continuation rate for transfeminine individuals was 81.0% (95% CI, 72.0-90.0) vs 64.4% (95% CI, 56.0-72.8) for transmasculine individuals (log-rank test χ^2, 11.860) (Fig. 3). Patients who were younger than 18 years of age when starting hormones were less likely to discontinue use than patients who were 18 years of age and older. The 4-year continuation rate among people who started treatment under 18 years of age was 74.4% (95% CI, 66.0-82.8) and the rate among people who were ≥ 18 years was 64.4% (95% CI, 56.0-72.8) (log-rank test χ^2, 4.461) (Fig. 4). Family income (enlisted vs officer insurance sponsor; log-rank test χ^2, 0.013) and family member type (spouse vs child; log-rank test χ^2, 1.002) had no influence on continuation rates. Starting hormones before or after official coverage of gender-affirming medical care by TRICARE on September 1, 2016, also had no influence on continuation rates (log-rank test χ^2, 0.728).

Table 1. Sample demographics (n = 952)

Demographic group	%
Gender identity	
Transfeminine	34.1
Transmasculine	65.9
Age at Initiation of Gender-Affirming Hormones	
<18 years old	39.1
≥18 years old	60.9
Insurance sponsor rank	
Enlisted (high school or some college)	70.6
Officer (college education and beyond)	29.4
Family member type	
Dependent child	90.1
Spouse	9.9
Started gender-affirming hormones before or after approval of gender-affirming care as an official TRICARE benefit	
Before approval (October 2009-August 2016)	42
After approval (September 2016-June 2018)	58.0
	Mean ± SD (range)
Days between stopping gender-affirming hormones and last visit	324 ± 274 (91-1602)

Gender-affirming medical care became an authorized TRICARE benefit for dependents on September 1, 2016.

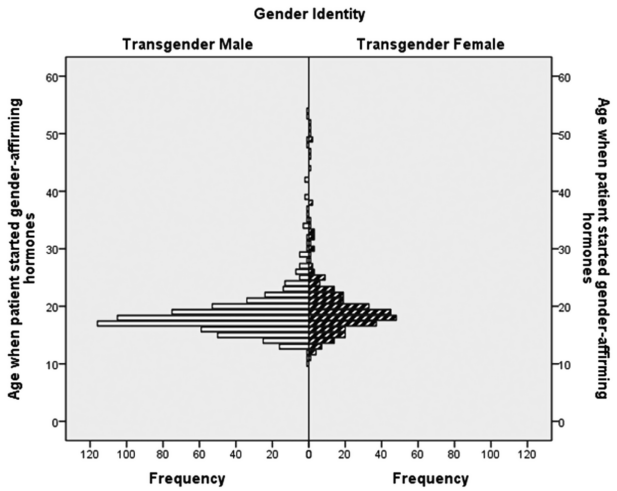

Figure 1. Age at initiation of gender-affirming hormones by sex assigned at birth.

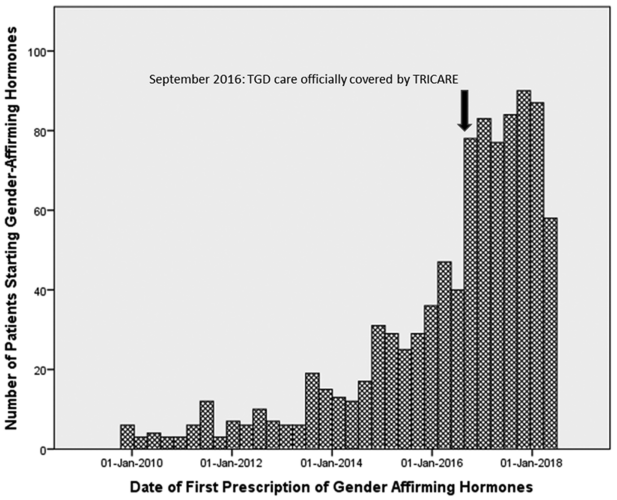

Figure 2. Incidence of gender-affirming hormone initiation over time.

In a Cox regression model containing assigned gender and age at initiation of hormones, transmasculine individuals were more than twice as likely to stop obtaining hormones in the MHS compared with transfeminine individuals (hazard ratio 2.40; 95% CI, 1.50-3.86) and people who started hormones after turning 18 years of age were more likely to stop obtaining gender-affirming hormones compared with people who started hormones before age 18 years (hazard ratio, 1.69; 95% CI, 1.14-2.52) (Table 2).

Discussion

Our study documented higher gender-affirming hormone continuation rates among transfeminine individuals and by patients who started hormones before reaching the age of legal majority in a population with universal insurance and access to low or no-cost medical and pharmaceutical care. Family socioeconomic status, family member type, and the official status of gender-affirming care as a TRICARE-covered benefit at the time the patient began taking gender-affirming hormones had no influence on continuation of gender-affirming hormones.

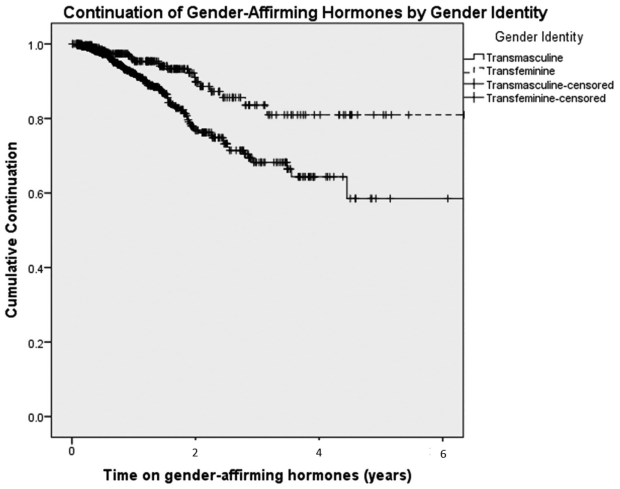

Figure 3. Continuation of gender-affirming hormones by gender identity.

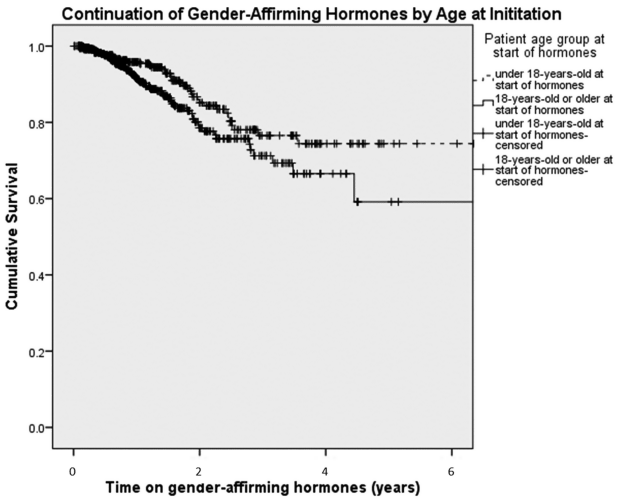

Figure 4. Continuation of gender-affirming hormones by age at initiation.

Table 2. Multivariate regression: independent association of age and gender identity on discontinuation of gender-affirming hormones

Demographic factor	Risk of discontinuing of gender-affirming hormones
Gender identity	Hazard ratio (95% CI)
Transfeminine	Reference
Transmasculine	2.40 (1.50-3.86)
Age at initiation of gender-affirming hormones	
<18 years old	Reference
≥18 years old	1.69 (1.14-2.52)

We noted a higher hormone continuation rate among TGD individuals who were younger than 18 years old at the time of first use of gender-affirming hormones compared with those who were aged 18 years and older when starting hormones. This has not been documented in previous studies.

The patients who started before turning 18 years would require parental consent for this treatment, whereas those aged 18 years and older do not. Parents who consent to use

of gender-affirming hormones likely have a higher level of support for their child's gender affirmation on average than parents who do not. Parental support plays an important role in the mental health of TGD youth (21). A prior study of adults found that lack of family support for a TGD individual's gender was associated with a history of discontinuing social or medical gender affirmation (7). Higher parental support may explain the higher continuation rate among patients who start gender-affirming hormones as minors compared with people who start as adults.

Regardless of the reason for the higher hormone continuation rate among TGD youth, this finding provides support for the idea that TGD individuals below the age of legal majority, with the assistance of their parents or legal guardians and health care providers, can provide meaningful informed assent for gender-affirming hormones and do not appear to be at a higher risk of future discontinuation of gender-affirming hormones because of their young age alone.

There was a higher gender-affirming hormone continuation rate among transfeminine individuals compared with transmasculine individuals in our study. This has not been observed in previous studies. The reasons for this difference cannot be determined using the data from this study. If confirmed in future studies, this would suggest a need to ensure routine screening of transmasculine patients for osteoporosis risk after oophorectomy, especially if this procedure occurs at a younger age.

As in a previous study, there was an increase in the number of patients presenting for gender-affirming care over time (10, 22). However, unlike previous studies, the coverage status of gender-affirming care in our study changed over time. We noted a large increase in patients presenting for care after designation of gender-affirming care as a covered benefit in the MHS.

This leads to a concern that patients and providers who were engaging in gender-affirming care in the MHS before it was officially sanctioned were different than the patients and providers who did not start engaging in gender-affirming care in the MHS until after it was officially sanctioned. However, we did not see a difference in continuation rates between these 2 groups.

The large number of adolescents in our study, the longitudinal data for TGD individuals in a naturalistic and varied clinical setting, use of objective measures of ongoing hormone use, and comparison of gender-affirming hormone use among adolescents and adults are unique strengths of our study, but there are several limitations that must be noted.

We only collected information on medication refills obtained using a single insurance plan. If patients elected to pay out of pocket for hormones, accessed hormones through nonmedical channels, or used a different insurance plan to pay for treatment before and/or after obtaining gender-affirming hormones using TRICARE insurance, we did not capture this information. This means that our findings are likely an underestimate continuation rates among transgender patients.

We attempted to address our concern about overestimating discontinuation rates by only recording cessations among patients who stopped obtaining prescriptions for gender-affirming hormones while continuing to receive medical care using TRICARE insurance for more than 90 days. We would miscategorize patients as terminations if patients elected to obtain their gender-affirming medications using alternative payment options while continuing to receive other medical care using TRICARE.

However, the medication copay for generic medications purchased using TRICARE is quite low at $0 to $3 per prescription when compared with other private insurance programs in the United States. For example, a transgender woman using TRICARE insurance would pay a total of $0 to $72 for a 1-year supply of estrogen and spironolactone. For transgender women with private insurance in the United States, the out-of-pocket expenses for gender-affirming medications would be $230 per year and $500 per year for transgender men with insurance (23). This cost difference makes it less likely that a patient would continue to use TRICARE for medical care but elect to use a different insurer to obtain gender-affirming hormones.

This study was limited by reliance on accuracy of billing data and lack of patient-level data. We cannot know why patients in our study stopped obtaining refills of gender-affirming hormones using their TRICARE insurance. Many factors inform an individual patient's desire or ability to continue obtaining refills of gender-affirming hormones including gender identity, treatment intentions, difficulty finding a provider who offers gender-affirming care, satisfaction with treatment outcomes, or social context.

In a previous study, only 16% of TGD individuals who stopped gender-affirming hormones cited a change in gender identity or mental health concerns as a reason to discontinue social or medical gender affirmation (7). Many of the individuals who reported stopping gender-affirming hormones reported subsequently restarting treatment or the intention to restart treatment (7).

The lack of patient level detail in our study makes it impossible to predict individual patient outcomes with our findings. However, our findings can still be useful to inform policy makers or legislators when assessing the risk of transgender care for minors.

A related limitation is our reliance on the gender marker at the first medical encounter as a proxy for sex assigned at birth. It is possible that this information is wrong or reflects a change in gender marker that occurred before the beginning of our study interval. We attempted to address this concern using our inclusion criteria. For example, with our inclusion criteria, we would incorrectly include a cis-male patient who was assigned male at birth, changed the sex recorded in the electronic medical record to female, received a transgender-related diagnosis at 2 different medical encounters, and then elected to fill 2 prescriptions for testosterone during the same time period he had the 2 transgender-related medical encounters. This combination would likely be a rare event and, if present, have a minimal impact on the findings of the study.

Before September 2016, gender-affirming care was not an officially covered health care benefit under TRICARE (16). Patients may have had trouble finding a TRICARE-approved clinician who would prescribe hormones or a pharmacy that would fill the prescription in their area, especially in cases where they initiated care in 1 location and then they or their family moved. However, we did not see a difference in continuation rates between patients who started hormones before or after gender-affirming care becoming an officially covered benefit.

Determining if these differences in continuation rates exist in other groups of TGD individuals and determining if there

are differences in reasons for discontinuation by gender identity or age is an important topic for future studies. Future prospective studies should investigate the rate of hormone discontinuation between transfeminine and transmasculine individuals to determine whether the same pattern of discontinuation is observed. The reasons for discontinuing treatment and whether patients anticipate restarting treatment at a future date would also be important to assess. Finally, it would be useful to prospectively assess the number of TGD individuals who experience regret after starting gender-affirming hormones and if there are any associated factors that can be used to identify patients at a higher risk of regret. This would assist clinicians in providing nuanced counseling regarding treatment options to TGD individuals before starting hormones.

Conclusion

In our study, transmasculine individuals were more likely to discontinue use of gender-affirming hormones during the first 4 years of use than transfeminine individuals. We also found that individuals who start gender-affirming hormones before reaching the age of legal majority are less likely to subsequently discontinue use when compared with individuals who start hormones after becoming a legal adult. If replicated in future studies, the improved continuation rate among patients who are not legal adults at the time of treatment should provide some reassurance to those concerned about the ability of minors to provide informed assent to use of gender-affirming hormones. A higher continuation rate among minors could also be used to inform the actions of legislators and judges who wish to prohibit gender-affirming treatment for minors to protect them from the consequences of health care decisions they make with the assistance of their parents and health care providers.

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Disclosures

The authors report no competing interests.

Data Availability

A deidentified copy of the dataset for this study is available from the authors on reasonable request

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Current Concerns About Gender-Affirming Therapy in Adolescents

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Abstract

Purpose of Review Results of long-term studies of adult transgender populations failed to demonstrate convincing improvements in mental health, and some studies suggest that there are treatment-associated harms. The purpose of this review is to clarify concerns about the rapid proliferation of hormonal and surgical care for the record numbers of youth declaring transgender identities and seeking gender reassignment procedures.

Recent Findings Systematic reviews of evidence conducted by public health authorities in Finland, Sweden, and England concluded that the risk/benefit ratio of youth gender transition ranges from unknown to unfavorable. As a result, there has been a shift from "gender-affirmative care," which prioritizes access to medical interventions, to a more conservative approach that addresses psychiatric comorbidities and psychotherapeutically explores the developmental etiology of the trans identity. Debate about the safety and efficacy of "gender-affirming care" in the USA is only recently emerging.

Summary The question, "Do the benefits of youth gender transitions outweigh the risks of harm?" remains unanswered because of a paucity of follow-up data. The conclusions of the systematic reviews of evidence for adolescents are consistent with long-term adult studies, which failed to show credible improvements in mental health and suggested a pattern of treatment-associated harms. Three recent papers examined the studies that underpin the practice of youth gender transition and found the research to be deeply flawed. Evidence does not support the notion that "affirmative care" of today's adolescents is net beneficial. Questions about how to best care for the rapidly growing numbers of gender-dysphoric youth generated an intensity of divisiveness within and outside of medicine rarely seen with other clinical uncertainties. Because the future well-being of young patients and their families is at stake, the field must stop relying on social justice arguments and return to the time-honored principles of evidence-based medicine.

Keywords Transgender · Gender dysphoria · Gender incongruence · Puberty blockers · Gender-affirming care · The Dutch protocol

Introduction

The fundamental basis for concern about "gender-affirming" interventions for adolescents, and socially transitioned children who will soon be adolescents, is how they will fare in the ensuing decades [1•]. There are significant knowledge gaps about the balance of benefits and harms as patients live their lives.

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Medicine has provided treatments for transgender-identified adolescents for over 25 years [2–6]. These treatments emerged in the late 1980s to early 1990s in large part in response to the suboptimal outcomes of transitioned adults, with the hope that early gender transition may improve outcomes [3]. Despite claims of the lifesaving nature of gender transition for adults, none of the many studies convincingly demonstrated enduring psychological benefits. The longest-term studies, with the strongest methodologies, reported markedly increased morbidity and mortality and a persistently high risk of post-transition suicide among transitioned adults [7, 8••, 9].

The lack of credible evidence of benefits of gender transition has come into focus for today's transgender-identified youth, whose numbers have sharply increased. The presentation of gender dysphoria has markedly changed in recent years [10]: the sex ratio of youth presenting in medical settings has

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reversed from primarily male to primarily female [11], with the preponderance of youth whose transgender identity emerged for the first time in adolescence and in the context of significant pre-existing mental illness and neurocognitive disorders [12]. These changes began to manifest around 2006 but became pronounced around 2014–2015 [13]. Nonetheless, many clinicians and policymakers promulgate that science long ago established the benefits of gender transition for these adolescents [14–18].

There has never been a dispute about whether medical and surgical interventions can feminize or masculinize secondary and some primary sex characteristics. For children and adolescents, the debate is not whether such transformations are possible, but "at what age can youth meaningfully consent," "upon fulfilling which criteria," and perhaps most importantly, "just because we can – should we?" [1•]. Such questions have provoked an intensity of divisiveness within and outside of medicine rarely seen with other clinical uncertainties [18–22]. This passion reflects decidedly different prioritization of *scientific evidence*, *medical ethics*, and *social values*. We elaborate on each below.

Disagreement About the Scientific Evidence

While several European countries recognized deficiencies in the evidence supporting the highly medicalized "gender-affirming" approach to treating gender-dysphoric youth [1•, 33••, 34••, 35, 36], in North America, the narrative that "gender-affirmative care has been scientifically proven" has been remarkably resilient [23••]. Its justification rests on several key assumptions misrepresented as proven facts [15, 24]:

1. The emergence of a trans identity is the result of reaching a higher level of self-awareness.
2. Whether the trans-identity emerges in very young children, older children, teens, or mature adults, it is authentic and will be lifelong.
3. All gender identity variations are biologically determined and inherently healthy.
4. The frequently co-occurring psychiatric symptoms are a direct result of gender incongruence (the so-called "minority distress" model).
5. The only way to relieve, or prevent, psychiatric problems is to alter the body at the earliest signs of puberty.
6. Psychological evaluations and attempts to address psychiatric comorbidities should only be used to support transition.
7. Attempts to resolve gender dysphoria with psychotherapy range from ineffective to harmful.
8. Gender-dysphoric youth must have unquestioning social, hormonal, and surgical support for their current gender identities and desired physical appearance.
9. All individual embodiment goals, even those that do not occur in nature, must be fulfilled to the full extent technically possible.
10. Science has proven the benefits of early gender transition, and low rates of regret and detransition further validate the practice.

These unproven or disproven assumptions [24] have created a narrative that has misled physicians, parents, and patients to conclude that meeting a young gender dysphoric individual's desired body modification goals provides the only chance for a full, successful, happy life. It has positioned invasive medical interventions for children and adolescents as a civil right, rather than as medical interventions.

The most fundamental of these assumptions are that a teenager's *transgender identity, once expressed, is permanent*; that it will cause *lifelong suffering* if no medical interventions are offered; and that "gender-affirming" *interventions are safe and effective* at improving short-term and long-term psychological outcomes. All three premises are deeply flawed, as we explain below.

Identity Development in Teenagers Is Far from Complete

Answering the question, "Who am I?" is the primary "developmental task" of adolescence [25]. Children and adolescents are too young to assume their current gender identity is permanent. Adults should know that young people's sexual orientations and gender identities fluctuate as they gain more life experiences [26].

Among the many facets of identity, the development of sexual orientation is particularly relevant as gay, lesbian, and bisexual individuals often have extended periods of suffering from gender dysphoria in their younger years [27]. The current overall crisis in mental health among youth and especially girls [28] may introduce further complexity into the identity development process. As many as 70% or more of youth who present with gender identity concerns for the first time in adolescence had psychiatric diagnoses prior to presenting with gender dysphoria [29]. The strong connection between a trans identity in adolescence and the presence of neurocognitive diagnoses [29, 30] deserves additional consideration, as individuals on the autism spectrum are often gender nonconforming. These factors may play a role in the emergence of a transgender identity as a maladaptive mechanism for understanding their distress.

The natural arc of adolescence is the eventual resolution of identity confusion and consolidation of a healthy, multifaceted identity. Problematically, every stage of "gender-affirming" care disrupts the natural course of identity development.

Goals Have Shifted from Reducing Suffering to Achieving Personal "Embodiment Goals"

For decades, gender specialists told the public that gender/sex incongruence created such suffering that these interventions are often "lifesaving." In 2022, the justification for these interventions changed. WPATH "Standards of Care 8" explicitly instructed providers to rely on the "Gender Incongruence" ICD-11 diagnosis [31], which does not require the presence of distress [32].

This recommendation came with an extensive list of medical procedures that WAPTH deems medically necessary for nonbinary patients, including the construction of a neovagina while retaining penis and testicles, and "nonbinary mastectomies" that preserve some of the female breast tissue but resize and reposition the nipple and areola to make the breast appear more masculine. Procedures ranging from "flat front" obliteration of sex organs for those with a eunuch gender identity, to uterine transplantation for male-to-female individuals wishing to pursue childbearing, are also listed as medically necessary [31, p. 136].

Although achieving body modification goals can be very satisfying to patients, clinicians should not confuse it with improved functioning in relational, sexual, educational, substance dependence, and vocational aspects of life—the domains of mental health. Nor can it be claimed to be "lifesaving."

Medical and Surgical Gender Transition Has Not Resulted in Credible Mental Health Improvements

Despite the promise that gender transition is key to ameliorating the suffering of gender-dysphoric youth, systematic reviews of evidence failed to find trustworthy evidence of such improvements. The well-known National Institute for Health and Care Excellence (NICE) reviews, commissioned by the NHS, the UK's health authority, evaluated the first two stages of medical gender transition for youth: puberty blockers and cross-sex hormones [33••, 34••]. In both reviews, the studies that reported positive findings were found to be unreliable due to poor methodology.

In the case of puberty blockers, the reviews found no evidence of improvements in key areas of mental health:

> "The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning), in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up. Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance" [33••, p. 13].

For cross-sex hormones, the review found that improvements in mental health were *highly uncertain* and had to be carefully weighed against the risks of hormonal interventions [34••]. Having conducted their own systematic review of evidence [35], the Swedish health authority came to the even starker conclusion that for most adolescents, the risks of hormones outweigh the benefits [87••]. The Finnish health authority, and the Florida health authority, came to similar conclusions after their own systematic reviews/overviews of systematic reviews [36, 37••].

Since the practice of gender-transitioning youth did not begin to be widely scaled until about 2015, the existing systematic reviews of evidence for young people are limited by very short-term follow-up. Therefore, it is informative to look at studies that followed lifelong trajectories of individuals who medically transitioned decades ago, although they represent a different demographic group (most transitioned when they were older). Unfortunately, these long-term data do not show that hormonal and surgical transitions result in lasting mental health improvements in transgender-identified individuals, and some evidence even suggests the possibility of treatment-associated harms [7, 40•].

A well-known 30-year Swedish follow-up study compared medically transitioned individuals to cisgender age-matched peers on key measures of morbidity and mortality [7]. The study found sharply elevated rates of suicide among transitioned adults (19 times higher than controls overall, and 40 times higher for female-to-male individuals [7, Table S1]) and significantly elevated all-cause morbidity and mortality, with survival curves between transitioned adults and their cisgender matched controls markedly diverging at the 10-year mark and beyond.

A more recent long-term Swedish study also failed to find that either hormones [39••] or surgery [8••, 40•] improved long-term mental health outcomes of gender dysphoric adults. Originally, the surgical outcomes showed some promise [39••]; however, the methodology was found to be deeply flawed [8••], and upon reanalysis of the surgery data, it emerged that not only did those who refrained from surgery fare no worse, but they also had half as many serious suicidal attempts [40•]. This difference did not reach the threshold of statistical significance, but the apparent doubling in serious suicide attempts among surgically transitioned individuals, as compared to gender-dysphoric controls who did not have surgery, is clinically meaningful and problematic.

Yet another long-term Dutch follow-up of transitioned individuals concluded that "suicide death risk is higher in trans people than in the general population" and that suicide deaths occurred during every stage of transitioning"—from those who were still in the evaluation phase, to those who underwent complete gender transition [41, p. 486].

Two recent US-based publications highlighted high rates of mental health problems, including depression, anxiety, substance abuse disorder, suicidality, cardiovascular disease, obesity, cancer, and sexually transmitted infections such as HIV, HPV, syphilis, and hepatitis C in community samples of adults who identify as transgender [42, 43]. Although community samples can suffer from extensive methodological problems [44], there is little debate about the high burden of physical and mental health illness in this population. The explanations offered for these health disparities focus on minority stress, discrimination, and barriers to obtaining health care including fear of mistreatment in health facilities [42, 43]. Conspicuously absent from the discussion is the possibility that the mental health of some trans persons may be intrinsically compromised.

The position that poor mental health problems are either merely co-occurring with, or a direct result of the experience of "gender incongruence"—with no acknowledgement of the possibility of reverse causation —is reinforced in the WPATH "Standards of Care 8" Assessment section for adults, which states that uncontrolled mental health problems should only rarely impede the provision of hormones and surgery [31, p. 37]. While the adolescent chapter acknowledges the difficulties of working with adolescents who have psychiatric illnesses, the focus is on controlling problems just enough to ensure that young patients can provide valid consent to gender reassignment, participate in postoperative care, and adhere to ongoing hormone treatment [31]. The predominance of pre-existing mental health problems prior to the onset of gender dysphoria in youth [29], and the implications for the future durability of a transgender identity as youth mature, is not considered. In 2022, two prominent gender specialists expressed concern that trans-identifying adolescents are too quickly diagnosed and rushed to irreversible body-modifying interventions [45, 46].

Collision of Ethical Principles

When treating transgender-identified adolescents, clinicians invariably confront three ethical principles—above all, do no harm (nonmaleficence); act in the patient's best interests (beneficence); and respect of patient autonomy [47]. These principles uncomfortably collide in the minds of many clinicians. There seems to be no simple resolution.

To avoid *harm*, clinicians conceptualize the specific physiologic, medical, social, and psychological dangers that parents and patients need to understand, attempt to avoid, or accept. Here are examples from each danger category associated with medical gender transition: sexual dysfunction and infertility [49, 50]; shortened lifespan due to increased medical morbidity [7, 51]; difficulties in romantic partnerships [52, 53]; substance abuse and addiction [54]. Advocates of the medical transition of youth point to the harms of "doing nothing" to stop natural puberty, which subjects youth to distress and necessitates more invasive procedures later in life to "undo" the irreversible effects of puberty on the body [55]. Unlike the risks of transition-associated harms which have been demonstrated, avoidance of *future harms* by undergoing a medical transition in adolescence remains at best an unproven theory. Blocking puberty at Tanner stage 2 not only removes the possibility of fertility preservation [15], but also greatly complicates future genital surgeries due to insufficient tissue [56]. The death of one of the 70 youths in the famous "Dutch study" [5] due to complications from genital surgery was likely a direct consequence of early puberty blockade [57•].

To ensure *beneficence*, clinicians need to understand the benefits of gender transition, when they appear, and the extent to which they endure over time. Initially, a high level of satisfaction is expected as desired changes such as softened skin or, conversely, facial hair appear [58••]. Surgery can further improve appearance and satisfaction, although its rate of complications is significant [59, 60], and it does not clearly improve mental health [7, 8••]. However, at some point, the interventions reach their limit. While the face, chest, and/or genitals can be surgically altered, overall skeletal size or hand size will continue to appear incongruent, and dysphoria may persist [61].

To respect patient *autonomy*, clinicians need to determine when an adolescent has the cognitive maturational capacity and life experience to consent to potentially irreversible medical and surgical interventions. However, because of the maturational capacities of children or young adolescents, it is the parents who are actually exercising the autonomy. This can be seen in families in which parents support transition and those who do not. As soon as parents consent to the first stage of gender transition, a child's future medical transition trajectory is virtually assured [62•, 63•]. While children "assent" to the interventions, recent research about the capacity of adolescents to make decisions related to future reproductive function is not reassuring [64].

Clash of Value Systems

Absent certainty about the optimal treatment of the high number of youth currently presenting with gender dysphoria [23••], decisions are made based on core values.

Those who insist that a young person has the right to receive any medical intervention they desire now, and the right to regret that intervention later, privilege *autonomy* above all else. The "patient autonomy" argument is compromised by the very young age of the many affected patients, and a common tendency among gender-affirming providers to exaggerate the benefits of the practice, while downplaying the risks and uncertainties [1•, 20].

Those who advocate for sharply curbing the practice of medical interventions in gender-diverse minors because they view the practice as a major source of iatrogenic harm, privilege the principle of *non-maleficence*.

The two positions on the issue of youth gender transition also distinctly clash over the value of *beneficence*. Each side claims they are pursuing beneficence, but sharply disagree on the solution: one side insists that the most benefit is derived by undergoing a transition as early in puberty as possible to achieve the best possible cosmetic outcomes, while the other asserts that achieving cognitive maturity, emotional stability, and obtaining life experiences (including sexual experiences) prior to making the decision to undergo irreversible transition will provide the most long-term benefit for affected individuals.

Significance of Regret and Detransition

Proponents of gender-transitioning youth insist the benefits of the practice are self-evident even if systematic reviews of evidence cannot detect them. To support their view, they quote exceedingly low regret rates of less than 1–2% [65, 66]. This implies that 98–99% of transitioned individuals are happily situated throughout their lives. This conclusion is inaccurate, for three reasons.

First, follow-up studies exploring regret and quality of life suffer from very high rates (20–60%) of loss to follow-up [67], which means the most adversely affected, including dissatisfied, sick, or deceased patients, may be lost to follow-up at a disproportionately high rate. *Second*, these rates were obtained from individuals transitioning under much different circumstances than the ones found today. They were mature adults who passed rigorous psychological screenings, which today are viewed as "discriminatory gatekeeping."

Third, and perhaps most important, is the question of how these studies defined regret. Each study's methodology differed, but generally speaking, regret has been traditionally defined very narrowly as a request for legal document change or a return to the same clinic that facilitated the original transition to start medical detransition. Even when these criteria were met, not every study would consider someone who wanted to reverse their transition as a regretter. For example, Keira Bell, arguably the most famous young adult regretter, whose case led the UK to reevaluate their approach to gender dysphoric youth, would not have been counted as a regretter in frequently-cited "low regret" studies [65]. This is because the studies required regretters to have had their gonads removed, while the only surgery Keira received was a double mastectomy.

Regret

Regret is a common, if not universal, human experience. Individuals who underwent medical transition are no exception. Regret does not preclude benefits, which typically appear first. The "honeymoon period" can last from several months to several years [68], with adverse effects emerging 8–10 years following transition [65, 69] among mature adult transitioners. Among the more recently transitioning cohorts comprised primarily of youth, there appears to be a shorter time to regret and a subsequent desire to detransition, around 3–6 years on average, with longer time to regret and detransition among biological males [70•, 71].

There are many contributing factors to regret. Many teens consenting to gender reassignment lack sexual experiences [72] and few anticipate wanting to have children in the future [64]. Later, as sexual dysfunction because of hormones, surgery, or anxiety about physical intimacy becomes a recurrent experience, regret appears. Reproductive regret can be significant, as was evident in the data presented at WPATH Symposium [73, 74••].

Strained intrafamilial bonds, inability to find a stable relationship, the experience of discrimination, need for ongoing medical care, substance use to quell anxiety and depression—matters that they may have been warned about—begin to create waves of regret. Some eventually express regret over not having had a chance to explore their concerns in psychotherapy before they transitioned [70•, 71].

There must be a hierarchy of intensity of regret related to the situations patients ultimately find themselves in. The most extreme form of regret is post-transition suicide and suicide attempts. Individuals who undergo medical detransition to restore the body to its pre-transitioned state are also high on this hierarchy. Lower on this hierarchy are those who regret their transitions but due to the irreversible changes to their bodies' anatomy and function, adaptively choose to make the best of their lives without detransitioning. Regret and acceptance can co-exist.

Detransition

Physicians providing gender transition of youth claim that they have never met a detransitioned patient. This is not

surprising: recent research with detransitioners indicated that three-quarters do not return to the treating providers to tell them about detransition [70•].

Detransition has become much more visible in recent years [70•, 71, 75–83, 84••, 85]. However, it was only recently that the rates of detransition began to be quantified. According to recent UK and US data, 10–30% of recently transitioned individuals detransition a few years after they initiated transition [82, 83, 84••]. Detransition does not invariably mean regret about the original transition. Not all detransitioned individuals have expressed regret. Those who have, are often angry at themselves for their naïve adolescent certainty and disturbed about medical professionals' unconcerned compliance with their requests. A growing number of malpractice lawsuits by regretful youth [85] is likely in the future.

The Reversal of "Gender-Affirming Care"

In the last 36 months, there has been sharply increased scrutiny of the practice of youth gender transition worldwide. Systematic reviews of evidence from Europe failed to demonstrate the hoped-for meaningful improvements in youth's mental health functioning and exposed significant risks, including demonstrated risks to bone development [33••, 34••, 35, 36].

Three different studies [1•, 57•, 74••] recently shone a spotlight on the original Dutch research [4, 5], which launched the experimental practice of pediatric gender transition into mainstream medical practices shortly after its publication. The studies argued that the Dutch research failed to demonstrate any clinically significant changes in standard measures of psychological health and that the main finding of the resolution of gender dysphoria was likely invalid due to the reversal of the scale scoring between baseline and follow-up [1•, 74••]. The Dutch research also raised serious ethical questions, as nearly all the youth in the Dutch research who were transitioned and became sterile had been same-sex attracted at baseline [57•]. Overall, the researchers deemed the Dutch studies unfit for clinical or policy decision-making due to the high risk of methodological bias [1•, 74••].

Commensurate with these conclusions, in the last 3 years, three European countries—Finland, Sweden, and England—have reversed their unquestioning belief in "affirmative care" by setting new national health policies that prioritize mental health interventions as the first and often only treatment available outside of clinical research settings [86, 87••, 88].

This reckoning has also begun in France, Australia, and the US state of Florida, and most recently, Norway [89–92]. Many US state laws have been introduced to limit or ban gender transitions of youth [93]. The reluctance of the US medical societies to recognize the apparent problems with medical "gender affirmation" of youth may have contributed to the unfortunate and preventable politicization of this complex issue.

Conclusions

Fulfilling the diagnostic criteria for gender dysphoria (DSM) or gender incongruence (ICD) in children or adolescents today does not predict its persistence in the future. Doctors may be incorrect in their assumptions about the causes, persistence, and future trajectory of adolescent gender dysphoria. The rapidly rising numbers of gender dysphoric youth treated with hormones and surgeries and the delayed onset of regret mean that the scale of possible iatrogenic harm will not be known for several years.

The evidence base for gender-affirming interventions is sparce and of very low quality. While the evidence of benefits is highly uncertain, the harms to sexual and reproductive functions are certain, and many uncertainties about the long-term health effects exist. As a result, it is hard to ethically justify continuing to use hormones and surgeries as first-line "treatment" for gender dysphoric youth.

Political arguments relying on social justice, civil rights, and freedom of expression are compelling and powerful in the public arena. Few mental health professionals would argue against these vital human rights. Nonetheless, they tend to complicate clinicians' consideration of how to respond to gender dysphoric adolescents and their families.

Parents want to know, "Where is this identity coming from?" "What about my child's previous difficulties?" and critically, "Will transition give my child the best chance for a happy and fulfilling life?" Clinicians are ethically bound to honestly represent the uncertainty of the current state of knowledge, rather than asserting that body modification is the best, safest, and most effective treatment. When a concerned family seeks our counsel, they are seeking our knowledge, not our political ideation and beliefs.

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Data Availability Data sharing is not applicable as no new data were generated or analyzed during this study.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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group of gender dysphoric individuals who underwent surgery, and a "control" group gender dysphoric individuals who refrained from surgery. The new analysis showed no statistically significant differences in long-term mental health outcomes measures between the two. It also revealed twice as many serious suicidal attempts in the group that underwent surgery compared to the controls, although the difference did not rise to the level of statistical significance, likely because the sample was underpowered.

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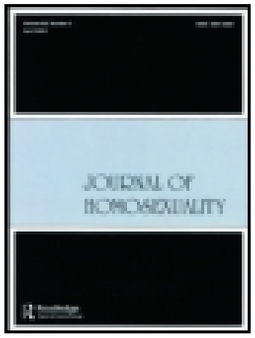

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Detransition-Related Needs and Support: A Cross-Sectional Online Survey

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Detransition-Related Needs and Support: A Cross-Sectional Online Survey

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ABSTRACT

The aim of this study is to analyze the specific needs of detransitioners from online detrans communities and discover to what extent they are being met. For this purpose, a cross-sectional online survey was conducted and gathered a sample of 237 male and female detransitioners. The results showed important psychological needs in relation to gender dysphoria, comorbid conditions, feelings of regret and internalized homophobic and sexist prejudices. It was also found that many detransitioners need medical support notably in relation to stopping/changing hormone therapy, surgery/treatment complications and reversal interventions. Additionally, the results indicated the need for hearing about other detransitioners' experiences and meeting each other. A major lack of support was reported by the respondents overall, with a lot of negative experiences coming from medical and mental health systems and from the LGBT+ community. The study highlights the importance of increasing awareness and support given to detransitioners.

KEYWORDS

Detransition; gender dysphoria; gender identity; cross-sex hormones; detransitioners; transgender; transition; support

Introduction

In recent years, there has been an increasing interest in the phenomenon of detransition. Many testimonies have been shared by self-identified detransitioners online and detrans communities have formed on social media. This phenomenon started to attract the attention of scholars, who have emphasized the need for research into the specific needs of this group (e.g., Butler & Hutchinson, 2020; Entwistle, 2020; Hildebrand-Chupp, 2020). A few case studies have been conducted in order to explore individual experiences of detransition (Pazos-Guerra et al., 2020; Turban & Keuroghlian, 2018). The latter studies highlighted the complexity of detransition experiences but did not provide sufficient data to assess the general needs and characteristics of detransitioners. The current study aims to explore this issue in more depth and to serve as a basis for future research on the phenomenon of detransition.

To date there has been little agreement on a definition of the word "detransition." As explained by Expósito-Campos (2021), this term has been used interchangeably to refer to what he perceives to be two distinctive situations: in

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the first, the detransitioning individual stops identifying as transgender; in the second, they do not. It is therefore necessary here to clarify exactly what is meant when writing about detransition.

In this paper, I will be using the following concepts: "medical detransition," "social detransition" and (male or female) "detransitioner." Medical detransition refers to the process of ceasing/reversing the medical aspects of one's medical transition. This might include stopping or changing hormone therapy and undergoing reversal surgeries, among others. Likewise, social detransition refers to the process of changing/undoing the social aspects of one's social transition. For example, it might include presenting oneself as one's birth sex again, changing one's post-transition name or going back to using the pronouns associated with one's birth sex.

The term "detransitioner" will be used here to refer to someone who possibly underwent some of these medical and/or social detransition steps and, more importantly, who identifies as a detransitioner. It is important to add this dimension, because the act of medical/social detransition can be performed by individuals who did not cease to identify as transgender and who do not identify as detransitioners or as members of the detrans community. Furthermore, some individuals might identify as detransitioners after having ceased to identify as trans, while not being in a position to medically or socially detransition due to medical or social concerns. As Hildebrand-Chupp (2020) puts it: "[B]ecoming a detransitioner involves a fundamental shift in one's subjective understanding of oneself, an understanding that is constructed within these communities." (p.802). More qualitative research should be conducted in order to better understand how members of the detrans community define themselves and make sense of their own detransition process. However, this goes beyond the scope of this study.

The creation of support and advocacy groups for detransitioners in recent years (e.g., DetransCanada, n.d., Detrans Voices, n.d., The Detransition Advocacy Network, n.d., Post Trans, n.d.) testifies to the formation of a detrans community whose members have specific needs. Scholars and clinicians have recently started raising concerns around the topic (e.g., Butler & Hutchinson, 2020; Entwistle, 2020; Hildebrand-Chupp, 2020; Marchiano, 2020). However, little research has been done specifically into the characteristics of this seemingly growing community.

Two informal surveys conducted by detransitioners (Hailey, 2017; Stella, 2016) have explored the demographics and (de)transition experiences of members of online female detrans communities. These will constitute interesting points of comparison in the discussion section of the current research.

The purpose of this exploratory study is to offer an overview of the current needs of detransitioners from online detrans communities, which will hopefully serve as a useful basis for further experimental studies around the topic of detransition. The current research primarily seeks to address the following

questions: What are the current needs of detransitioners? What support is given to detransitioners in order to fulfil these needs?

Methods

Procedure

A cross-sectional survey was conducted, using online social media to recruit detransitioners. Access to the questionnaire was open from the 16th of November until the 22nd of December 2019. Any detransitioner of any age or nationality was invited to take part in the study. The survey was shared by Post Trans (www.post-trans.com)—a platform for female detransitioners—via public posts on Facebook, Instagram and Twitter. Participants were also recruited through private Facebook groups and a Reddit forum for detransitioners (r/detrans). Some of the latter platforms were addressed exclusively to female detransitioners. The purpose of the study was presented as gaining a better understanding of detransitioners' current needs. Potential participants were asked to fill out the form and share it to fellow detransitioners. All participants have been fully anonymized.

Everyone who answered "yes" to the question "Did you transition medically and/or socially and then stopped?" was selected in the study. The individual questionnaires of the 9 respondents who answered "no" to this question were looked at closely, in order to assess whether they should be included in the study. Eight of them were added to the final sample, as their other answers indicated that their experiences lead them to identify as detransitioners.

This research was approved by the Ethics Committee for Noninvasive Research on Humans in the Faculty of Society and Economics of the Rhine-Waal University of Applied Sciences

Questionnaire design

The questionnaire consisted of 24 questions (see Appendix). The first series of questions was aimed at defining the profile of the respondent (age, sex, country, etc.), the second was asking about relevant aspects of transition and detransition experiences (transition type, gender dysphoria, therapy, medical interventions, reasons for detransitioning etc.), and the third focused on the needs encountered as well as the support (or lack of) received during the process of detransition (medical, psychological, legal and social needs and support).

Most of the items were multiple-choice questions. The conception of the multiple choices was based on observations drawn from several detransition online resources and forums. An open "other" category was available when relevant for the respondents to write in possibly lacking options. The survey

was designed to leave a lot of free space to add answers, since the detransition population is still very much under-researched and there is a lot to learn from each of its members. This is why a more qualitative approach was taken for the last question notably, leaving an open field for adding comments about the support—or lack of—received while detransitioning. This qualitative data was analyzed through the identification of recurrent themes, which will be presented in the results section.

Participants

A total of 237 participants were included in the final sample. The large majority was female; 217 female (92%) for 20 male respondents (8%). This was determined based on the answers to the question: "What sex were you assigned at birth?" The average age was 25.02 years (SD = 7.72), ranging from 13 to 64. The mean age of female detransitioners (M = 24.38; SD = 6.86) was lower than that of male detransitioners (M = 31.95; SD = 12.26).

Around half of the sample (51%) reported coming from the United States and close to a third from Europe (32%). Fifteen respondents are from Canada (6%), twelve from Australia (5%), and one from each of the following countries: Brazil, Kazakhstan, Mexico, Russia and South Africa.

Close to two thirds (65%) transitioned both socially and medically; 31% only socially. A few respondents rightly criticized the fact that the option of medically transitioning only was not available in the questionnaire. The absence of this option needs to be kept in mind when looking at the results.

Around half (51%) of the respondents started socially transitioning before the age of 18, and a quarter (25%) started medically transitioning before that age as well. The average age of social transition was 17.96 years (17.42 for females; 23,63 for males) (SD = 5.03) and that of medical transition was 20.70 years (20.09 for females; 26.19 for males) (SD = 5.36). Fourteen percent of the participants detransitioned before turning 18. The average age of detransition was 22.88 years (22.22 for females; 30.00 for males) (SD = 6.46). The average duration of transition of the respondents (including both social and medical transition) was 4.71 years (4.55 for females; 6.37 for males) (SD = 3.55).

Eighty percent of the male detransitioners underwent hormone therapy, compared to 62% for female detransitioners. Out of the respondents who medically transitioned, 46% underwent gender affirming surgeries.

Results

For sake of clarity, the results will be presented based on the three categories mentioned above in the methods section: profile of the respondents, relevant aspects of transition and detransition and, finally, detransition-related needs and support. The qualitative results will be displayed at the end of this section.

Profile of the respondents

Most of the information related to the profile of the respondents can be found in the methods section. The sample showed a high prevalence of comorbidities, considering that over half of the participants (54%) reported having had at least 3 diagnosed comorbid conditions (out of the 11 conditions listed in the survey—see Table 1). The most prevalent diagnosed comorbid conditions are depressive disorders (69%) and anxiety disorders (63%), including PTSD (33%) (see Table 1).

Relevant aspects of transition and detransition

A great majority of the sample (84%) reported having experienced both social and body dysphoria. (Social dysphoria being defined as a strong desire to be seen and treated as being of a different gender, and body dysphoria as a strong desire to have sex characteristics of the opposite sex/rejection of your own sex). Eight percent reported having experienced only body dysphoria, 6% only social dysphoria and 2% neither of them.

Forty-five percent of the whole sample reported not feeling properly informed about the health implications of the accessed treatments and interventions before undergoing them. A third (33%) answered that they felt partly informed, 18% reported feeling properly informed and 5% were not sure.

The most common reported reason for detransitioning was realized that my gender dysphoria was related to other issues (70%). The second one was health concerns (62%), followed by transition did not help my dysphoria (50%), found alternatives to deal with my dysphoria (45%), unhappy with the social changes (44%), and change in political views (43%). At the very bottom of the list are: lack of support from social surroundings (13%), financial concerns (12%) and discrimination (10%) (see Figure 1).

34 participants (14%) added a variety of other reasons such as absence or desistance of gender dysphoria, fear of surgery, mental health concerns related

Table 1. Number of participants with comorbid conditions.

Comorbid condition	Diagnosed	Suspected
Depressive disorder	163 (70%)	32 (14%)
Anxiety disorder	149 (63%)	43 (18%)
Post-traumatic stress disorder	79 (33%)	63 (27%)
Attention deficit disorder	57 (24%)	50 (21%)
Autism spectrum condition	47 (20%)	61 (26%)
Eating disorder	46 (19%)	58 (25%)
Personality disorder	40 (17%)	26 (11%)
Obsessive compulsive disorder	35 (15%)	44 (19%)
Polycystic ovary syndrome (only females)	22 (10%)	13 (6%)
Dissociative identity disorder	14 (6%)	23 (10%)
Schizo-spectrum disorder	5 (2%)	9 (4%)

"Diagnosed" and "Suspected" were mutually exclusive categories.

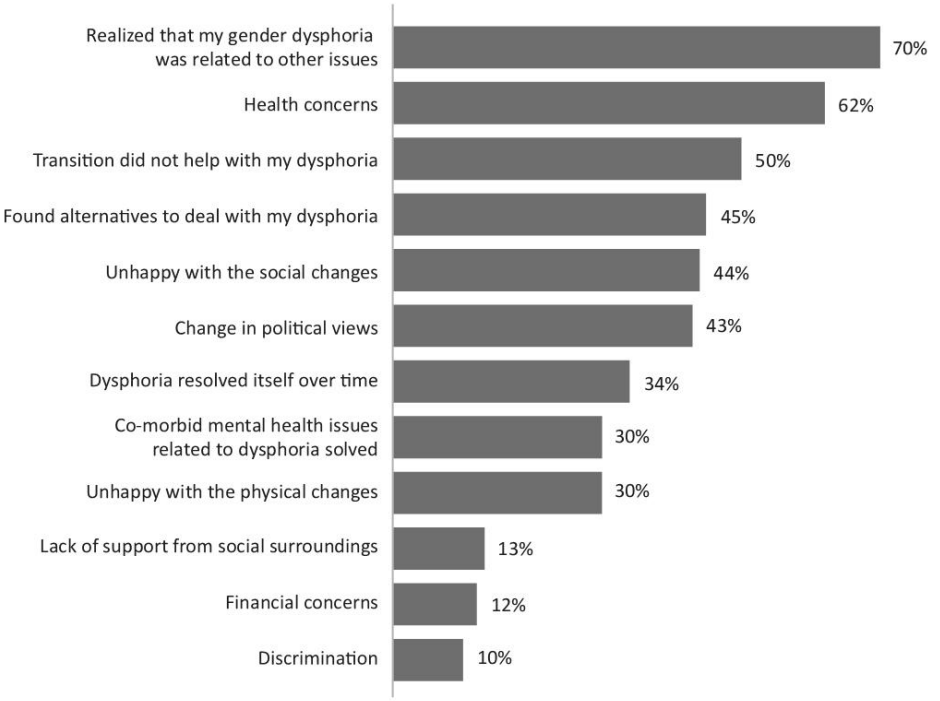

Figure 1. Reasons for detransitioning.

to treatment, shift in gender identity, lack of medical support, dangerosity of being trans, acceptance of homosexuality and gender non-conformity, realization of being pressured to transition by social surroundings, fear of surgery complications, worsening of gender dysphoria, discovery of radical feminism, changes in religious beliefs, need to reassess one's decision to transition, and realization of the impossibility of changing sex.

Detransition-related needs and support

The different types of needs were divided into four categories in the questionnaire: medical, psychological, legal and social needs.

Medical needs

The most commonly chosen answer was the need for receiving accurate information on stopping/changing hormonal treatment (49%), followed by receiving help for complications related to surgeries or hormonal treatment (24%) and receiving information and access to reversal surgeries/procedures (15%). Forty-six percent of the participants reported not having any detransition-related medical need. Sixteen respondents (7%) added another non-listed answer, such as tests to determine current reproductive health, information

about long-term effects of hormone therapy, about the health consequences of having had a full hysterectomy and about pain related to chest binding.

Psychological needs

Psychological needs appeared to be the most prevalent of all, with only 4% of the respondents reporting not having any. The answers working on comorbid mental issues related to gender dysphoria and learning to cope with gender dysphoria; finding alternatives to medical transition are at the top of the list, both with 65%. Below that, learning to cope with feelings of regret (60%), followed by learning to cope with the new physical and/or social changes related to detransitioning (53%) and learning to cope with internalized homophobia (52%). Thirty-four respondents (14%) added another non-listed answer, such as trauma therapy, learning how to deal with shame and internalized misogyny, how to cope with rejection from the LGBT and trans communities and how to deal with the aftermath of leaving a manipulative group. Other answers disclosed the need for help recovering from addictive sexual behavior related to gender dysphoria, psychosexual counseling and peer support.

Legal needs

More than half of the sample (55%) reported not having any detransition-related legal need. The main legal need expressed was changing back legal gender/sex marker and/or name (40%), followed by legal advice and support to take legal action over medical malpractice (13%). Five respondents (2%) added another non-listed answer, such as employment legal aid and support to take legal action for having been forced to go through a sterilization.

Social needs

The big majority of the respondents reported a need for hearing about other detransition stories (87%). The second most common answer was getting in contact with other detransitioners (76%), followed by receiving support to come out and deal with negative reactions (57%). Thirty-three respondents (14%) added another non-listed answer such as being accepted as female while looking male, help navigating social changes at the workplace, building a new social network, more representation of butch lesbians, real life support and finding a community.

When looking at from whom the respondents received support while transitioning and detransitioning, it appears that the biggest source of help comes from online groups/forums/social media for both transition and detransition (65%). The support received from friends, partner(s) and family is a little higher for detransition (64%) than for transition (56%).

Only 8% of the respondents reported having received help from an LGBT+ organization while detransitioning, compared to 35% while transitioning.

Similarly, 5% reported having received help from a trans-specific organization while detransitioning, compared to 17% while transitioning.

A total of 29% reported having received support for their detransition from the medical professionals that helped them during their transition. In contrast, 38% sought support from a new therapist/doctor. A part of the sample reported not receiving help from anybody for transitioning (8%) and for detransitioning (11%) (see Figure 2).

Around half of the respondents (51%) reported having the feeling of not having been supported enough throughout their detransition, 31% said they did not know and 18% answered that they had received enough support.

Qualitative results

Two open-ended questions allowed participants to write more extensively about their needs and support in the questionnaire. The first one enabled the respondents to write about any additional need that they encountered while detransitioning, while the second asked about the support—or lack of—that they had received.

Additional comments about needs

Thirty-seven participants (16%) left various comments about specific needs that they experienced during their transition and detransition.

Several respondents expressed the need for different types of therapy and counseling for dealing with issues of dissociation, childhood sexual trauma, anorexia, relationship issues and body issues caused by irreversible gender affirming surgeries. A participant also mentioned the importance of help revolving around suicide prevention for those who need it.

Additionally, someone emphasized the need for therapists to validate the feelings of being harmed by transition that some detransitioners experience, rather than dismissing or opposing them. Similarly, another respondent expressed the need for non-judgmental medical practitioners. Someone else described the need for as much medical autonomy as possible and a total freedom from psychology and psychiatry. A participant also explained that she would have needed to know the health risks of chest binding before experiencing them.

Furthermore, two respondents highlighted the need to look into individual experiences and needs without forcing them into a rigid model of transition. Others wrote about the need for more information about detransition and a better general understanding of this phenomenon.

Lastly, a few female detransitioners expressed the need for being valued as a woman, for learning about feminist theories and for more gender-nonconforming role models.

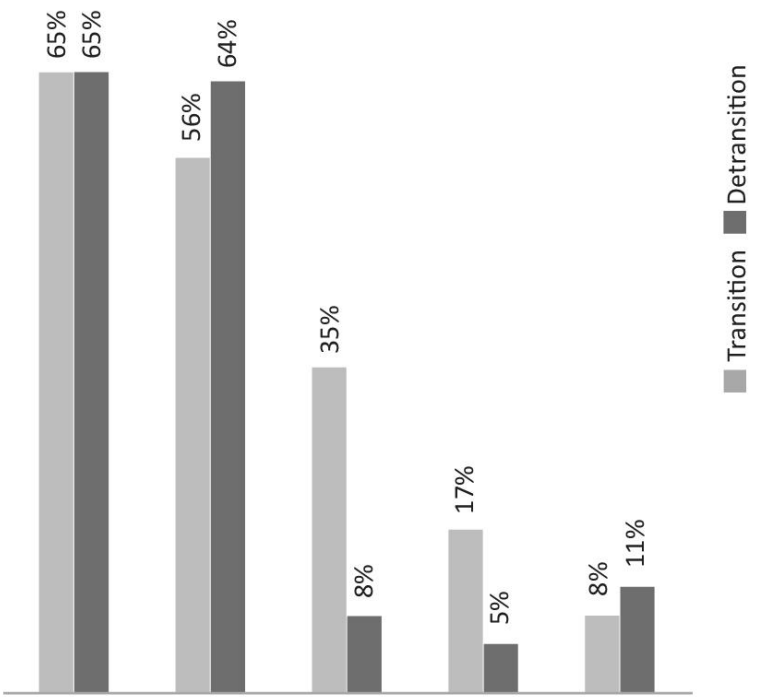

Figure 2. Comparison between transition and detransition support.

Additional comments about support

At the end of the questionnaire, a second open-ended question invited the participants to give further comments about the support—or lack of—that they had received during their detransition process.

A third of the participants (34%) answered this question, often with long and detailed accounts of their personal experiences with regard to this aspect. The most common themes identified were: loss of support from the LGBT community and friends (see Table 2), negative experiences with medical professionals (see Table 3), difficulty to find a detrans-friendly therapist and lack of offered alternatives to transitioning (see Table 4), as well as isolation and lack of overall support. Some gave more positive accounts of the support that they had received from their family, partners and friends and emphasized their important role.

A recurrent theme in the answers was a sense amongst respondents that it was very difficult to talk about detransition within LGBT+ spaces and with trans friends. Many expressed a feeling of rejection and loss of support in relation to their decision to detransition, which lead them to step away from LGBT+ groups and communities (see Table 2).

Whilst a minority reported positive experiences with medical professionals during their detransition, most participants expressed strong difficulties finding the help that they needed during their detransition process. Participants' own descriptions of the nature of these difficulties can be found in Table 3.

Another reported issue was the difficulty of finding a therapist willing and able to look at the factors behind gender dysphoria and to offer alternatives to transitioning. Some respondents highlighted the fact that they were

Table 2. Extracts about experiences of exclusion from LGBT+ communities.

"The LGBT+ community doesn't support detransitioners and I lost all LGBT+ friends I had because they deemed me transphobic/terfy, only non-LGBT+ friends supported me."
"Where I live detransitioners are seen bad for most of the LGBT community, so it's hard to talk about it with freedom."
"It is unacceptable that, at least in my experience, detransition is not something allowed to be talked about in LGBT spaces."
"Only lesbians and feminists helped me. The trans and queer community demonized me and ostracized me for my reidentification."
"I lost a lot of support and attracted a lot of hostility from trans people when I detransitioned socially. I also deal with a lot of people assuming that my dysphoria is gone entirely/cured because I have detransitioned socially, and decided not to go through with medical transition."
"Lgbt organizations don't want to talk about detransition. I did not feel welcome at lgbt events after I detransitioned."
"Telling my trans friends that I'm desisting is nearly impossible. The community is too toxic to allow any kind of discussion about alternatives to transition, sources of dysphoria beyond 'that's just who you are', or stories about detransitioners."
"I've been shunned by most of my trans identifying friends. I had to leave my old doctor, therapist and LGBT group out of shame and embarrassment."
"I have several de-trans friends whom had permanent body alterations they regretted that led to more dysphoria and eventually their suicides. Biggest factors were a lack of medical support and outright rejection from LGBT organisations/communities."
"I still have transgender friends who don't want me to talk about detransition. They're okay with me being detransitioned, but they don't want me to criticize transition or discuss the negative side effects of HRT."

Table 3. Extracts about negative medical experiences during detransition.

"I needed gender and transition experienced providers to assist with my medical detransition, but none of them seemed to understand or provide the type of care I needed, despite my self-advocacy. I got better care from providers outside of the LGBT and transgender specialty clinics."
"I still struggle to find a doctor who has knowledge of detransition and the effects HRT had on me/my best course of action since stopping."
"When I first brought up wanting to stop T to my doctor, they were very dismissive and condescending about it."
"My experience with transition left me with greatly diminished faith in medicine and zero faith in the mental health profession. I now avoid all doctors most of the time (unless I am convinced they are the only way to access a strongly evidence-based treatment or diagnostic tool for a condition which causes more suffering than doctors themselves- many do not) and totally avoid any contact with mental health professionals, and am much better off for it."
"As soon as I 'detransed' I was discharged from all gender services, despite asking for help in dealing with sex dysphoria should it arise again."
"I had no medical help from the doctor who prescribed me T, she wanted nothing to do with me."
"The team that transitioned you is not willing to help you detransition. You need new doctors."
"The medical team that helped me transition is helpful, but they are also causing a lot of hassle, which is very frustrating for me. Like for example they keep me stuck with my male sex marker for I don't know how long, and they don't believe I'm sure enough that I want to detransition, because they think I should have consistent 'reverse dysphoria' and mine kinda isn't so consistent."
"My hormone blocker implant is several years old and is only barely still functioning but they will not remove it. It's in my arm and I have no contact with the doctor because he shut down his business apparently."

Table 4. Extracts about the difficulty of finding a detrans-friendly therapist.

"It is very hard to find a therapist who won't tell you it's 'internalized transphobia' or that dealing with dysphoria in other ways is 'conversion therapy'."
"The only thing that comes to mind is one of the therapists I had, who pushed me not to detransition."
"Therapists are unprepared to handle the detrans narrative and some that I have seen since detransitioning have pushed the trans narrative. Some therapists couldn't tell the difference between being transgender and having internalized misogyny and homophobia."
"I could have benefitted from counseling but don't trust psychologists ideological bias."
"I struggled to find a therapist who supported questioning my trans identity and considering alternatives to transitioning; most only knew how to encourage transitioning and reinforced the harmful ideas that led to my wrongly identifying as FtM in the first place."
"I was doubtful that transition would help my dysphoria before beginning and was assured by multiple professionals that transition was The Solution and proven to work for everyone with dysphoria. A 'gender specialist' therapist flat-out told me that transitioning was the only method of reducing dysphoria that worked when I expressed my desperation for an alternate solution."
"The gender clinic I went to basically told me that the only way to deal with gender dysphoria was transitioning even when I told them I wanted to detransition."
"I struggled to find a therapist who supported questioning my trans identity and considering alternatives to transitioning; most only knew how to encourage transitioning and reinforced the harmful ideas that led to my wrongly identifying as FtM in the first place."
"The biggest issue for me was that when I did try to get support from a therapist or psychologist on entangling the actual reasons behind my dysphoria and how to deal with it, and deal with detransitioning, nobody had any clue or any experience, so they couldn't help me. Which made me even feel more lonely, and made detransitioning so much harder mentally than transitioning was."

cautious regarding the possible ideological bias or lack of knowledge of therapists.

Overall, most respondents explained that their detransition was a very isolating experience, during which they did not receive enough support. However, some participants emphasized the fact that the support that they received from their family, partners and friends, as well as online detrans groups and lesbian and feminist communities was extremely important and valuable to them.

Discussion

The present study was designed to better understand the needs of detransitioners, as well as the support—or lack of—that they are currently receiving. In order to do so, members of online detrans communities were recruited to answer a survey, in which questions were asked about their demographics, their transition and detransition experiences and the needs that they faced as well as the support that they received while detransitioning. In this section, I will discuss the results in relation to the main research question of the current study: What are the needs of detransitioners?

The sample surveyed appeared to be mostly female, young, from Western countries, with an experience of both social and medical transition and a high prevalence of certain comorbid conditions. The current study found that most detransitioners stopped transitioning before their mid-twenties, after an average of 4 years of transition. This observation is consistent with that made by Stella (2016) in her informal study on female detransitioners. The average transition age of the 203 respondents of her survey was 17.09 years, compared to 17.42 years in female detransitioners of the current study. The average detransition age of her sample was 21.09 years, compared to 22.22 years here.

Another finding of the current study was that a majority of the sample underwent hormone therapy (62% for females; 80% for males) and 45% of those who medically transitioned underwent gender affirming surgeries. This is likely to have implications in terms of the medical needs faced by this population. Close to half of the sample (49%) reported a need for receiving accurate information on stopping or changing hormone therapy, and almost a quarter (24%) reported the need for receiving help for complications related to surgeries or hormone therapy. The latter finding is concerning when looking at the negative medical experiences described by respondents in Table 3. Participants recounted situations in which their doctors either did not believe them, did not listen to them, refused them services, or simply did not have the required knowledge to help them during their detransition process. These experiences had a negative impact on some of the participants' trust in healthcare providers.

Similarly, the current study suggested that detransitioners have important psychological needs. This was made visible on the one hand through the fact that a majority of respondents (65%) reported the need for help in working on comorbid mental conditions related to gender dysphoria and in finding alternatives to medical transition. Other needs were reported by a majority of participants, such as learning to cope with feelings of regret (60%), learning to cope with the new physical and/or social changes related to detransitioning (53%) and learning to cope with internalized homophobia (52%). On the other hand, the high prevalence of comorbid conditions described in Table 1 might also be an indicator of important psychological needs. These results are similar

to that found by Hailey (2017) in her informal survey of comorbid mental health in detransitioned females. In her study, 77% reported a diagnosis of a depressive disorder (compared to 70% here), 74% of the sample reported a diagnosis of an anxiety disorder (compared to 63% here), 32% reported a diagnosis of PTSD (compared to 33% here) and 22% reported a diagnosis of an eating disorder (compared to 19% here). This is also very concerning information considering the descriptions made by detransitioners about the difficulty of finding a therapist willing or able to help them, and of finding alternative ways to deal with gender dysphoria after detransitioning (see Table 4).

The majority (84%) of the respondents reported having experienced both body and social gender dysphoria. Half of the sample (50%) later reported having decided to detransition due to the fact that their transition did not alleviate their gender dysphoria. Others (45%) reported having found alternative ways to deal with their gender dysphoria (see Figure 1). These results highlight the necessity to start looking into alternative solutions for treating gender dysphoria, in order to help those who did not find medical and/or social transition fulfilling.

In addition to that, 70% of the sample reported having realized that their gender dysphoria was related to other issues. Further research should be conducted in order to identify the ways in which other issues such as comorbid mental health conditions, trauma or internalized misogyny and homophobia possibly interact with gender dysphoria, and what can be done to alleviate them.

Furthermore, the high prevalence of autism spectrum condition (ASC) (20%) found in detransitioners in the current study, which is supported by Hailey (2017) findings (15%), also constitutes an interesting avenue for future research. Previous studies have provided evidence suggesting a co-occurrence of gender dysphoria and ASC (e.g., De Vries, Noens, Cohen-Kettenis, Van Berckelaer- Onnes, & Doreleijers, 2010; Glidden, Bouman, Jones, & Arcelus, 2016; VanderLaan et al., 2014; Van Der Miesen, Hurley, & De Vries, 2016; Zucker et al., 2017), which might explain the high number of detransitioners with an ASC diagnosis found in the current study.

In general, support given to detransitioners seems to be very poor at the moment, considering the fact that only 18% of the participants in the current study reported having received enough support during their detransition.

Based on the results of the current study, it appears that detransitioning is often accompanied by a break with LGBT+ communities. Only 13% of the participants reported having received support from an LGBT+ or trans-specific organization while detransitioning, compared to 51% while transitioning (see Figure 2). In addition to that, many respondents described experiences of outright rejection from LGBT+ spaces due to their decision to detransition (see Table 2). Looking at studies showing the positive role

of peer support and trans community connectedness on the mental health of its members (Johnson & Rogers, 2019; Pflum, Testa, Balsam, Goldblum, & Bongar, 2015; Sherman, Clark, Robinson, Noorani, & Poteat, 2020), it seems reasonable to suspect that this loss of support experienced by detransitioners must have serious implications on their psychological well-being.

Fortunately, the current study shows that detransitioners have access to other sources of support, online (groups, forums, social media) and in their social surroundings (family, partners and friends) (see Figure 2). Online groups and websites for detransitioners seem to be particularly important in light of the social needs expressed by the respondents of the current study. An overwhelming majority of respondents reported the need for hearing about other detransition stories (87%) and for getting in contact with other detransitioners (76%). Detransitioners need platforms and spaces where they can connect with each other and build a community. This point is best illustrated by the following account of one participant: "I found the peer support I received through other detransitioned women to be totally adequate and feel I benefited substantially from learning how to exist without institutional validation."

Conclusion

The aim of the present research was to examine detransitioners' needs and support. The four categories of needs (psychological, medical, legal and social) that were created for sake of clarity in the survey were a simplification of the real complexity of the experiences made by detransitioners and they have their limitations. Nonetheless, these categories enabled the current study to uncover the fact that most detransitioners could benefit from some form of counseling and in particular when it comes to psychological support on matters such as gender dysphoria, comorbid conditions, feelings of regret, social/physical changes and internalized homophobic or sexist prejudices. Medical support was also found to be needed by many, in order to address concerns related to stopping/changing hormone therapy, surgery/treatment complications and access to reversal interventions. Furthermore, the current study has shown that detransitioners need spaces to hear about other detransition stories and to exchange with each other.

Unfortunately, the support that detransitioners are receiving in order to fulfill these needs appears to be very poor at the moment. Participants described strong difficulties with medical and mental health systems, as well as experiences of outright rejection from the LGBT+ community. Many respondents have expressed the wish to find alternative treatments to deal with their gender dysphoria but reported that it was impossible to talk about it within LGBT+ spaces and in the medical sphere.

These accounts are concerning and they show the urgency to increase awareness and reduce hostility around the topic of detransition among healthcare providers and members of the LGBT+ community in order to address the specific needs of detransitioners.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Appendix.

Full Questionnaire

(1) How old are you?
(2) What country are you living in?
(3) What sex were you assigned at birth?
- Female
- Male
- Other:

(4) How do you see yourself now? (Tick all that apply)
- Woman
- Man
- Trans man
- Trans woman
- Female detransitioner
- Male detransitioner
- Non binary
- Other:

(5) Did you transition socially and/or medically and then stopped?
- Yes, both
- Only socially
- No

(6) Did you experience body dysphoria and/or social dysphoria? (Body dysphoria = strong desire to have sex characteristics of the opposite sex/rejection of your own sex; Social dysphoria = strong desire to be seen and treated as being of a different gender)
- Yes, both
- Only body dysphoria
- Only social dysphoria
- No

(7) Who helped you starting your social/medical transition? (Tick all that apply)
- A medical team specialized in transition
- An LGBT+ organization
- A trans-specific organization
- A therapist/doctor
- Online groups/forums/social media
- Friends, partner(s) and family
- Nobody
- Other:

(8) If you transitioned medically, how long were you in therapy before getting any hormones or surgeries? (in months; write 0 if none)

(9) During your transition, did you undergo some of the following interventions/treatments? (Tick all that apply)
- Hormone blockers
- Feminizing hormone treatment
- Masculinizing hormone treatment
- Gender affirming surgery(ies)
- No

(10) Do you feel like you were properly informed about the health implications of these treatments/interventions before undergoing them?
- Yes
- Partly
- No
- I am not sure

(11) What were the reasons that made you stop transitioning/detransition? (Tick all that apply)
- Health concerns
- Change in political views
- Transition did not help with my dysphoria
- Lack of support from social surroundings
- Discrimination
- Financial concerns
- Dysphoria resolved itself over time
- Unhappy with the physical changes
- Unhappy with the social changes
- Comorbid mental health issues related to dysphoria solved
- Realized that my gender dysphoria was related to other issues
- Found alternatives to deal with dysphoria
- Other:

(12) Were you diagnosed with or do you suspect having any of the following conditions?

	Diagnosed	Suspected	No
Attention Deficit (Hyperactive) Disorder			
Autism Spectrum Condition			
Anxiety Disorders			
Depressive Disorders			
Dissociative Identity Disorder			
Eating Disorders			
Obsessive Compulsive Disorder			
Polycystic Ovary Syndrome			
Post Traumatic Stress Disorder			
Personality Disorders			
Schyzo-spectrum Disorder			

(13) If you transitioned socially, at what age did you start?
(14) If you transitioned medically, at what age did you start?
(15) At what age did you start detransitioning/stop transitioning?
(16) What are the medical needs that you had while detransitioning/stopping your transition? (Tick all that apply)
- Receiving accurate information on stopping/changing hormonal treatment
- Receiving information and access to reversal surgeries/procedures
- Receiving help for complications related to surgeries or hormonal treatment
- None
- Other:

(17) What are the psychological needs that you had while detransitioning/stopping your transition? (Tick all that apply)
- Learning to cope with gender dysphoria; finding alternatives to medical transition
- Learning to cope with the new physical and/or social changes related to detransitioning
- Learning to cope with feelings of regret
- Learning to cope with internalized homophobia
- Working on comorbid mental issues related to gender dysphoria
- None
- Other:

(18) What are the legal needs that you had while detransitioning/stopping your transition? (Tick all that apply)
- Changing back legal gender/sex marker and/or name
- Legal advice and support to take legal action over medical malpractice
- None
- Other:

(19) What are the social needs that you had while detransitioning/stopping your transition? (Tick all that apply)
- Getting in contact with other detransitioners
- Receiving support to come out and deal with negative reactions
- Hearing about other detransition stories
- None
- Other:

(20) Is there any other need that you would like to mention?

(21) Which of these needs did you get support for?

	Full support	Partly	Not at all	Not needed
Medical needs				
Psychological needs				
Legal needs				
Social needs				

(22) From whom? (Tick all that apply)
- The medical team that helped me transition
- An LGBT+ organization
- A trans specific organization
- The therapist/doctor who supported me through my transition
- A new therapist/doctor
- Online groups/forums/social media
- Friends, partner(s) and family
- Nobody
- Other:

(23) Do you feel like you have received enough support throughout your detransition process overall?
- Yes
- No
- I don't know

(24) If you have any comment concerning the support/lack of support you received during your detransition, you can write it here.

Chapter 2: What Is Evidence-Based Medicine?

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Introduction

Evidence-based medicine (EBM) involves conscientiously working with patients to help them resolve (sometimes) or cope with (often) problems related to their physical, mental, and social health. The EBM approach necessitates awareness and understanding of clinical research *evidence*. For those involved in making health care decisions, EBM encompasses creating implementation strategies to ensure practice evidence that is well grounded in best evidence research summaries.

At the core of EBM is a care and respect for patients who will suffer if clinicians fall prey to muddled clinical reasoning and to neglect or misunderstanding of research findings. Practitioners of EBM strive for a clear and comprehensive understanding of the evidence underlying their clinical care and work with each patient to ensure that chosen courses of action are in that patient's best interest. Practicing EBM requires clinicians to understand how uncertainty about clinical research evidence intersects with an individual patient's predicament and preferences. In this chapter, we outline how EBM proposes to achieve these goals and, in so doing, define the nature of EBM.

Three Fundamental Principles of EBM

Conceptually, EBM involves 3 fundamental principles. First, optimal clinical decision making requires awareness of the best available evidence, which ideally will come from systematic summaries of that evidence. Second, EBM provides guidance to decide whether evidence is more or less trustworthy —that is, how confident can we be of the properties of diagnostic tests, of our patients' *prognosis*, or of the impact of our therapeutic options? Third, evidence alone is never sufficient to make a clinical decision. Decision makers must always trade off the benefits and *risks*, *burden*, and costs associated with alternative management strategies and, in doing so, consider their patients' unique predicament and *values and preferences*.[1]

Best Evidence Summaries

In 1992, Antman et al[2] published an article that compared the recommendations of experts for management of patients with myocardial infarction to the evidence that was available at the time the recommendations were made. Figures 2-1 and 2-2 summarize their results in *forest plots*. Both are cumulative *meta-analyses*: the first of thrombolytic therapy for myocardial infarction and the second for lidocaine antiarrhythmic therapy. In both cases, the line in the center represents an *odds ratio* of 1.0 (treatment is neither beneficial or harmful). As in any forest plot, the dots represent the best estimates of *treatment effect* (often from individual studies; in this case from the totality of accumulated evidence), and the associated lines represent the 95% *confidence intervals* (CIs).

FIGURE 2-1

Thrombolytic Therapy in Acute Myocardial Infarction

Abbreviation: CI, confidence interval; RCTs, randomized clinical trials.

This is a cumulative meta-analysis of thrombolytic therapy for myocardial infarction. The line down the center, the odds ratio, equals 1.0. The dots represent best estimates, and the lines around the dots are 95% CIs. The numbers on the left side of the figure are trials and patient totals across trials.

Early on, the CIs are very wide. By 10 trials, it appears therapy reduces mortality, but the effect is still uncertain. By 30 trials, the effect seems secure. However, 40 000 more patients were enrolled after the answer was in. Why?

The right side of the figure displays current reviews and textbook recommendations as data accumulated. Recommendations are in favor ("Yes"), against ("No"), or "Not mentioned." Two key points: (1) at the same time, experts disagreed, and (2) it took 10 years for experts to catch up with evidence.

Adapted from Antman et al.[2]

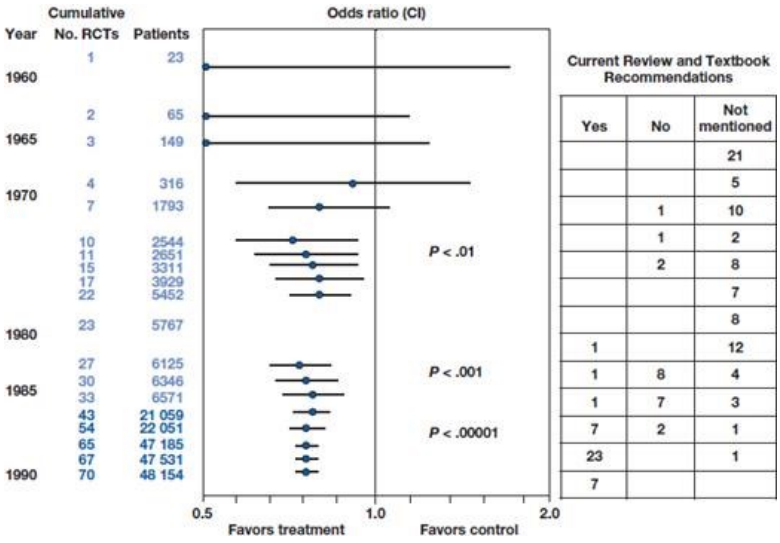


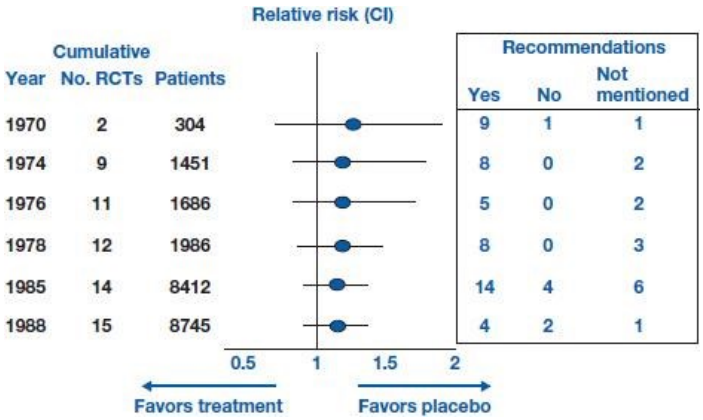
FIGURE 2-2

Prophylactic Lidocaine in Acute Myocardial Infarction

Abbreviation: CI, confidence interval; RCTs, randomized clinical trials.

This slide shows a cumulative meta-analysis of the effect of prophylactic lidocaine in preventing death from myocardial infarction. In this case, there is never any evidence of benefit. Ultimately, harm is not proved, but there clearly is no benefit. Most experts, however, were recommending therapy despite RCT evidence. Also, as in Figure 2-1, there was a lot of disagreement among experts.

Adapted from Antman et al.[2]



The "Patients" column presents the total number of patients enrolled in all *randomized clinical trials* (RCTs) conducted to the date specified in the "Year" column—the reason we call it a cumulative meta-analysis. In both figures, early on, with relatively few patients, the CIs are wide, but they progressively narrow as new trials were reported.

For the thrombolytic example, by 10 trials and approximately 2500 patients, it appears that thrombolytic therapy reduces mortality, but the CIs are still wide enough to permit residual uncertainty. By 30 trials and more than 6000 patients, the reduction in odds of death of approximately 25% seems

secure.

Despite this apparently definitive result, additional trials that enrolled 40000 patients—half of whom did not receive the benefits of life-prolonging thrombolytic therapy—were conducted. Why was this necessary?

The right side of each figure, which presents the guidance expressed in then-current reviews and textbooks as the data were accumulating, provides the answer to this question. Until approximately a decade after the answer was in, there was considerable disagreement among experts, with many recommending against, or not mentioning, thrombolytic therapy. To the detriment of patients who did not receive thrombolytic therapy during this period, it took a decade for the experts to catch up with the evidence.

Figure 2-2 tells a perhaps even more disturbing story. This cumulative meta-analysis reveals that there was never any RCT evidence that suggested a lower mortality with prophylactic lidocaine after myocardial infarction—indeed, *point estimates* suggested an increase in death rate. Nevertheless, although we once again see widespread disagreement among the experts, most texts and reviews were recommending prophylactic lidocaine during the 2 decades during which the RCT evidence was accumulating.

Why the expert disagreement, the lag behind the evidence, and the recommendations inconsistent with the evidence? These stories come from the era before *systematic reviews* and meta-analyses were emerging in the late 1980s. If the evidence summaries presented in the forest plots had been available to the experts, they would have grasped the benefits of thrombolytic therapy far earlier than they did and abandoned prophylactic lidocaine far earlier. Indeed, following EBM principles that limit reliance on biologic rationale and place far more emphasis on empirical evidence (see Chapter 3, Evidence-Based Medicine and the Theory of Knowledge), the experts may never have started using lidocaine.

Rational clinical decisions require systematic summaries of the best available evidence. Without such summaries, clinicians—expert or otherwise—will be unduly influenced by their own preconceptions and by unrepresentative and often lower-quality evidence. This, the first principle of EBM, immediately raises another question: “How does one recognize the best evidence?”

Guides to Confidence in Estimates

Summaries of the best evidence for diagnosis, prognosis, or treatment present evidence, respectively, for how to interpret test results, predict patients' likely fate, or understand the impact of alternative management strategies. Sometimes, such evidence is trustworthy—we have high confidence in estimates of test properties, patients' prognosis, or treatment effects. At other times, limitations in evidence leave us uncertain. Evidence-based medicine provides guidance to distinguish between these situations and the range of confidence between them.

Historically, EBM answered the question, “What is the best evidence?” with *hierarchies of evidence*, the most prominent of which was the hierarchy related to evidence that supported therapeutic interventions (Figure 2-3). Issues of diagnosis or prognosis require different hierarchies. For studies of the accuracy of diagnostic tests, the top of the hierarchy includes studies that enrolled patients about whom clinicians had diagnostic uncertainty and that undertook a *blind* comparison between the candidate test and a *criterion standard* (see Chapter 18, Diagnostic Tests, and Chapter 20, Prognosis). For prognosis, prospective *observational studies* accurately documenting *exposures* and outcomes and following up all patients during relevant periods would sit atop the hierarchy.

FIGURE 2-3

Hierarchy of Evidence

Because we would like to optimally individualize patient care, n-of-1 randomized clinical trials are at the top of the hierarchy of study designs, followed by conventional randomized trials. Next in the hierarchy are observational studies; we should try to find studies that focus on outcomes important to the patient. Next, if there are no clinical studies available, we may look at basic scientific research, although caution must be used in extrapolating the results to the clinical setting. Clinical experience is at the bottom of the hierarchy, either your own or that of colleagues or experts.

Returning to the hierarchy of therapy, noting the limitations of human intuition,[3] EBM places the unsystematic observations of individual clinicians lowest on the hierarchy. Noting that predictions based on physiologic experiments are often right but sometimes disastrously wrong, EBM places such experiments at the next step up in the hierarchy. Observational studies that measure the apparent impact on *patient-important outcomes* and RCTs constitute the next 2 steps up the hierarchy of evidence.

All of the sources of evidence mentioned thus far involve generalizations from groups of patients to an individual, and all are limited in this regard. The same strategies that minimize *bias* in conventional therapeutic trials that involve multiple patients, however, can guard against misleading results in studies that involve single patients.[4] In the *n-of-1 RCT*, a patient and clinician are blind to whether that patient is receiving active or *placebo* medication. The patient makes quantitative ratings of troublesome symptoms during each period, and the n-of-1 RCT continues until both the patient and the clinician conclude that the patient is or is not obtaining benefit from the target intervention. An n-of-1 RCT can provide definitive evidence of treatment effectiveness in individual patients[5,6] and is thus at the top of the evidence hierarchy. Unfortunately, n-of-1 RCTs are restricted to chronic conditions with treatments that act and cease acting quickly and are subject to considerable logistic challenges. We therefore must usually rely on studies of other patients to make inferences regarding our patient.

This hierarchy is far from absolute, and a more sophisticated framework has emerged for judging confidence in estimates of effect. Table 2-1 summarizes that framework, formulated by the *GRADE* (*Grading of Recommendations Assessment, Development and Evaluation*) Working Group, originally to provide an approach to the development of *clinical practice guidelines.*[7,8] The GRADE approach involves rating our confidence in estimates of the effects of health care interventions (also referred to as quality of evidence) as high, moderate, low, or very low. Consistent with the previous hierarchy approach, in the GRADE guidance, RCTs begin as high confidence and observational studies begin as low confidence. We lose confidence in a body of RCT evidence, however, if studies have major problems in design and execution (*risk of bias*); results are *imprecise, inconsistent*, or *indirect* (eg, the population of interest differs from the population studied—see Chapter 13.4, Surrogate Outcomes); or we have a high suspicion of *publication bias* (see Chapter 23, Understanding and Applying the Results of a Systematic Review and Meta-analysis). When a body of RCT evidence suffers from a number of these limitations, the confidence in estimates may be low or even very low.

TABLE 2-1

Confidence Assessment Criteria[8]

Study Design	Confidence in Estimates	Lower If ...[a]	Higher If ...[a]
Randomized trial	High	Risk of bias −1 Serious −2 Very serious	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient
	Moderate	Inconsistency −1 Serious −2 Very serious	
Observational study	Low	Indirectness −1 Serious −2 Very serious	
	Very low	Imprecision −1 Serious −2 Very serious	
		Publication bias −1 Likely −2 Very likely	

[a]Minus and plus signs refer, respectively, to rating down and rating up confidence in estimates. The 1 refers to rating down or up by 1 level (eg, from high to moderate or moderate to high), and the 2 refers to rating down or up by 2 levels (eg, high to low or low to high).

Similarly, if treatment effects are sufficiently large and consistent, the GRADE approach allows for moderate or even high confidence ratings from carefully conducted observational studies. For example, observational studies have allowed extremely strong inferences about the efficacy of insulin in diabetic ketoacidosis or that of hip replacement in patients with debilitating hip osteoarthritis.

The EBM approach implies a clear course of action for clinicians addressing patient problems. They should seek the highest-quality evidence available to guide their clinical decisions. This approach makes it clear that any claim that there is no evidence for the effect of a particular treatment is a non sequitur. The available evidence may warrant very low confidence—it may be the unsystematic observation of a single clinician or physiologic studies that point to mechanisms of action that are only indirectly related—but there is always evidence.

Evidence Is Never Enough to Drive Clinical Decision Making

First, picture a woman with chronic pain from terminal cancer. She has come to terms with her condition, resolved her affairs, said her good-byes, and wishes to receive only palliative care. She develops severe pneumococcal pneumonia. Evidence that antibiotic therapy reduces morbidity and mortality from pneumococcal pneumonia warrants high confidence. This evidence does not, however, dictate that this patient should receive antibiotics. Her values—emerging from her comorbidities, social setting, and beliefs—are such that she would prefer to forgo treatment.

Now picture a second patient, an 85-year-old man with severe dementia who is mute and incontinent, is without family or friends, and spends his days in apparent discomfort. This man develops pneumococcal pneumonia. Although many clinicians would argue that those responsible for his decision making should elect not to administer antibiotic therapy, others would suggest that they should. Again, evidence of treatment effectiveness does not automatically imply that treatment should be administered.

Finally, picture a third patient, a healthy 30-year-old mother of 2 children who develops pneumococcal pneumonia. No clinician would doubt the wisdom of administering antibiotic therapy to this patient. This does not mean, however, that an underlying value judgment has been unnecessary. Rather, our values are sufficiently concordant, and the benefits so overwhelm the risk of treatment that the underlying value judgment is unapparent.

By values and preferences, we mean the collection of goals, expectations, predispositions, and beliefs that individuals have for certain decisions and their potential outcomes. The explicit enumeration and balancing of benefits and risks that are central to EBM bring the underlying value judgments involved in making management decisions into bold relief.

Acknowledging that values play a role in every important patient care decision highlights our limited understanding of how to ensure that decisions are consistent with individual and, where appropriate, societal values. As we discuss further in the final section of this chapter, developing efficient processes for helping patients and clinicians work together toward optimal decisions consistent with patient values and preferences remains a frontier for EBM.

Next, we comment on additional skills that clinicians must master for optimal patient care and the relation of those skills to EBM.

Clinical Skills, Humanism, and EBM

In summarizing the skills and attributes necessary for *evidence-based practice*, Box 2-1 highlights how EBM complements traditional aspects of clinical expertise. One of us, an intensive care specialist, developed a lesion on his lip shortly before an important presentation. He was concerned and, wondering whether he should take acyclovir, proceeded to spend the next 30 minutes searching for and evaluating the highest-quality evidence. When he began to discuss his remaining uncertainty with his partner, an experienced dentist, she cut short the discussion by exclaiming, “But, my dear, that isn't herpes!”

BOX 2-1

Knowledge and Skills Necessary for Optimal Evidence-Based Practice

- Diagnostic expertise
- In-depth background knowledge
- Effective searching skills
- Effective critical appraisal skills
- Ability to define and understand benefits and risks of alternatives
- In-depth physiologic understanding that allows application of evidence to the individual
- Sensitivity and communication skills required for full understanding of patient context
- Ability to elicit and understand patient values and preferences and work with patients in shared decision making

This story illustrates the necessity of obtaining the correct diagnosis before seeking and applying research evidence regarding optimal treatment. After making the diagnosis, the clinician relies on experience and background knowledge to define the relevant management options. Having identified those options, the clinician can search for, evaluate, and apply the best evidence regarding patient management.

In applying evidence, clinicians rely on their expertise to define features that affect the applicability of the results to the individual patient. The clinician must judge the extent to which differences in treatment (for instance, local surgical expertise or the possibility of patient *nonadherence*) or patient characteristics (such as age, comorbidity, or the patient's personal circumstances) may affect estimates of benefit and risk that come from the published literature.

We note that some of these skills—the sensitivity to the patient's unique predicament and the communication skills necessary for shared decision making—are often not typically associated with EBM. We believe they are, in fact, at the core of EBM. Understanding the patient's personal circumstances is of particular importance and requires advanced clinical skills, including listening skills and compassion. For some patients, incorporation of patient values for major decisions will mean a full enumeration of the possible benefits, risks, and inconveniences associated with alternative management strategies. For some patients and problems, this discussion should involve the patient's family. For other problems—the

discussion of *screening* with prostate-specific antigen with older male patients, for instance—attempts to involve family members might violate cultural norms.

Some patients are uncomfortable with an explicit discussion of benefits and risk and object to clinicians placing what they perceive as excessive responsibility for decision making on their shoulders. In such cases, it is the physician's responsibility to develop insight to ensure that choices will be consistent with the patient's values and preferences while remaining sensitive to the patient's preferred role in decision making.

Additional Challenges for EBM

Busy clinicians—particularly those early in their development of the skills needed for evidence-based practice—will find that they often perceive time limitations as the biggest challenge to evidence-based practice. This perception may arise from having inadequate access to various evidence-based resources. Fortunately, a tremendous array of sophisticated evidence-based information is now available for clinicians working in high-income countries, and the pace of innovation remains extremely rapid (see Chapter 5, Finding Current Best Evidence).

Access to preprocessed information cannot, however, address other skills required for efficient evidence-based practice. These skills include formulating focused clinical questions, matching prioritized questions to the most appropriate resources, assessing confidence in estimates, and understanding how to apply results to clinical decision making. Although these skills take time to learn, the reward in terms of efficient and effective practice can more than compensate.

Another challenge for evidence-based practice is ensuring that management strategies are consistent with patients' values and preferences. In a time-constrained environment, how can we ensure that patients' involvement in decision making has the form and extent that they desire and that the outcome reflects their needs and desires? Evidence-based medicine leaders are now making progress in addressing these challenges.[9,10]

This book deals primarily with decision making at the level of the individual patient. Evidence-based approaches can also inform health care policy making, day-to-day decisions in public health, and systems-level decisions, such as those facing hospital managers. In each of these areas, EBM can support the appropriate goal of gaining the greatest health benefit from limited resources.

In the policy arena, dealing with differing values poses even more challenges than in the arena of individual patient care. Should we restrict ourselves to alternative resource allocation within a fixed pool of health care resources, or should we consider expanding health care services at the cost, for instance, of higher tax rates for individuals or corporations? How should we deal with the large body of observational studies that suggest that social and economic factors may have a larger influence on the health of populations than health care provision? How should we deal with the tension between what may be best for a person and what may be optimal for the society of which that person is a member? The debate about such issues is at the core of evidence-based policy making in health care; it also has implications for decision making at the individual patient level.

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

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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

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Abbreviations: BMD, bone mineral density; DSD, disorder/difference of sex development; DSM, Diagnostic and Statistical Manual of Mental Disorders; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; MHP, mental health professional; VTE, venous thromboembolism.

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).

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1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal 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

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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

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Table 1. Definitions of Terms Used in This Guideline

Biological sex, biological male or female: 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.
Cisgender: This means not transgender. An alternative way to describe individuals who are not transgender is "non-transgender people."
Gender-affirming (hormone) treatment: See "gender reassignment"
Gender dysphoria: 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.
Gender expression: 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.
Gender identity/experienced gender: 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.
Gender identity disorder: 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."
Gender incongruence: 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.
Gender variance: See "gender incongruence"
Gender reassignment: 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.
Gender-reassignment surgery (gender-confirming/gender-affirming surgery): These terms refer only to the surgical part of gender-confirming/gender-affirming treatment.
Gender role: 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.
Sex designated at birth: This refers to sex assigned at birth, usually based on genital anatomy.
Sex: 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.
Sexual orientation: 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.
Transgender: 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.
Transgender male (also: trans man, female-to-male, transgender male): This refers to individuals assigned female at birth but who identify and live as men.
Transgender woman (also: trans woman, male-to female, transgender female): This refers to individuals assigned male at birth but who identify and live as women.
Transition: 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.
Transsexual: 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).

Reference: American Psychiatric Association (14).

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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 ≥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 |⊕⊕◯◯)

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 |⊕⊕◯◯)

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 μg/kg/d
- 10 μg/kg/d
- 15 μg/kg/d
- 20 μg/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 μg/24 h (cut 25-μg patch into quarters, then halves)
- 25 μg/24 h
- 37.5 μg/24 h
- Adult dose = 50–200 μg/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 mg/m^2/2 wk (or alternatively, half this dose weekly, or double the dose every 4 wk)
- 50 mg/m^2/2 wk
- 75 mg/m^2/2 wk
- 100 mg/m^2/2 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.

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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

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Table 11. Hormone Regimens in Transgender Persons

Transgender females[a]	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch (New patch placed every 3–5 d)	0.025–0.2 mg/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.

[a]Estrogens used with or without antiandrogens or GnRH agonist.

[b]Not available in the United States.

[c]One thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

[d]Avoid 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. 5α-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 17β-estradiol, or transdermal 17β-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