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Review: Puberty blockers for transgender and gender diverse youth—a critical review of the literature

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Background: Increasingly, early adolescents who are transgender or gender diverse (TGD) are seeking gender-affirming healthcare services. Pediatric healthcare providers supported by professional guidelines are treating many of these children with gonadotropin-releasing hormone agonists (GnRHa), which reversibly block pubertal development, giving the child and their family more time in which to explore the possibility of medical transition. **Methods:** We conducted a critical review of the literature to answer a series of questions about criteria for using puberty-blocking medications, the specific drugs used, the risks and adverse consequences and/or the positive outcomes associated with their use. We searched four databases: LGBT Life, PsycINFO, PubMed, and Web of Science. From an initial sample of 211 articles, we systematically reviewed 9 research studies that met inclusion/exclusion criteria. **Results:** Studies reviewed had samples ranging from 1 to 192 (N = 543). The majority (71%) of participants in these studies required a diagnosis of gender dysphoria to qualify for puberty suppression and were administered medication during Tanner stages 2 through 4. Positive outcomes were decreased suicidality in adulthood, improved affect and psychological functioning, and improved social life. Adverse factors associated with use were changes in body composition, slow growth, decreased height velocity, decreased bone turnover, cost of drugs, and lack of insurance coverage. One study met all quality criteria and was judged 'excellent', five studies met the majority of quality criteria resulting in 'good' ratings, whereas three studies were judged fair and had serious risks of bias. **Conclusion:** Given the potentially life-saving benefits of these medications for TGD youth, it is critical that rigorous longitudinal and mixed methods research be conducted that includes stakeholders and members of the gender diverse community with representative samples.

Key Practitioner Message

- Increasing numbers of early adolescents who are transgender or gender diverse (TGD) and seeking professional help.
- Pubertal development may lead to (a) greater anxiety about sexual identity and (b) suicidal thoughts among TGD.
- Professional organizations, such as the Endocrine Society and the World Professional Association for Transgender Health (WPATH), have recommended the use of puberty-blocking hormones to arrest pubertal development, thus allowing early adolescents and their families more time to consider the possible outcomes of gender reassignment.

What is new?

- This article is a report of a critical and systematic review of literature about the use of puberty-blocking hormones among TGD, the positive, and the negative outcomes associated with their use.
- The findings of this systematic review can guide healthcare professionals in their discussions with TGD youth and their families as they consider the risks and benefits of puberty suppression.

What is significant for clinical practice?

- A summary of current research on the use of puberty-blocking hormones suggests that clinicians follow the guidelines offered by the Endocrine Society and WPATH to enhance the positive outcomes associated with use of these medications.
- Clinicians and researchers should work together to conduct well-designed and rigorous longitudinal and mixed methods studies of TGD youth using GnRHa.

Keywords: Transgender; adolescent; puberty blockers; critical review

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Introduction

Recently, there has been an increase in the number of parents seeking medical advice and care for their early adolescent children who are transgender or gender diverse [TGD] (Bonifacio & Rosenthal, 2015; Turban, 2017). A study of a representative sample of middle school youth in San Francisco using the Youth Risk Behavior Survey (YRBS) showed that 1.3% self-identified as transgender (Shields et al., 2013); in the 2017, YRBS data collected from a nationally representative sample of high school students ($N = 131,901$), 1.8% responded 'Yes, I am transgender', and another 1.6% responded, 'I am not sure if I am transgender' (Johns et al., 2019, p. 68). Compared to their cisgender peers, these gender diverse youth bear a disproportionate burden for mental health problems including substance use and suicide attempt (Lowry et al., 2018).

Hormonal treatment, including the use of puberty suppressing drugs, provides a potentially life-saving solution for these patients, yet for this specific population of patients, the long-term consequences of these drugs are relatively unknown (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Vrouenraets, Fredriks, Hannema, Cohen-Kettenis, & DeVries, 2015). For children and adolescents who experience gender dysphoria (GD), the possibility of receiving this treatment provides hope; however, the lack of longitudinal evidence may lead to barriers in accessing and receiving treatment. Two groups, the World Professional Association for Transgender Health (WPATH, s2011) and the global Endocrine Society in the United States (Hembree et al., 2009, 2017), have provided consensus expert guidelines for the use of puberty-blocking agents in children and early adolescents with GD. The use of these medications, in many early pubertal children, is an important component of gender-affirming care (Edwards-Leeper, Leibowitz, & Sangganjanavanich, 2016). These consensus guidelines have been critical in supporting the work of medical professionals who are balancing clinical judgment and evidence-based research in the care of these patients.

In a descriptive study of the physiological and psychological characteristics of 101 transgender youth between the ages of 12 and 24 years, Olson, Schrager, Belzer, Simons, and Clark (2015) found that these youth were aware of their gender incongruence at a mean age of 8.3 ± 4.5 years, over one-third experienced symptoms of clinical depression, and over half reported having suicidal thoughts at least once and about one in three had made one or more suicide attempts. Liu and Mustanski (2012) followed a community sample of 246 LGBT youth between the ages of 16 and 20 years prospectively and found that previous victimization predicted both self-harm and suicidal ideation. Clearly, the risk of adverse mental and physical outcomes among this population of youth is high. Thus, the need to find a way to prevent such dire consequences is equally high.

Researchers in the Netherlands conducted a qualitative study of 13 early adolescents (five trans girls and eight trans boys) and explored the perceptions of these adolescents (average age of 16 years 11 months) and the professional teams working with them about the use of puberty suppression in the form of gonadotropin-releasing hormone agonists (GnRHa) (Vrouenraets, Fredriks, Hannema, Cohen-Kettenis, & DeVries, 2016). Themes derived from interviews with these adolescents were that relative to using GnRHa for puberty suppression, (a) it is difficult to determine the appropriate age for starting the use of these hormones, (b) long-term effects of using suppression are unknown, and (c) both stereotypes and greater media attention create a social context that can be positive or negative. These themes were compared with data collected previously from professionals working with TGD youth and results in that study revealed that professionals worried more about long-term effects than did the youth, yet the youth worried more about the appropriate age for starting puberty suppression.

The advantages of using puberty suppression in children and adolescents with gender dysphoria have been identified as improving some psychological functioning such as decreased depression and improved global functioning. Identified disadvantages were unpleasant side effects such as hot flashes in AFAB youth treated later in puberty (e.g., Tanner stages 4–5), decreased growth velocity, and increased body mass index (Chew, Anderson, Williams, May, & Pang, 2018). In addition, bone turnover and bone mineral density have been shown to decrease with use of GnRHa, particularly in young transwomen (Vlot et al., 2017). A significant barrier to use of puberty suppressing medications is the high cost of the medications with insurance coverage for treatment of GD in children and early adolescents being highly variable and, in some cases, specific insurance plan exclusions (Stevens, Gomez-Lobo, & Pine-Twaddel, 2015).

The use of puberty suppressing drugs (e.g., gonadotropin-releasing hormone agonists or GnRHa) has long been viewed as the standard of care for children with central precocious puberty (Lee et al., 2014) and adverse physical and psychological effects have been rare (Krishna et al., 2019; Yu, Yang, & Hwang, 2019). GnRHa have also been used in adolescent females with endometriosis with mixed results (DiVasta & Laufer, 2013; Gallagher et al., 2018). Although these uses are beyond the scope of this review, it is important to acknowledge that risks and benefits among these disparate populations could differ.

Purpose

Despite the increase in demand for more healthcare services for TGD youth, research is still in its relative infancy. The purpose of this critical review is to present the current state of research on the use of puberty-blocking hormones in prepubescent TGD children/early adolescents.

Method

As authors of this review, we followed a seven-step method for critical reviews of the literature described by Cooper (2017). The seven steps are as follows: (a) formulate the problem; (b) search the literature; (c) gather information/data from the published studies; (d) evaluate the quality of the studies found; (e) analyze and integrate outcomes of the studies; (f) interpret the evidence found; and (g) present the results. Because there were no human subjects involved, we did not request institutional review board approval. We adhered to the Preferred Reporting

Items for Systematic Reviews and Meta-Analysis (PRISMA) as a guideline for reporting our process and displaying our decision points as shown in Figure 1 (Moher, Liberati, Tetzlaff, Altman, & the PRISMA Group, 2009).

Problem identification

The problem addressed in this review was identified in the introduction as a lack of knowledge about (a) the criteria for using puberty-blocking drugs; (b) the known risks associated with use of these drugs; and (c) the benefits of using such drugs with early adolescents. We specifically sought to answer the following questions relative to TGD early adolescents:

1 What prerequisite criteria (e.g., diagnosis of gender dysphoria; Tanner stage of sexual maturation) are being met before physicians administer gonadotropic-releasing hormone agonists (GnRHa)?

2 What specific drugs are used to suppress puberty in early adolescents?

3 What are the known risks and adverse outcomes of using GnRHa in early adolescents?

4 What have been the positive outcomes of using puberty suppression drugs in early adolescents?

Inclusion/exclusion criteria and literature search

Inclusion/Exclusion Criteria: Our inclusion criteria were that articles had to be either qualitative or quantitative research papers, written in English with a focus on the use of puberty-blocking drugs/hormones in early adolescents (e.g., ages 10–14) who self-identified as transgender or who had a medical diagnosis of gender dysphoria. The researchers had to identify risks and/or benefits associated with the use of these medications. Our exclusion criteria were editorials, letters to the editor, systematic reviews, and opinion pieces.

We consulted a health sciences librarian skilled in searching the literature on healthcare topics. She performed the search using four relevant and accessible databases: LGBT Life,

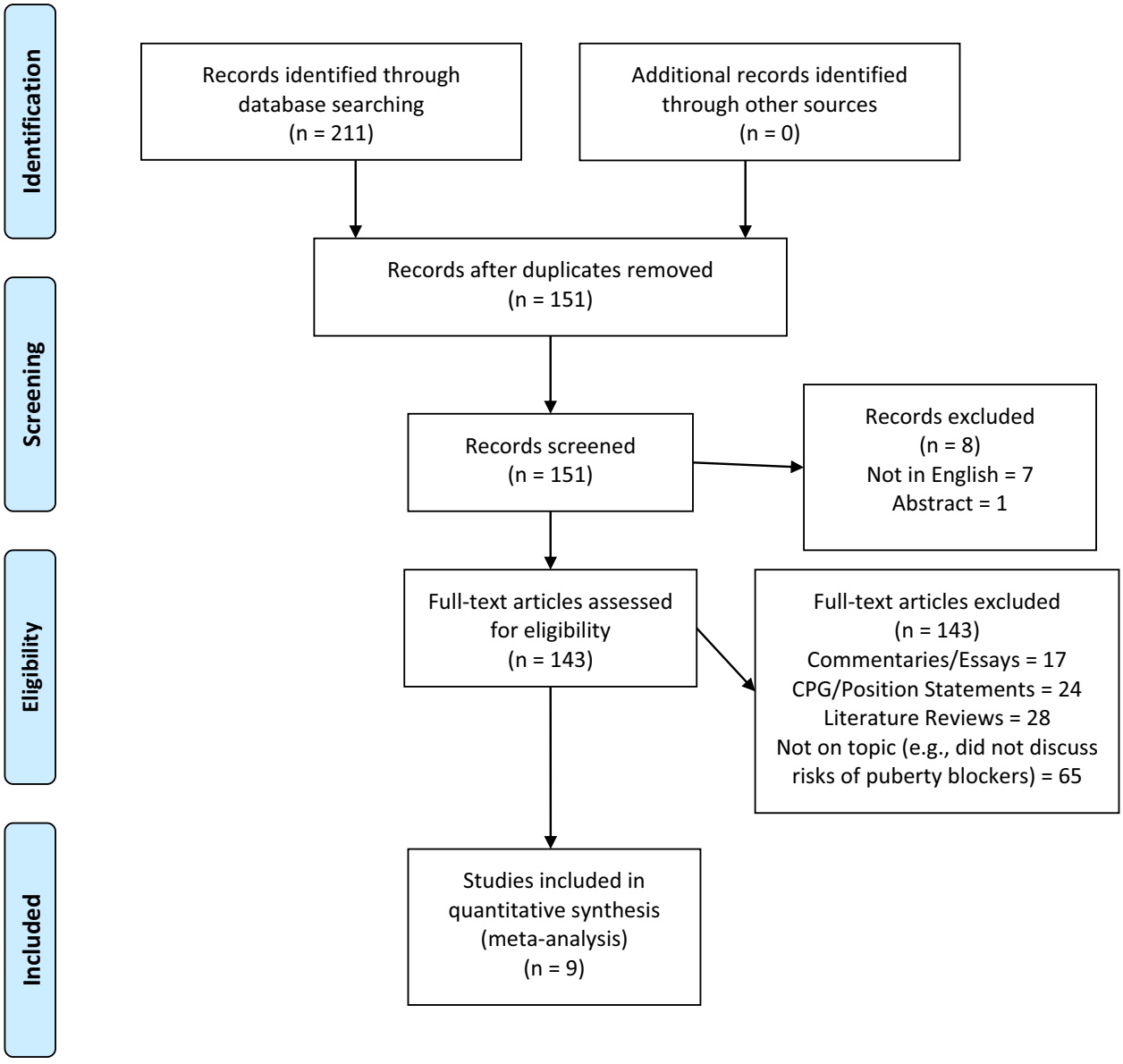

Figure 1. PRISMA flow diagram. CPG, Clinical Practice Guidelines

PsycINFO, PubMed, and Web of Science. Search strategies were composed for each database, using subject headings and keywords to recover articles on transgender persons and puberty blockers, puberty suppressors, or puberty inhibitors. Table 1 details the search terms for each database.

Our search resulted in a sample of $N = 211$ (Figure 1). We first removed duplicates, then divided the identified articles evenly among the first three authors. Using a screening checklist designed specifically for this review, we examined the abstract and the entire published paper to answer the following questions:

1 Was the paper written in English?
2 Was the focus of the paper on transgender youth/children or prepubescent children/early adolescents with gender dysphoria?
3 Did the article focus on the use of puberty-blocking drugs/hormones such as gonadotropin-releasing hormone analog (GnHRa)?
4 Did the authors identify risks and/or benefits associated with the use of these hormones?
5 Did the study use a qualitative or quantitative research design?
6 Was the paper a systematic or integrative literature review?

All papers for which the first five questions were answered affirmatively and the last question was not, were retained for full review.

Data extraction

After screening the articles, we developed a data extraction tool that included the name of the first author and date of the publication, the purpose of the study, a description of the sample (e.g., number and age of participants), prerequisites identified prior to use of puberty-blocking drugs, the names or types of drugs used, the youth's Tanner stage at the time the drugs were first administered, identified risks or adverse outcomes, positive outcomes, and our quality assessment value (see details below, in Step Four). We then extracted data from each article included to describe our sample and to address our research questions.

Evaluation of quality of studies

To determine the quality of each paper, two authors independently completed a checklist for each of the studies, compared their ratings and discussed differences until coming to consensus. We used one of three checklists, depending on the type of study design, to evaluate the quality of the information found in our literature sample and to report any type of bias found in the process. The three checklists were specific for evaluating the quality of retrospective chart reviews (Vassar & Holzmann, 2013), Joanna Briggs Institute (JBI) Critical Appraisal Checklist for cross-sectional and observational studies, and the JBI Critical Appraisal Checklist for Case Reports (Joanna Briggs Institute, 2018). In assessing the quality of retrospective chart reviews, we created a checklist with the 10 questions specified by Vassar and Holzmann (2013) and arbitrarily created ratings of *poor* (1–3 yes answers), *fair* (4–6 yes answers), and *good* (7–10 yes answers). In using the JBI checklists, we computed a percentage of met criteria to determine quality and followed the same rating categories of *poor*, *fair,* and *good*. For all checklists used, if all criteria were met, the study was given a rating of *excellent*.

Analysis of outcomes and interpretation of evidence

Data analyzed for the nine articles included in this review were derived from retrospective chart reviews, case reports, a cross-sectional study, and prospective, observational studies. Thus, no statistical analysis nor meta-analysis could be done. Rather,

Table 1. Terms used to search four databases related to use of puberty blockers for early adolescents

Step	Term(s)
Database: LGBT Life	
1	puberty
2	suppress OR suppression OR suppressing OR suppressor OR suppressors OR inhibit OR inhibitor OR inhibitors OR inhibiting OR block OR blocker OR blockers OR blocking
3	1 AND 2
Database: PsycINFO	
1	transgender OR gender nonconforming OR nonbinary
2	puberty
3	suppress OR suppression OR suppressing OR suppressor OR suppressors OR inhibit OR inhibitor OR inhibitors OR inhibiting OR block OR blocker OR blockers OR blocking
4	2 AND 3
5	1 AND 4
Database: PubMed	
1	('Transgender Persons'[Mesh] OR transgender [Title/Abstract] OR gender [2:17PMitle/Abstract][9:27 AMitle/Abstract] OR nonbinary[Title/Abstract]
2	puberty[Title/Abstract] OR prepuberty[Title/Abstract] OR prepubertal [Title/Abstract] OR prepubescent[Title/Abstract] OR prepubescence[Title/Abstract]
3	blocker[Title/Abstract] OR blockers[Title/Abstract] OR suppressor[Title/Abstract] OR suppressors[Title/Abstract] OR inhibitor [Title/Abstract] OR inhibitors[Title/Abstract] OR hormone suppressor[Title/Abstract]
4	bicalutamide[Title/Abstract] AND anastrozole [Title/Abstract]
5	3 OR 4
6	2 AND 5
7	'Gonadotropin-Releasing Hormone'[Mesh] OR gonadotropin- Releasing hormone[Title/Abstract] OR GnRH[Title/Abstract] OR histrelin[Title/Abstract] OR leuprorelin[Title/Abstract]
8	6 OR 7
9	1 AND 8
Database: Web of Science	
1	transgender OR gender nonconforming OR gender nonconforming OR nonbinary
2	puberty OR prepuberty OR prepuberty OR pubescent OR pubescence
3	suppress OR suppression OR suppressing OR suppressor OR suppressors OR inhibit OR inhibitor OR inhibitors OR inhibiting OR block OR blocker OR blockers OR blocking
4	2 AND 3
5	gonadotropin-releasing hormone OR GnRH or histrelin OR leuprorelin
6	bicalutamide OR anastrozole
7	5 OR 6
8	4 OR 7
9	1 AND 8

data derived to answer our research questions are presented in the next step showing our results.

Results

Our searches yielded a total of 151 unique articles (after all duplicates were removed) related to the search terms. Details of the nine articles retained for review are in Table 2; all were published recently, between 2011 and 2020. Of these, four articles were retrospective chart reviews, two were case reports, one was cross-sectional, one was a prospective study to evaluate the efficacy and safety of using a GnRHa (triptorelin) drug over time in transgender adolescents (Schagen, Cohen-Kettenis, Delemarre-van de Waal, & Hannema, 2016). Sample sizes in these studies ranged from 1 to 192. The samples were 9–35 years of age and included a total of 296 transgender females, assigned male at birth (AMAB) and 404 transgender males, assigned female at birth (AFAB) and 2 who were undecided patients assigned male at birth ($N = 702$). Race/ethnicity was not reported in 6/9 (66.7%) of the studies reviewed. In the other three studies, the vast majority of the samples (96%, 83.5%, and 68.5% respectively) were Caucasian/White.

Prerequisite criteria

The prerequisite criteria that were met before physicians administered GnRHa drugs to early adolescents were not reported in four of the studies (Klaver et al., 2018; Nahata, Quinn, Caltabellotta, & Tishelman, 2017; Turban, King, Carswell, & Keuroghlian, 2020; de Vries, 2011). Other criteria mentioned were as follows: (a) being screened by a mental health professional who made a diagnosis of gender dysphoria (Khatchadourian, Amed, & Metzer, 2014; Vlot et al., 2017); and (b) diagnosis of gender identity disorder or lifelong extreme gender dysphoria and living in a supportive environment (Cohen-Kettenis, Schagen, Steensma, DeVries, & Delemarre-van de Waal, 2011; Schagen et al., 2016); and (c) gender dysphoria and gender incongruence (Schneider et al., 2017).

Table 2. Articles in a critical review of literature on use of puberty blockers in prepubescent child

Author, date	Purpose	Sample	Prerequisites for Drug Use	Tanner Stage at Initiation	Hormones or Drugs Used	Risks or Adverse Outcomes	Positive Outcomes
Cohen-Kettenis et al. (2011)	Case report to describe a 22-year follow-up of FtM treated with GnRH analogs at age 13.	*N* = 1 AFAB; age 35 years. Race/ethnicity not reported.	States 'fulfilled the current criteria for GnRH analog treatment eligibility' (p. 844). Does not explicitly list what these were. Diagnosis of gender identity disorder at age 16 (p. 843).	B3; P3	Triptorelin at age 13.7 years 3.75 mg q 4 weeks IM. Age 18.6 stopped triptorelin and initiated testosterone-ester mixture.	None reported directly for GnRHa use. At age 35 FSH and LH were elevated owing to gonadectomy	At age 35, all anthropomorphic measurements were within normal limits (50th percentile ± 2 *SD*); fasting labs within normal limits. Patient is 'still convinced that his choice to live as a man was the right one' (p. 846).
De Vries et al. (2011)	Prospective follow-up to compare GD and psychological functioning before and after puberty suppression.	*N* = 70 Mean age = 13.6 (1.8) years Race/ethnicity N\not reported	Not provided in this paper.	Not provided in this paper.	GnRHa, but no drug name given.	AFAB had more anxiety and anger and had more problem behaviors than AMAB. GD was not significantly changed over time.	Both AFAB and AMAB showed significant fewer emotional and behavior problems over time. Both also reported decreases in depressive symptoms and increases in global functioning.
Khatchadourian et al. (2014)	Retrospective chart review; describe patient characteristics, treatment, & response	*N* = 84: 45 AFAB; 37 AMAB 2 undecided natal males Ages 11.4–19.8 years. Race/ethnicity not reported.	Screened by mental health professional. Tanner 2 or +. Diagnosis of gender dysphoria by Utrecht Scale or other scales.	Tanner stage 2	GnRHa 14/15 FtM transitioned to testosterone (7 continued GnRHa, 7 discont. GnRHa). GnRHa to 11 MtF (5 rec'd estrogen and 1		13 months = not pursue change. Drug name not provided.

(continued)

Table 2. (continued)

Author, date	Purpose	Sample	Prerequisites for Drug Use	Tanner Stage at Initiation	Hormones or Drugs Used	Risks or Adverse Outcomes	Positive Outcomes
					of these DC'd GnRHa; 1 stopped due to emotional lability; 1 stopped due to heavy smoking. One MtF stopped GnRHa after		
One stopped GnRHa due to mood swings & emotional lability.	Need long-term follow-up studies. FtM patients who undergo mastectomy have more favorable post-op outcomes. Should be told about fertility preservation.						
Klaver et al. (2018)	Retrospective design. Examine how body shape and composition change during treatment with GnRHa	*N* = 192: 71 AMAB 121 AFAB Age 22 years. 3 Asian, 3 Black American, 184 Caucasian (96%)	Diagnosis of gender dysphoria.	Breast stage 2 for girls (age 14.5). Gonad stage 3 for boys (age 15.3)	Sub-q GnRHa 3.75 for 4 weeks. No drug name provided. Added cross-sex hormones at age 16.	Greater changes in body composition (> fat in MtF and < fat in FtM compared to cisgender).	Earlier treatment associated with closer resemblance to desired sex
Nahata et al. (2017)	Retrospective medical record review to examine mental health diagnoses, self-injurious behaviors, school victimization, and rates of insurance for hormone therapy.	*N* = 79: *n* = 28 AMAB *n* = 51 AFAB Ages 9–18 years 83.5% White 6.3% Black 6.3% biracial 2.5% American Indian 1.3% Hispanic	Diagnosis of gender dysphoria and 'readiness' for hormone treatment by psychiatrist (p. 189)	Beginning at Tanner 2–3	27 received GnRHa but no drug name was given.	Cost of GnRHa = up to $25k per year. Only 8 of 27 had insurance coverage	Not reported
Schagen et al. (2016)	Prospective observational study to evaluate efficacy and safety of GnRHa (triptorelin)	*N* = 116: 49 AMAB 67 AFAB Ages 11.1–18.6 years. Race/ethnicity not reported.	Diagnosis of gender identity disorder, lifelong extreme gender dysphoria, psychologically stable, living in supportive environments.	Median Tanner stage at initiation MtF- 4 FtM -	3.75 mg IM Triptorelin (GnRHa) every 4 weeks after initial at 0, 2, 4 week dosing	Decreased alkaline phosphatase - probably related to slowed growth velocity; decrease in lean body mass % and increase in fat %; decreased height velocity.	All subjects had suppressed gonadotropin and sex steroids; testicular volume decreased in MtF and menses ceased in FtM. No sustained creatinine or LFT abnormalities
Schneider et al. (2017)	Longitudinal case report of	*N* = 1 Age 11,	Diagnosis of gender	Tanner stage 2		Global IQ decreased	

(continued)

Table 2. (continued)

Author, date	Purpose	Sample	Prerequisites for Drug Use	Tanner Stage at Initiation	Hormones or Drugs Used	Risks or Adverse Outcomes	Positive Outcomes
	effects of puberty suppression on brain white matter.	FMAB. Race/ethnicity not reported.	dysphoria and gender incongruence.		Leuprorelin 3.75 mg. IM/ every 28 days	slightly, some difficulty in math and exact sciences.	Improvement in affective and social life.
Turban et al. (2020)	Cross-sectional survey to relate access to puberty blockers in adolescence and mental health outcomes in adulthood.	*N* = 89 who received puberty blockers between ages 9 and 16. From national Transgender Survey.	Not provided in this paper.	Not provided in this paper.	Not provided in this paper.	None noted	Decreased lifetime suicidal ideation and past-month psychological distress and binge drinking. Reduced lifetime illicit drug use.
Vlot et al. (2017)	Retrospective study of bone turnover markers and bone density in adolescents receiving GnRHa and later HRT	*N* = 70: 28 AMAB 42 AFAB Ages 11.5–18.6. Race/ethnicity not reported.	Diagnosis of gender dysphoria	FtM - start at T2+; MtF - start testicle volume at least 6–8 ml or when T2-3	Triptorelin 3.75 mg subcutaneously every 4 weeks At 16 yo - testosterone or estradiol added.	Decrease in bone turnover markers ICTP and P1NP, also coincides with decrease in BMAD Z scores primarily in lumbar spine (most hormone sensitive); even after HRT started, in most, pretreatment Z scores were not reached even after 24 months on HRT	Some recovery of BMAD Z scores after HRT started

Abbreviations: AFAB, males, assigned female at birth; AMAB, females, assigned male at birth; GD, gender dysphoria; GnRHa, gonadotropin-releasing hormone agonist.

Drugs used to suppress puberty

The GnRH analogue drug named to suppress puberty in children in four of the reviewed studies was triptorelin (Cohen-Kettenis et al., 2011; Schagen et al., 2016; Vlot et al., 2017) and leuprorelin (Schneider et al., 2017). The other five studies just used the term GnRHa but provided no specific drug name. Gender-affirming drugs such as testosterone and estradiol were mentioned in some studies as added later in the treatment protocols.

Risks/adverse outcomes

Known risks and adverse outcomes of using GnRHa in children included mood swings and emotional lability (Khatchadourian et al., 2014). Klaver et al. (2018) reported different changes in body composition between patients AMAB and patients AFAB after treatment; persons AMAB had increased fat whereas AFAB persons had decreased fat compared to cisgender peers. Nahata et al. (2017) reported the cost of using GnRHa as an adverse byproduct of this treatment in addition to the lack of insurance coverage. Other adverse risks associated with use of these hormones included slow growth, decrease in lean body mass, increased fat, and decreased height velocity (Schagen et al., 2016); and decrease in bone turnover markers (Vlot et al., 2017).

Positive outcomes associated with GnRHa

Positive outcomes associated with using GnRHa drugs with adolescents included anthropomorphic measurements returning to normal limits in adulthood (Cohen-Kettenis et al. 2011); and better outcomes for patients assigned female at birth who also underwent mastectomy (Khatchadourian et al., 2014). Schagen et al. (2016) reported positive changes in secondary sexual characteristics along with the lack of sustained creatinine or LFT abnormalities. Schneider et al. (2017) reported the individual's improvement in affective and social life. Similarly, de Vries et al. (2011) found

significant improvements in general functioning, decreases in depressive symptoms, and decreases in emotional and behavioral problems. One study reported no positive outcomes (Nahata et al., 2017). Importantly, when compared to youth who did not receive pubertal suppression, those who did showed lower lifetime rates of suicidal ideation (Turban et al., 2020).

Quality

Table 3 is a summary of the quality checklists used to determine quality in the four studies that were retrospective chart reviews. In sum, three of the studies were deemed of fair quality with relatively high risk for bias. These studies had quality scores that were 4 and 5 criteria out of 10 that were met; one study was assessed as good with a score of 7 out of 10 criteria met. The risk of bias in the studies with fair quality was owing to such things as not reporting how data abstractors were trained and monitored, lack of standardized abstraction forms, and lack of procedural manual or description of data abstraction process in the study. None of the studies reviewed here reported having pilot tested the data collection method or tools. All of these studies met the criterion for addressing ethical and legal concerns.

The prospective studies by de Vries et al. (2011), and Schagen et al. (2016), plus the cross-sectional study by Turban et al. (2020), which were assessed using the JBI checklist, earned 'good' ratings as shown in Table 4. The study by Cohen-Kettenis et al. (2011) was a single case study, for which we used the JBI Critical Appraisal Checklist for Case Reports (Joanna Briggs Institute, 2018), was rated excellent, having met all eight criteria (100%). We also used the JBI Critical Appraisal Checklist for Case Reports for the other single case study by Schneider et al. (2017) and rated it good, with 7 of 8 criteria met (87.5%). The checklists for these two case reports are in Table 5.

Discussion

The studies identified and reviewed here are current with publication dates ranging from 2011 to 2020. As adolescents, their families, and healthcare providers seek more guidance about using GnRHa drugs to suppress puberty, the findings from this critical review are timely, unique, and useful. Given the relatively short amount of time that GnRHa drugs have been used for patients with GD, it is not unexpected that we found no longitudinal empirical studies to guide practice in this expanding population, although studies are currently underway (Olson-Kennedy et al., 2019). At present, the lack of longitudinal data remains a gap in the literature. From an exhaustive search of four databases, however, we were able to answer our four research questions with data from a total sample of $N = 702$ youth described in a mere nine published articles. The samples ranged not only in size (1–192) but also in age (9–35). Although race/ethnicity was reported in <67% of the studies, where it was, the vast majority of participants were Caucasian or White. Clearly, more studies

Table 3. Vassar & Holzmann's quality checklist for retrospective chart reviews of articles in critical review of puberty-blocking drugs (by first author)

Quality Question	Khatchadourian	Klaver	Nahata	Vlot
1. Are there well-defined and clearly articulated research questions?[a]	Aim to describe cohort in hospital Yes = 1	Aim to examine changes and compare Yes = 1	Goals to examine prevalence of mental health diagnoses and insurance coverage. Yes = 1	Objective to investigate course of three bone turnover markers during Rx. Yes = 1
2. Is there clear evidence of an a priori sampling plan?	No = 0	Yes = 1	Yes = 1	Yes = 1
3. Were the variables operationalized adequately?	(e.g., age at first visit, natal sex, Tanner at first visit). Yes = 1	Yes = 1	Yes = 1	Yes = 1
4. Were data abstractors trained and monitored throughout the study?	No = 0	No/not stated = 0	Yes = 1	No = 0
5. Was a standardized abstraction form used?	No/uncertain = 0	No/not stated = 0	Yes = 1	No = 0
6. Was there a procedural manual or description for data abstraction?	No/uncertain = 0	No/not stated = 0	No = 0	No = 0
7. Were there explicit inclusion and exclusion criteria?	Yes = 1	Yes = 1	Yes = 1	Yes = 1
8. Were interrater/intrarater reliability addressed?	No = 0	No = 0	No = 0	No = 0
9. Was there a pilot test of the data collection and analysis?	No/uncertain = 0	No = 0	No = 0	No = 0
10. Were ethical and legal considerations addressed?	Yes = 1	Yes = 1	Yes = 1	Yes = 1
OVERALL ASSESSMENT	Fair: 4/10	Fair: 5/10	Good: 7/10	Fair: 5/10

[a]If there was a clear aim, objective, or goals for the study, and research questions could be inferred, we rated this criterion as 'yes'.

Table 4. Joanna Briggs Institute's critical appraisal checklist for cross-sectional and prospective observational studies

	de Vries et al. (2011)	Schagen et al. (2016)	Turban et al. (2020)
1. Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y
2. Were the study subjects and the setting described in detail?	Y	Y	NA
3. Was the exposure measured in a valid and reliable way?	U	Y	Y
4. Were objective, standard criteria used for measurement of the condition?	Y	Y	Y
5. Were confounding factors identified?	N	U	Y
6. Were strategies to deal with confounding factors stated?	N	U	Y
7. Were the outcomes measured in a valid and reliable way?	Y	Y	U
8. Was appropriate statistical analysis used?	Y	Y	Y
TOTAL PERCENTS	62.5%	75%	85.7%%

Legend: Y = yes; N = no; U = unclear; NA = not applicable. Denominator does not include items judged 'NA'.

Table 5. Joanna Briggs institute's critical appraisal checklist for case report reports

Criteria	Cohen-Kettenis et al. (2011)	Schneider et al. (2017)
1. Were patient's demographic characteristics clearly described and presented?	Yes	Yes
2. Was the patient's history clearly described and presented as a timeline?	Yes	Yes
3. Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes
4. Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes
5. Was the intervention(s) or treatment procedure(s) clearly described?	Yes	Yes
6. Was the postintervention clinical condition clearly described?	Yes	No
7. Were adverse events (harms) or unanticipated events identified and described	Yes	Yes
8. Does the case report provide takeaway lessons?	Yes	Yes
TOTAL criteria met	8/8 = 100%	7/8 = 87.5%

are needed to address the needs of this diverse and expanding population.

Being screened by a mental health professional to establish a diagnosis of gender dysphoria (GD) or gender identity disorder (GID) was found as a prerequisite to using puberty-blocking drugs in half of the studies. The studies that included older samples, meaning that diagnostic prerequisites were met prior to publication of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013), reported using a diagnosis of gender identity disorder (GID) rather than GD. Authors of all the studies reviewed here noted that this diagnosis was an essential starting point before considering the use of puberty suppressors. All studies in this sample also included not initiating puberty suppressing drugs prior to the onset of puberty. These recommendations are consistent with guidelines published by WPATH (2011) and the Endocrine Society (2017), which note that hormonal therapies should not be instituted prior to the onset of puberty. They are also consistent with a gender-affirming conceptualization of care based on the premise that society upholds diversity in gender development and expression (Edwards-Leeper et al., 2016, p 165).

There was general agreement that gonadotropin-releasing hormone analogue (GnRHa) drugs are preferred for puberty suppression. Five of the papers reviewed here described the use of triptorelin or leuprorelin (off-label), followed by sex-affirming hormones. The other four papers did not give the name of the drugs used, but the authors wrote that GnRHa drugs were administered. These procedures follow the 'Dutch protocol' outlined by Delemarre-van de Waal and Cohen-Kettenis (2006) in which 3.75 mg. of triptorelin is given every four weeks intramuscularly or subcutaneously when adolescents have reached Tanner stages 2–3 and have been diagnosed with gender dysphoria (previously gender identity disorder).

As for positive outcomes, improved psychological health was identified in this review (Turban et al., 2020; de Vries et al., 2011). The most recent study by Turban et al. (2020) was the first to demonstrate that access to pubertal suppression during adolescence was associated with decreased lifetime suicidality among transgender adults. In a prospective, longitudinal investigation, de Vries et al. (2011) reported improvements in general functioning as well as decreases in depressive symptoms and emotional and behavioral problems. The findings of these two studies are further supported by a recent longitudinal investigation that found youth aged 9–25 years who engaged in gender-affirming endocrine treatment (i.e., puberty suppression or cross-sex hormones) demonstrated improved mental health over time (Achille et al., 2020). The chance to have more time to consider medical transition was helpful to the young person in one of the case study reports (Cohen-Kettenis et al., 2011). Despite these psychosocial improvements, most of the studies reviewed here focused on biological outcomes rather than psychosocial ones. Although the biological outcomes that affirm the patient's gender are critical to the success of using puberty-blocking drugs, a more holistic view including psychosocial outcomes are equally important to ensure all needs of patients are being met. Such a holistic view highlights both the physical and mental health implications of access to puberty suppression. As the Endocrine Society (2017) indicate, transgender individuals in puberty should be cared for by a multi-disciplinary team that can address both mental and physical health concerns simultaneously.

As other studies have shown, risks and adverse outcomes described in these studies included emotional lability, changes in body composition (e.g., fat deposits), decreased height velocity, decreased bone turnover, decreased bone mineral density, high cost of these drugs, and inadequate insurance coverage. These findings raise issues with important policy implications and beg for further study.

We need more studies that address the potential positive and negative outcomes related to the use of puberty-blocker therapies not only as they affect the individual but also as they affect the family. Families with health insurance policies that do not support all the services described in the WPATH standards of care for transgender adolescents may suffer financial hardships that could be prevented with additional research demonstrating long-term benefits of this treatment (Padula & Baker, 2017). Families may also need counseling and support groups to deal with issues such as stigma, uncertainty about the future (Gray, Sweeney, Randazzo, & Levitt, 2016), grief and family conflict as youth begin to consider seriously pursuing puberty suppression (Ashley, 2019). Research confirms that TGD youth who lack family and other forms of social support bear a heavy burden of psychological distress (McConnell, Birkett, & Mustanski, 2016).

The quality of the studies reviewed was modest but promising. In all the studies reviewed, the primary risk for bias was selection of the samples, but this may be unavoidable given that the population in each case is already self-selected. Nearly half (44%) of the studies reviewed were retrospective chart reviews and only one of these was rated as 'good', which meant that it had a relatively low risk for bias compared to the others. Because the other three studies omitted important criteria for retrospective chart reviews, they reflected fairly large risks for bias, particularly concerning the inexact methods by which data were extracted from the patients' records. Although the remaining studies were deemed 'good' or 'excellent' in terms of meeting more criteria for their respective study designs, these designs provided low-level evidence: case reports, prospective observational, and cross-sectional studies. Case studies are considered to be the weakest of designs or lowest form of evidence, containing threats to internal validity including history, maturation, and mortality (Campbell & Stanley, 1963; Cochrane, n.d.). These findings suggest the need for additional studies to be conducted using more rigorous designs with fewer threats to internal validity.

The findings from this review support the position taken by Reisner et al. (2016) that we need more longitudinal studies on youth who have taken puberty-blocking drugs in adolescence. Such studies as well as studies using mixed methods designs could document both biological and psychosocial changes over time and are able to provide a more holistic and comprehensive view of how the use of such agents affects the lives of individuals as they explore this critical time of development. Moreover, qualitative studies are needed to document the first-person experiences of TGD youth, as Vrouenraets et al. (2016) have also suggested.

Additional research can lend more strength to current clinical guidelines and assist clinicians in caring for these patients and their families especially as questions arise during treatment. Underscoring the need for ongoing research, access to puberty blockers, and the potential benefits that they provide, is not universal and varies greatly by geography, insurance status, healthcare provider availability among other factors (Kimberly et al., 2018). An increase in high-quality longitudinal data should lend additional support to what healthcare providers are witnessing clinically: improvements in short- and long-term health outcomes of these very vulnerable youth. With additional research should come increased access to these treatment modalities and improvements in mental health outcomes.

Limitations

This study was limited to a review of papers published in English, thus we may have missed important findings published in other languages and other countries. This study was also limited to only four databases. Other databases may have included studies that we missed. Our specific research questions also may have limited our inclusion criteria. Despite these limitations, the findings are strengthened by our adherence to a critical and systematic review process, including the extensive search assistance from an experienced science librarian (last author), and the relatively large number of total participants in the nine studies reviewed.

Implications

The implications for multidisciplinary teams of healthcare professionals working with this population are that this body of research supports the use of puberty suppression in early adolescents who are carefully screened for gender dysphoria and who have reached an early stage of pubertal development.

Conclusion

Despite a recent increase in the number of TGD youth seeking healthcare services for their gender dysphoria, there exists a relatively small amount of research regarding the positive and negative short- and long-term effects of using GnRHa drugs to suppress puberty and to allow more time for gender identity exploration. The need for additional well-designed longitudinal and mixed methods studies is critical to support and even improve current practice for this very vulnerable population. Although large long-term studies with diverse and multicultural populations have not been done, the evidence to date supports the finding of few serious adverse outcomes and several potential positive outcomes. This literature suggests the need for TGD youth to be cared for in a manner that not only affirms their gender identities but that also minimizes the negative physical and psychosocial outcomes that could be associated with pubertal development.

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Ethical approval

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References

Achille, C., Taggart, T., Eaton, N.R., Osipoff, J., Tafuri, K., Lane, A., & Wilson, T.A. (2020). Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. *International Journal of Pediatric Endocrinology*, *8*. https://doi.org/10.1186/s13633-020-00078-2

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders* (5th edn). Arlington, VA: American Psychiatric Publishing.

Ashley, F. (2019). Puberty blockers are necessary, but they don't prevent homelessness: Caring for transgender youth by supporting unsupportive parents. *The American Journal of Bioethics*, *19*, 87–89.

Bonifacio, H.J., & Rosenthal, S.M. (2015). Gender variance and dysphoria in children and adolescents. *Pediatric Clinics of North America*, *62*, 1001–1016.

Campbell, D.T., & Stanley, J.C. (1963). *Experimental and quasi-experimental designs for research*. Boston: Houghton Mifflin Company.

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics*, *14*, e2017374.

Cochrane Consumer Network (n.d.) Levels of evidence. Available from: https://consumers.cochrane.org/levels-evidence

Cohen-Kettenis, P.T., Schagen, S.E.E., Steensma, T.D., DeVries, A.L.C., & Delemarre-van de Waal, H.A. (2011). Puberty suppression in a gender-dysphoric adolescent: A 22 -year follow-up. *Archives of Sexual Behavior*, *40*, 843–847.

Cooper, H. (2017). *Research synthesis and meta-analysis: A step-by-step approach* (5th edn). Los Angeles: Sage.

de Vries, A.L.C., Steensma, T.D., Doreleijers, T.A.H., & Cohen-Kettenis, P.T. (2011). Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. *Journal of Sexual Medicine*, *8*, 2276–2283.

Delemarre-van de Waal, H.A., & Cohen-Kettenis, P.T. (2006). Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspects. *European Journal of Endocrinology*, *155*, S131–S137.

DiVasta, A., & Laufer, M.R. (2013). The use of gonadotropin releasing hormone analogues in adolescent and young patients with endometriosis. *Current Opinion in Obstetrics and Gynecology*, *25*, 287–292.

Drummond, K.D., Bradley, S.J., Peterson-Badali, M., & Zucker, K.J. (2008). A follow-up study of girls with gender identity disorder. *Developmental Psychology*, *44*, 34–45.

Edwards-Leeper, L., Leibowitz, S., & Sangganjanavanich, V.F. (2016). Affirmative practice with transgender and gender nonconforming youth: Expanding the model. *Psychology of Sexual Orientation and Gender Diversity*, *3*, 165–172.

Endocrine Society (2017). Guidelines and clinical practice. Available from: practice/clinical-practice-guidelines/gender-dysphoria-gender-https://www.endocrine.org/guidelines-and-clinical-incongruence [last accessed 25 June 2019].

Gallagher, J.S., Missmer, S.A., Hornstein, M.D., Laufer, M.R., Gordon, C.M., & DiVasta, A.D. (2018). Long-term effects of gonadotropin-releasing agonists and add-back in adolescent endometriosis. *Journal of Pediatric and Adolescent Gynecology*, *31*, 376–381.

Gray, S.A.O., Sweeney, K.K., Randazzo, R., & Levitt, H.M. (2016). "Am I doing the right thing?": Pathways to parenting a gender variant child. *Family Process*, *55*, 123–138.

Hembree, W.C., Cohen-Kettenis, P., Delemarre-van de Waal, H.A., Gooren, L.J., Meyer, W.J., Spack, N.P., … & Montori, V.M. (2009). Endocrine treatment of transsexual persons: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology, and Metabolism*, *94*, 3132–3154.

Hembree, W.C., Cohen-Kettenis, P.T., Gooren, L., Hannema, S.E., Meyer, W.J., Murad, M.H., … & T'Sjoen, G.G. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: An endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology and Metabolism*, *102*, 3869–3903.

Joanna Briggs Institute (2018). Critical appraisal tools. The University of Adelaide. Available from. http://joannabriggs.org/research/critical-appraisal-tools.html [last accessed 5 May 2019].

Johns, M.A., Lowry, R., Andrzejewski, J., Barrios, L.D., Demissie, Z., McManus, T., … & Underwood, J.M. (2019). Transgender identitiy and experiences of violence victimization, substance use, suicide risk, and sexual risk behaviors among high school students—19 states and large urban school districts, 2017. *Morbidity and Mortality Weekly Report*, *68*, 67–71.

Khatchadourian, K., Amed, S., & Metzer, D.L. (2014). Clinical management of youth with gender dysphoria in Vancouver. *The Journal of Pediatrics*, *164*, 906–911.

Kimberly, L.L., Folkers, K.M., Friesen, P., Sultan, D., Quinn, G.P., Bateman-House, A., … & Salas-Humara, C. (2018). Ethical issues in gender-affirming care for youth. *Pediatrics*, *142*, e20181537.

Klaver, M., de Mutsert, R., Wiepjes, C.M., Twisk, J.W.R., den Heijer, M., Rotteveel, J., & Klink, D.T. (2018). Early hormonal treatment affects body composition and body shape in young transgender adolescents. *Journal of Sexual Medicine*, *15*, 251–260.

Krishna, K.B., Fuqua, J.S., Rogol, A.D., Klein, K.O., Popovic, J., Houk, C.P., … & Lee, P.A. (2019). Use of gonadotropin-releasing ormone analogs in children: Update by an international consortium. *Hormone Research in Paediatrics*, *91*, 357–372.

Lee, J.W., Kim, H.J., Choe, Y.M., Kang, H.S., Kim, S.I., Jun, Y.H., & Lee, J.E. (2014). Significant adverse reactions to long-acting gonadotropin-releasing hormone agonists for the treatment of central precocious puberty and early onset puberty. *Annual Pediatric Endorinology Metabolism*, *19*, 135–140.

Liu, R.T., & Mustanski, B. (2012). Suicidal ideation and self-harm in lesbian, gay, bisexual, and transgender youth. *American Journal of Preventive Medicine*, *42*, 221–228.

Lowry, R., Johns, M.M., Gordon, A.R., Austin, B., Robin, L.E., & Kann, L.K. (2018). Nonconforming gender expression and associated mental distress and substance use among high school students. *JAMA Pediatrics*, *172*, 1020–1028.

McConnell, E., Birkett, M., & Mustanski, B. (2016). Families matter: Social support and mental health trajectories among lesbian, gay, bisexual, and transgender youth. *Journal of Adolescent Health*, *59*, 674–680.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., & the PRISMA Group (2009). Reprint—Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *Physical Therapy*, *89*, 873–880.

Nahata, L., Quinn, G.P., Caltabellotta, N.M., & Tishelman, A.C. (2017). Mental health concerns and insurance among transgender adolescents. *LGBT Health*, *4*, 188–193.

Olson, J., Schrager, S.M., Belzer, M., Simons, L.K., & Clark, L.F. (2015). Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. *Journal of Adolescent Health*, *57*, 374–380.

Olson-Kennedy, J., Chan, Y.-M., Garofalo, R., Spack, N., Chen, D., Clark, L., … & Rosenthal, S. (2019). Impact of early medical treatment for transgender youth: Protocol for the longitudinal, observational trans youth care study. *JMIR Research Protocols*, *8*, e14434.

Padula, W.V., & Baker, K. (2017). Coverage for gender-affirming care: Making health insurance work for transgender Americans. *LGBT Health*, *4*(4), 244–247.

Reisner, S.L., Deutsch, M.B., Bhasin, S., Bockting, W., Brown, G.R., Feldman, J., … & Goodman, M. (2016). Advancing methods for US transgender health research. *Current Opinion in Endocrinology Diabetes Obesity*, *23*, 198–207.

Schagen, S.E.E., Cohen-Kettenis, P.T., Delemarre-van de Waal, H.A., & Hannema, S.E. (2016). Efficacy and safety of gonadotropin-releasing hormone agonist treatment to suppress puberty in gender dysphoric adolescents. *The Journal of Sexual Medicine*, *13*, 1125–1132.

Schneider, M.A., Spritzer, P.M., Soll, B.M.B., Fontanari, A.M.V., Carneiro, M., Tovar-Moll, F., … & Lobato, M.I.R. (2017). Brain maturation, cognition and voice pattern in a gender dysphoria case under pubertal suppression. *Frontiers in Human Neuroscience*, *11*, 528.

Shields, J.P., Cohen, R., Glassman, J.R., Whitaker, K., Franks, H., & Bertolini, I. (2013). Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *Journal of Adolescent Health*, *42*, 248–250. https://doi.org/10.1016/j.jadohealth.2012.06.016

Stevens, J., Gomez-Lobo, V., & Pine-Twaddell, E. (2015). Insurance coverage of puberty blocker therapies for transgender youth. *Pediatrics*, *136*, 1029–1031.

Turban, J.L. (2017). Transgender youth: The building evidence base for early social transition. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*, 101–102.

Turban, J.L., King, D., Carswell, J.M., & Keuroghlian, A.S. (2020). Pubertal suppression for transgender youth and risk of suicidal ideation. *Pediatrics*, *145*, e20191725.

Vassar, M., & Holzmann, M. (2013). The retrospective chart review: Important methodological considerations. *Journal of Educational Evaluation for Health Professions*, *10*, 1–7.

Vlot, M.C., Klink, D., den Heijer, M., Blankenstein, M.A., Rotteveel, J., & Heijboer, A. (2017). Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. *Bone*, *95*, 11–19.

Vrouenraets, L.J.J.J., Fredriks, A.M., Hannema, S.E., Cohen-Kettenis, P.T., & DeVries, M.C. (2015). Early medical treatment of children and adolescents with gender dysphoria: An empirical ethical study. *Journal of Adolescent Health*, *57*, 367–373.

Vrouenraets, L.J.J.J., Fredriks, A.M., Hannema, S.E., Cohen-Kettenis, P.T., & DeVries, M.C. (2016). Perceptions of sex, gender, and puberty suppression: A qualitative analysis of transgender youth. *Archives of Sexual Behavior*, *45*, 1697–1703.

World Professional Association for Transgender Health (2011). Standards of care for the health of transsexual, transgender, and gender nonconforming people (7th version). Available from: https://www.wpath.org/media/cms/Documents/Web%20Transfer/SOC/Standards%20of%20Care%20V7%20-%202011%20WPATH.pdf [last accessed 10 December 2020].

Yu, R., Yang, S., & Hwang, T. (2019). Psychological effects of gonadotropin-releasing hormone agonist treatment in girls with central precocious puberty. *Journal of Pediatric Endocrinology and Metablism*, *32*, 1071–1075.

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