Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review

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abstract

CONTEXT: Hormonal interventions are being increasingly used to treat young people with gender dysphoria, but their effects in this population have not been systematically reviewed before.

OBJECTIVE: To review evidence for the physical, psychosocial, and cognitive effects of gonadotropin-releasing hormone analogs (GnRHa), gender-affirming hormones, antiandrogens, and progestins on transgender adolescents.

DATA SOURCES: We searched Medline, Embase, and PubMed databases from January 1, 1946, to June 10, 2017.

STUDY SELECTION: We selected primary studies in which researchers examined the hormonal treatment of transgender adolescents and assessed their psychosocial, cognitive, and/or physical effects.

DATA EXTRACTION: Two authors independently screened studies for inclusion and extracted data from eligible articles using a standardized recording form.

RESULTS: Thirteen studies met our inclusion criteria, in which researchers examined GnRHas (n = 9), estrogen (n = 3), testosterone (n = 5), antiandrogen (cyproterone acetate) (n = 1), and progestin (lynestrenol) (n = 1). Most treatments successfully achieved their intended physical effects, with GnRHas and cyproterone acetate suppressing sex hormones and estrogen or testosterone causing feminization or masculinization of secondary sex characteristics. GnRHa treatment was associated with improvement across multiple measures of psychological functioning but not gender dysphoria itself, whereas the psychosocial effects of gender-affirming hormones in transgender youth have not yet been adequately assessed.

LIMITATIONS: There are few studies in this field and they have all been observational.

CONCLUSIONS: Low-quality evidence suggests that hormonal treatments for transgender adolescents can achieve their intended physical effects, but evidence regarding their psychosocial and cognitive impact are generally lacking. Future research to address these knowledge gaps and improve understanding of the long-term effects of these treatments is required.

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Transgender is a term used to describe an individual whose inner gender identity differs from their sex assigned at birth. This mismatch can cause distress and functional impairment, resulting in gender dysphoria (GD) or what was previously termed "gender identity disorder" (GID).[1,2]

Several hormonal treatment options are available for GD, the appropriateness of which depends on developmental stage. For instance, puberty can frequently exacerbate GD because of the development of unwanted secondary sexual characteristics,[3] which can be reversibly suppressed by using gonadotropin-releasing hormone analogs (GnRHas).[4,5] In comparison, gender-affirming hormones (GAHs; also known as cross-sex hormonal therapy) allow individuals to actively masculinize or feminize their physical appearance to be more consistent with their gender identity. As GAHs are only partially reversible, they are generally used only once an individual reaches the legal age of medical consent, which varies across countries.[5] In addition, antiandrogens, such as spironolactone and cyproterone acetate, can be used to counter the effects of testosterone in birth-assigned male individuals,[6,7] whereas progestins, such as norethisterone and medroxyprogesterone, are often employed to suppress menses in younger birth-assigned female individuals.

Authors of multiple studies have investigated the physical and psychosocial effects of different hormonal interventions in adults with GD. GAHs have been examined most extensively, with authors of systematic reviews indicating that GAHs improve multiple aspects of psychosocial functioning,[8,9] although they also increase serum triglycerides and risk of cardiovascular disease (including venous thrombosis, stroke, myocardial infarction, and pulmonary embolism).[10–12] Studies of antiandrogens in transfemale adults have revealed that cyproterone acetate is able to reduce levels of testosterone, whereas spironolactone has a synergistic effect with estrogen in improving both physical and hormonal outcomes.[13]

In contrast, studies of different hormonal treatments in young people with GD are scarce, meaning that clinicians have often had to extrapolate from adult studies. This is problematic for several reasons. Firstly, adolescence is a period of rapid development across multiple domains,[14] and studies of hormonal treatments in adults with GD may not readily translate to adolescents. Secondly, some hormone treatments used in young people with GD (eg, GnRHas and progestins) are either not commonly used in adults with GD or are used in adults for different reasons (eg, GnRHas for prostate cancer).[15] Finally, hormonal dosing regimens in adolescents with GD are frequently different from those used in adults, which is likely to affect outcomes.

Our purpose in this systematic review is, therefore, to evaluate the currently available evidence about the physical, psychosocial, and cognitive effects of different hormonal therapies in transgender youth. By doing so, we can directly inform clinical practice involving this population and highlight existing knowledge gaps.

METHODS

Eligibility Criteria

Studies were considered eligible if participants were given hormonal treatment (GnRHas, GAHs, antiandrogens, or progestins) and if analysis of psychosocial, cognitive, and/or physical effects of these hormones were included. Participants had to be younger than 25 years of age and described as transgender or diagnosed with GD and/or GID according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; or *International Classification of Diseases* criteria. This age range was selected to be consistent with the definition of adolescence used by the recent *Lancet* Commission on Adolescent Health.[16] Studies were excluded if the effects of hormonal therapy could not be separated from gender-affirming surgery, which could cause potential issues related to interpretation of results. We included all published study designs in any language, but conference abstracts or studies in which researchers failed to report results at the group level with at least 10 individuals were excluded.

Study Identification

The Medline (Ovid) and Embase (Ovid) databases were searched for references from January 1, 1946, to June 10, 2017, by using thesauri and/or keywords. PubMed was searched by using keywords to retrieve electronic publications and items not indexed in Medline. The Medline search strategy was adapted for use in Embase and PubMed with the main search terms as follows: (GD or transsexualism or "sexual and gender disorders" or transgender persons or gender identity), (drug therapy or therapeutic use or [hormonal or hormone*] or *steroids or exp gestagen or exp antiandrogen), and (adolescen* or pediatric* or pediatric* or youth* or teen or teens or teenage*). Detailed search histories are available on request. Additional items were identified by manually searching reference lists of relevant retrieved articles. Two reviewers independently assessed all study titles and abstracts to determine inclusion, with the full text being subsequently retrieved for potentially eligible studies to assess final suitability. Any disagreements

were resolved with discussion and consensus was reached for final articles.

Data Extraction

Two reviewers, working independently and in duplicate, used a standardized form to extract methodological, demographic, and outcome data. Data extracted included reported youth characteristics (number of participants pre- and posttreatment, participant age range, diagnosis of GD, birth-assigned sex, and gender identity), hormonal therapy features (type, dose, route, duration of treatment), study design, and outcomes of interest (length of follow-up duration, follow-up outcome measures, and treatment effect on outcome measures).

Quality Assessment

Risk of bias in studies was assessed by 2 authors working independently using a modified version of the Quality in Prognosis Studies (QUIPS) tool from a previous study.[17] The original QUIPS tool[18] was modified because confounders or prognostic factors were not analyzed in this review and thus did not apply.

Review Protocol

A detailed protocol is available at PROSPERO (identifier 42017056670).

Statistical Analysis

Effect sizes were calculated for results with reported means and SDs,[19–27] according to a previous study.[28] Unadjusted effect sizes using the posttest SD were calculated for the majority of studies, with an adjusted effect size using the experimental SD calculated only for 1 study with comparison between groups.[24]

Meta-analysis

Meta-analysis was planned for outcomes examined by 3 or more studies but was unable to be conducted because individual outcome effect sizes were available for a maximum of 2 studies.

RESULTS

Study Selection

The study selection process is depicted in Fig 1. Eighty-three potentially relevant studies were retrieved, of which 13[19–27,29–32] met the inclusion criteria and were systematically analyzed. In Table 1, we summarize the main characteristics of these 13 studies, and their key physical, psychosocial, and cognitive findings are outlined in Tables 2, 3 and 4, respectively. Because research from the same cohort was described in 2 of the studies,[26,27] they were considered as 1 study.

Quality Appraisal

In all studies, there was a medium to high risk of bias (Table 5). In most studies, there were only small sample sizes (minimum of 21 and maximum of 201), with <50 participants in 38.5% of the studies. There were controls in only 2 studies, and all studies were conducted in clinical populations. There was often significant loss to follow-up, attributed partially to most studies being retrospective with missing data. Overall, the tools used to measure the specific outcomes were valid and reliable, although there was no blinding or randomization in any of the studies.

PHYSICAL EFFECTS

All relevant results are shown in Table 2.

Sex Hormones and Secondary Sexual Characteristics

GnRHas

GnRHas were successful in suppressing sex hormone secretion with significant decreases in gonadotropin,[29] estradiol, and testosterone[19,21,29] levels, although 1 study only revealed a significant decrease in transfemale adolescents (birth-assigned male individuals identifying as female individuals).[19] There was decreased testicular volume in transfemale adolescents[19,21,29] and cessation of menses in transmale adolescents (birth-assigned female individuals identifying as male individuals),[21] although the latter often occurred after a withdrawal bleed in postmenarchal individuals. Furthermore, GnRHas were shown to decrease luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[19,21]

Progestin

Researchers in 1 study examined the effects of the progestin lynestrenol[30] in transmale adolescents. Although there was no report of the efficacy of lynestrenol in stopping menses, there were significant reductions in levels of serum sex-hormone binding globulin (SHBG) and LH, in addition to a significant increase in free testosterone (fT). FSH, estradiol, testosterone, and anti-Mullerian hormone had nonsignificant decreases.[30]

Antiandrogen

In one study, researchers studied the effects of the antiandrogen cyproterone acetate alone in transfemale adolescents.[22] It was effective in significantly suppressing endogenous sex hormones with significant reductions in testosterone and dehydroepiandrosterone in addition to nonsignificant decreases in estradiol and fT after 12 months, with no significant changes in LH, FSH, and SHBG. Cyproterone acetate was associated with a marked increase in prolactin of ∼2.5-fold that exceeded the normal reference range after 6 months but returned to the normal range after 12 months. No clinical consequences, including galactorrhea, were reported. Furthermore, 55.6% of participants

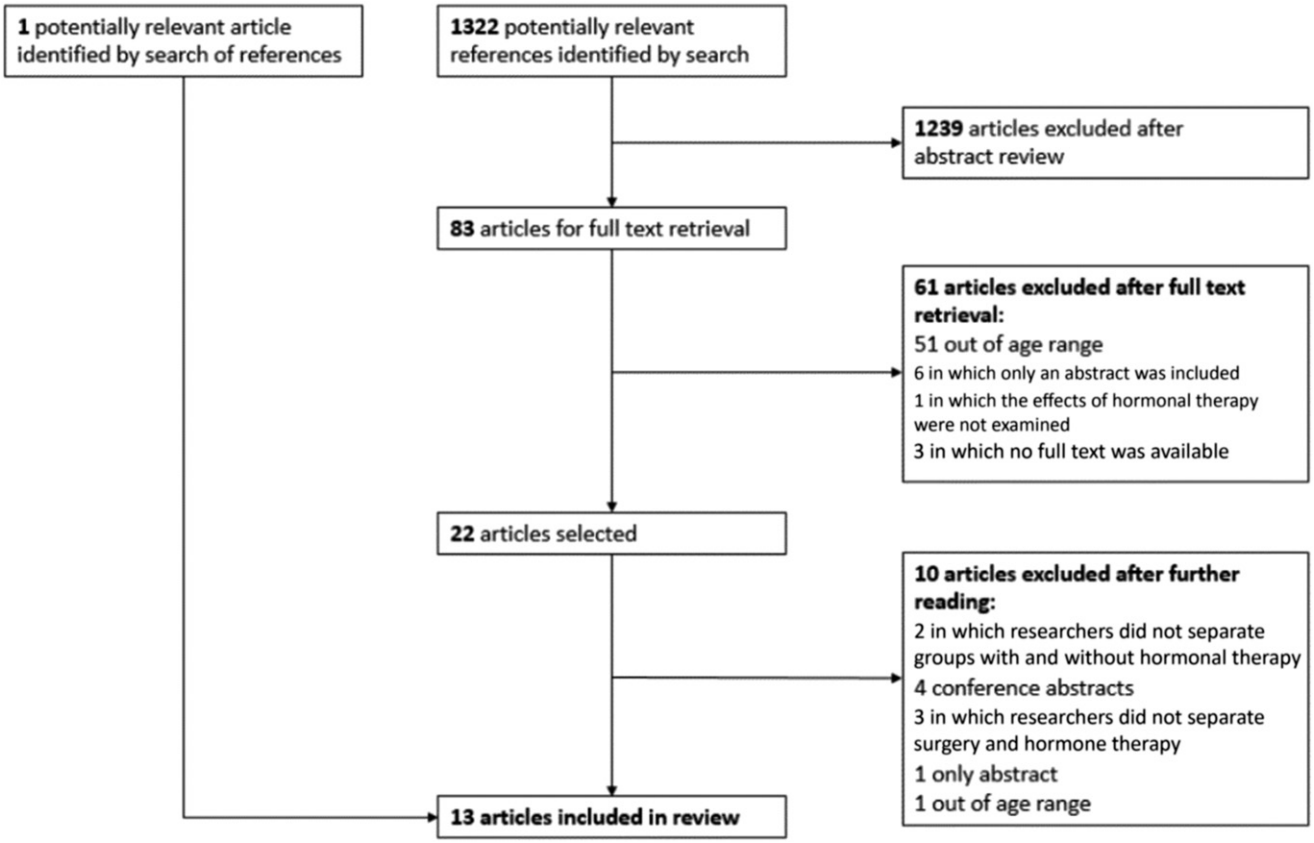

FIGURE 1
Flow diagram of study selection.

also reported decreased facial shaving frequency.[22]

Estrogen

Estrogen was successful in feminizing physical sex characteristics.[22,29] In 1 study, 66.7% of participants reached Tanner B3 stage (increase in breast and areola size), and 9.5% reached Tanner B4 (secondary mound created by areola and papilla) after treatment with cyproterone acetate and estrogen for at least 6 months.[22] However, breast development was found to be objectively dissatisfactory and subjectively less in size than expected for the majority.[22] There was a significant increase in serum estradiol after 6 months that reached the female reference range, whereas total testosterone decreased after 1 to 3 months to be outside of the male reference range.[22,32] Prolactin was unchanged.[22]

Testosterone

Testosterone resulted in virilization, including lower voice, clitoral enlargement, and body hair growth in a masculinized pattern.[29] Menses ceased in most transmale adolescents within 6 months, with an average time to cessation of 2.9 months.[20] Testosterone resulted in increased total testosterone and fT,[20,30,32] with most participants reaching levels within the normal male range after 6 months,[20,30] as well as significant decreases in LH and FSH.[30] This was accompanied by a decline in estradiol levels after 6 months,[20,30,32] which was statistically significant in 2 studies[20,30] but nonsignificant in 1 study.[32]

Side Effects

GnRHas

Hot flashes were a common side effect in transmale adolescents treated in late puberty (Tanner stages B4 and B5), although these decreased in frequency over time.[29] No other short-term side effects, including local reactions, were reported.

Progestin

Lynestrenol was evaluated as relatively safe, with the most common side effects being initial metrorrhagia (48.7%), headaches (12.1%), hot flashes (9.8%), and acne (which increased from 14.6% to 28.6%).[30]

Antiandrogens

Treatment with cyproterone acetate was evaluated to be relatively safe, with the most common side effect being fatigue (37%).[22]

Estrogen

Side effects reported with combined estrogen and cyproterone acetate

TABLE 1 Characteristics of 13 Studies on Hormonal Treatments in Transgender Youth

Study	Type of Study	Sample (*N*)	Gender Identity	Age, y ± SD	Loss to Follow-up, %	Effects Analyzed	Treatment	Duration of Treatment, y	Outcomes Examined
Delemarre-van de Waal and Cohen-Kettenis[29]	Prospective, longitudinal	21	11 transmale adolescents with GID, 10 transfemale adolescents with GID	Not mentioned	0	Physical	GnRHa	2 y or longer	Sex hormones and secondary sexual characteristics, safety profile, BMD, growth, and body composition
de Vries et al[27] (de Vries et al[26])[a]	Prospective, longitudinal	70 (55)	37 (33) transmale adolescents with GID, 33 (22) transfemale adolescents with GID	Baseline: 13.65 ± 1.85, at start of GnRHa: 14.75 ± 1.92, at start of GAH: 16.64 ± 1.90	Variable: 18–42[b]	Psychosocial	GnRHa, GAH (not assessed in de Vries et al[26])	GnRHa: average: 1.88 ± 1.05, range: 0.42–5.06	Psychological functioning, GD
Klink et al[19]	Retrospective, longitudinal	34	15 transfemale adolescents with GID, 19 transmale adolescents with GID	At start of GnRHa: transfemale adolescents: 14.9 ± 1.9, transmale adolescents: 5.0 ± 2.0; at start of GAH: transfemale adolescents: 16.6 ± 1.4, transmale adolescents: median of 16.4 and interquartile range of 2.3	Variable	Physical	GnRHa (only treatment studied), GAH	GnRHa: transfemale adolescents: average: 1.3, range: 0.5–3.8; transmale adolescents: average: 1.5, range: 0.25–5.2; GAH: transfemale adolescents: average: 5.8, range: 3–8; transmale adolescents: average: 5.4, range: 2.8–7.8	Sex hormones and secondary sexual characteristics, BMD, growth, body composition, and other physical effects
Olson et al[20]	Prospective, longitudinal	36	36 transmale transgender adolescents	18.7 ± 2.6	3	Physical	GAH (only testosterone)	Not mentioned	Sex hormones and secondary sexual characteristics, body composition, and other physical effects
Costa et al[25]	Prospective, longitudinal	201	124 transmale adolescents with GID, 77 transfemale adolescents with GID	Baseline: 15.52 ± 1.41, start of GnRHa: 16.48 ± 1.26	Variable: 0–65[a]	Psychosocial	GnRHa	Immediately eligible for GnRHa: average: 0.75 ± 0.59	GD-related discomfort, global psychosocial functioning

TABLE 1 Continued

Study	Type of Study	Sample (*N*)	Gender Identity	Age, y ± SD	Loss to Follow-up, %	Effects Analyzed	Treatment	Duration of Treatment, y	Outcomes Examined
Staphorsius et al[24]	Cross-sectional	116	22 transmale adolescents with GID, 18 transfemale adolescents with GID, 21 male control subjects, 24 female control subjects	Transmale adolescents: 15.8 ± 1.9, transfemale adolescents: 15.1 ± 2.4, male adolescents : 14.9 ± 1.5, female adolescents: 14.4 ± 1.8	26	Cognitive	GnRHa	GnRHa: average: 1.6 ± 1.0	Executive functioning
Burke et al[23]	Prospective, fMRI	62	21 transmale adolescents with GD, 20 male control subjects, 21 female control subjects	Transmale adolescents: 16.1 ± 0.8, control male subjects: 15.9 ± 0.6, control female subjects: 16.3 ± 1.0	8.1	Cognitive	GnRHa, GAH (testosterone)	GnRHa: average: 2, range: 0.17–4; testosterone: average: 0.83, range: 0.5–1.25	Mental rotation
Schagen et al[21]	Prospective, longitudinal	128	67 transmale adolescents with GID, 49 transfemale adolescents with GID	Transmale adolescents: 14.2, transfemale adolescents: 13.6	9	Physical	GnRHa	At least 0.25	Sex hormones and secondary sexual characteristics, growth, body composition, and other physical effects
Tack et al[30]	Retrospective, longitudinal	45	38 transmale adolescents with GID	15.8 at start of treatment	16	Physical	Androgenic progestin (lynestrenol), combination of androgenic progestin (lynestrenol) and GAH (testosterone)	Average of 10.5 for lynestrenol, average of 0.95 for lynestrenol and testosterone	Sex hormones and secondary sexual characteristics, safety profile, body composition, and other physical effects
Vlot et al[31]	Retrospective, longitudinal	70	42 transmale adolescents with GID, 28 transfemale adolescents with GID	GnRHa at start of treatment: transmale adolescents: 15.1, transfemale adolescents: 13.5; GAH at start of treatment: transmale adolescents: 16.3, transfemale adolescents: 16.0	20	Physical	GnRHa, GAH (testosterone and estrogen)	Not mentioned	Bone turnover, BMD, and growth

TABLE 1 Continued

Study	Type of Study	Sample (*N*)	Gender Identity	Age, y ± SD	Loss to Follow-up, %	Effects Analyzed	Treatment	Duration of Treatment, y	Outcomes Examined
Jarin et al[32]	Retrospective, longitudinal	116	72 transmale adolescents with GD, 44 transfemale adolescents with GD	Transmale adolescents: average of 16 (range of 13–22) at start of treatment, Transfemale adolescents: average of 18 (range of 14–25) at start of treatment	Variable	Physical	GAH (testosterone and estrogen treatment)	Not mentioned	Sex hormones and secondary sexual characteristics, body composition, and other physical effects
Tack et al[22]	Retrospective, longitudinal	27	27 transfemale adolescents with GD	Antiandrogen: 16.5 at start of treatment, combination of antiandrogen and GAH: 17.6 at start of treatment	22.2 (variable)	Physical	Antiandrogen (cyproterone acetate), combination of antiandrogen (cyproterone acetate) and GAH (estrogen treatment)	Antiandrogen: minimum of 0.5 (mean of 1.0), combination of antiandrogen and GAH: minimum of 0.5 (mean of 1.3)	Sex hormones and secondary sexual characteristics, safety profile, growth, body composition, and other physical effects

Note that transmale adolescents are birth-assigned female individuals who identify as male individuals, whereas transfemale adolescents are birth-assigned male individuals who identify as female individuals.

[a] These 2 studies involved the same cohort and were therefore considered as 1 study. The values in parenthesis are used to indicate the results of the earlier study,[26] in which researchers examined a smaller subset of the cohort subsequently examined in de Vries et al.[27]

[b] Variable loss to follow-up depending on test.

TABLE 2 Physical Effects of Hormonal Treatments in Transgender Youth

Study	Treatment	Outcome					
		Testosterone, Estradiol, and Gonadotropin Levels	Anthropometric Measurements	BMD	Body Composition	Safety Profile	Other Physical Effects
Delemarre-van de Waal and Cohen-Kettenis[29]	GnRHa	Decrease[a] in gonadotropin and sex hormone levels, decrease[a] in testicular volume in transfemale adolescents	Decrease[a] in height velocity, decrease[a] in height SDSs in youth who still have growth potential (related to bone age)	No change in bone density actual values but decrease[a] in standardized score (*z* score)	Increase[a] in fat mass percentage, decrease[a] in lean body mass percentage	Frequent hot flashes in transmale adolescents (when treated in late pubertal stages)	—
Delemarre-van de Waal and Cohen-Kettenis[29]	GAH (testosterone and estrogen)	Virilization of transmale adolescents (low voice, clitoris enlarged, facial and body hair growth) and transfemale adolescents (induced breast development)	Increase[a] in height (growth spurt) with androgen substitution therapy	Increase[a] in bone density (actual and *z* scores)	No effect on fasting glucose, insulin, cholesterol, HDL, and LDL levels	—	—
Klink et al[19]	GnRHa (only treatment studied), GAH	Decrease[b] in estradiol, decrease[b] in testosterone in transfemale adolescents with no change in transmale adolescents, decrease[b] in testicular volume in transfemale adolescents, decrease[c] in androstenedione, decrease[b] in LH and FSH	Increase[b] in height actual values, decrease[b] in height standardized values for transfemale adolescents, decrease[c] in height standardized values for transmale adolescents	Transfemale adolescents Lumbar spine: no significant changes in actual score and decrease[c] in *z* score Femoral nondominant: decrease[c] in actual and *z* scores Transmale adolescents Lumbar spine: decrease[c] in actual score and decrease[b] in *z* score Femoral nondominant: decrease[c] in actual and *z* scores	Increase[b] in wt for transfemale adolescents and transmale adolescents, increase[b] in BMI actual score for transfemale adolescents and transmale adolescents, nonsignificant changes in BMI SDSs for transfemale adolescents and transmale adolescents	—	—
Olson et al[20]	GAH (testosterone)	Increase[b] in total and fT levels, decrease[b] in normal and serum estradiol levels	—	—	Increase[b] in BMI, decrease[c] in total cholesterol	—	Increase[b] in Hb (but not to clinically significant levels), increase[b] in systolic BP and ALT (but not to clinically significant levels), decrease[c] in diastolic BP, increase[c] in AST

TABLE 2 Continued

Study	Treatment	Outcome					
		Testosterone, Estradiol, and Gonadotropin Levels	Anthropometric Measurements	BMD	Body Composition	Safety Profile	Other Physical Effects
Schagen et al[21]	GnRHa	Transmale adolescents: menses ceased; Transfemale adolescents: decrease[c] in testicular volume, decrease[c] in LH and FSH, and decrease[c] in gonadotropin, estradiol, and testosterone	Decrease[b] in height SDSs and increase[b] in height values in transfemale adolescents and transmale adolescents	—	Increase[b] in wt scores, increase[b] in BMI scores, increase[b] in BMI SDSs, increase[b] in fat percentage, decrease[b] in lean body mass percentage in transfemale adolescents and transmale adolescents	—	Decrease[b] in transmale creatinine levels; no significant change in y-glutamyl transferase, AST, and ALT; and decrease[b] in ALP in transfemale adolescents and transmale adolescents
Tack et al[30]	Androgenic progestin (lynestrenol)	Decrease[b] in LH; decrease[c] in FSH, estradiol, testosterone and AMH; decrease[b] in SHBG; increase[b] in fT	—	—	Increase[b] in wt and BMI during first 6 mo but back to baseline after 12 mo, no significant changes in total cholesterol and triglyceride levels, no significant change in HbA1c and HOMA, decrease[b] in mean HDL, increase[c] in mean LDL	Metrorrhagia mainly reported in first 6 mo, increase[a] in acne, most common safety profile of headache and hot flashes	Increase[b] in mean Hb and Hct, increase[b] in ALT, increase[c] in creatinine, increase[b] in fT4, no significant changes in AST and thyrotropin
Tack et al[30]	Combination of androgenic progestin (lynestrenol) and GAH (testosterone)	Decrease[b] in LH and FSH, decrease[c] in SHBG, increase[b] in testosterone and fT (reaching levels within male reference ranges), increase[c] in estradiol	Increase[a] in height and wt	—	Increase[b] in wt and BMI; no significant changes in total cholesterol, triglyceride levels, HDL and LDL mean levels, HbA1c, glucose levels, insulin levels, or HOMA index	Few had fatigue; increase[a] in acne and menorrhagia	Increase[b] in mean Hb and Hct levels, increase[b] in ALT and AST (but remained within male reference range), increase[b] in creatinine, decrease[c] in thyrotropin, decrease[b] in fT4

TABLE 2 Continued

Study	Treatment	Outcome					
		Testosterone, Estradiol, and Gonadotropin Levels	Anthropometric Measurements	BMD	Body Composition	Safety Profile	Other Physical Effects
Vlot et al[31]	GnRHa	—	Increase[c] in height and wt (significance level not reported)	Transmale adolescents Decrease[b] in bone density in hip for older bone age (actual and *z* scores) Decrease[b] in bone density in lumbar spine for older bone age (actual and *z* scores) Decrease[b] in bone density in lumbar spine for young bone age (*z* scores) Transfemale adolescents Decrease[b] in bone density in lumbar spine for young bone age (*z* scores)	—	—	—
Vlot et al[31]	GAH (testosterone and estrogen)	—	Increase[a] in height and wt	Transmale adolescents Increase[b] in bone density in hip and lumbar spine (actual and *z* scores) Transfemale adolescents Increase[b] in bone density in lumbar spine (actual and *z* scores) No significant changes in bone density in hip	—	—	—
Jarin et al[32]	GAH (testosterone)	Increase[c] in total testosterone after 1–3 mo, decrease[c] in estradiol	—	—	Increase[c] in BMI (no results for height and/or wt); no significant changes in LDL, total cholesterol, triglycerides, triglyceride to HDL ratio, and HbA1c; decrease[b] in HDL	—	Increase[b] in Hct and Hb; no significant changes in SUN, creatinine, prolactin, or AST; decrease[c] in ALT after 4–6 mo but returned to baseline

TABLE 2 Continued

Study	Treatment	Outcome					
		Testosterone, Estradiol, and Gonadotropin Levels	Anthropometric Measurements	BMD	Body Composition	Safety Profile	Other Physical Effects
Jarin et al[32]	GAH (estrogen)	Increase[b] in estradiol levels, decrease[b] in testosterone levels	—	—	No significant change in BMI (no results for height and/or wt), no significant changes in LDL, HDL, total cholesterol, triglycerides, and triglyceride to HDL ratio	—	No significant changes in BP (systolic and diastolic); initial decrease in Hct and Hb but returned to baseline; no significant changes in SUN, creatinine, prolactin, AST, or HbA1c; decrease[b] in ALT
Tack et al[22]	Antiandrogen (cyproterone acetate)	No significant changes in LH and FSH, decrease[c] in SHBG, decrease[b] in testosterone, nonsignificant decrease[c] in estradiol and fT, decrease[b] in dehydroepiandrosterone, decreased facial shaving frequency (55.60%). Breast development: Tanner B2 (14.8%) and B3 (14.8%)	Increase[b] in height, decrease[b] in height compared with male peers	—	No clinically important or statistically significant changes in wt and BMI, decrease[b] in triglycerides, no significant changes in total cholesterol, HDL, and LDL	Breast tenderness (7.4%), emotionality (11.10%), fatigue (36%), hot flashes (3.7%)	Increase[b] in prolactin (no clinical galactorrhea); decrease[b] in creatinine, Hb and Hct, but not outside of reference ranges; no significant changes in AST and ALT; no significant change in thyrotropin and fT4
Tack et al[22]	Combination of antiandrogen (cyproterone acetate) and GAH (estrogen treatment)	Decrease[b] in LH, decrease[c] in FSH, increase[b] in SHBG, increase[b] in estradiol, decrease[b] in testosterone and fT, no significant change in dehydroepiandrosterone, decreased shaving need (71.40%). Breast development: Tanner B3 (66.7%) and B4 (9.50%)	Increase[b] in height, decrease[b] in height compared with male peers	—	Breast tenderness (57.1%), emotionality (28.60%), hunger (24%), fatigue (14%), hot flashes (14.3%)	Increase[b] in BMI after 6–12 mo but BMI still less compared with Flemish male peers, increase[c] in wt, no significant changes in LDL, total cholesterol, HDL, and triglyceride levels	No significant changes in Hb and Hct, increase[b] in creatinine after 12 mo, no significant changes in AST and ALT, no significant change in thyrotropin and free thyroxin, decrease[b] in prolactin

Note that transmale adolescents are birth-assigned female individuals who identify as male individuals, whereas transfemale adolescents are birth-assigned male individuals who identify as female individuals. AMH, anti-Mullerian hormone; SUN, serum urea nitrogen; —, not applicable.

[a] Indicates that a *P* value was not calculated.

[b] Indicates significant change ($P < .05$).

[c] Indicates nonsignificant change ($P > .05$).

TABLE 3 Psychosocial Effects of Hormonal Treatments in Transgender Youth

Study	Treatment	Outcome					
		Global Functioning	Depression	Anger and Anxiety	Behavioral and Emotional Problems		GD and Body Image
de Vries et al[27] (de Vries et al[26])[a]	GnRHa, GAH (not assessed)	Increase[b] (increase[c])	Decrease[b]	Decrease[c]	CBCL: decrease[b] in total and internalizing scores, decrease[b] (decrease[c]) in externalizing scores	YSR: decrease[b] in total and internalizing scores, decrease[b] (decrease[c]) in externalizing scores	No significant effect[d]
Costa et al[25]	GnRHa	Increase[e]	—	—	—	—	—

Although influential articles in this field, Cohen-Kettenis and Van Goozen[33] and Smith et al[34] were unable to be included in our study because of their focus on patients after sex reassignment surgery. CBCL, Child Behavior Checklist; YSR, Youth Self Report; —, not applicable.

[a] These 2 studies involved the same cohort and were therefore considered as 1 study. Parentheses are used to indicate the results of the earlier study[26] in which researchers examined a smaller subset of the cohort subsequently examined in the previous study.[27]

[b] Indicates significant change ($P < .05$).

[c] Indicates nonsignificant change ($P > .05$).

[d] It is important to note that the Utrecht Gender Dysphoria Scale that was used to measure GD in this study has various limitations, especially in relation to individuals who have already undergone social transition. Thus, the reported lack of improvement in GD here may reflect a lack of sensitivity in detecting psychological benefits. For example, it has been indicated in clinical experience that GnRHas help to satisfy the desire to prevent development of unwanted secondary sex characteristics (which is a criterion for GD under the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* in young adolescents), but the Utrecht Gender Dysphoria Scale does not have any items that address this issue.

[e] Indicates that a *P* value was not calculated.

TABLE 4 Cognitive Effects of Hormonal Treatments in Transgender Youth

Study	Treatment	Outcome	
		Executive Functioning	Mental Rotation
Staphorsius et al[24]	GnRHa	No significant effect on Tower of London performance scores except for decrease[a] in accuracy in suppressed transfemale adolescents (but this was thought to be chance finding because of small sample size), no significant change in overall global functioning, exaggerated sex-typical brain activation of regions of interest	—
Burke et al[23]	GnRHa, GAH (testosterone treatment)	—	Inferred effect of GnRHa (transmale adolescents) At baseline, showed masculinized mental rotation–associated brain activation Testosterone treatment (transmale adolescents) Increase[b] in performance in mental rotation tasks, similar to control girls; increase[a] in bilateral parietal and left frontal activation

Note that transmale adolescents are birth-assigned female individuals who identify as male individuals, whereas transfemale adolescents are birth-assigned male individuals who identify as female individuals. —, not applicable.

[a] Indicates significant change ($P < .05$).

[b] Indicates that a *P* value was not calculated.

included breast tenderness (57.1%), emotionality (28.6%), hunger (23.8%), fatigue (14.3%), and hot flashes (14.3%).[22]

Testosterone

Few side effects were reported with testosterone treatment, with localized injection reactions (5.6%)[20] and fatigue (8%)[30] all relatively uncommon. However, acne (37.5%) and menorrhagia (25%) were common complaints.[30]

Bone Mineral Density

GnRHas in Transfemale Adolescents

Lumbar spine bone mineral density (BMD) *z* scores decreased after treatment with GnRHa monotherapy,[19,29,31] and this reduction was statistically significant in all[29,31] but 1 study.[19] When results were stratified by bone age, the mean reduction in *z* score was only significant (1.32) for individuals with a bone age <15 years.[31] Absolute lumbar spine BMD did not change over time, and thus the decrease in *z* scores after GnRHas likely reflects a failure to accrue BMD compared with age-matched peers. In 2 studies, researchers also examined BMD at the hip and femoral regions, which

TABLE 5 Risk of Bias for Studies of Effects of Hormonal Treatments in Transgender Youth

Study	Study Participation (Overall)	Study Attrition (Overall)	Outcome Measures (Overall)
Delemarre-van de Waal and Cohen-Kettenis[29]	High	High	Medium
de Vries et al[26,27]	High	High	Medium
Klink et al[19]	Medium	High	Medium
Olson et al[20]	Medium	High	Medium
Costa et al[25]	Medium	Medium	Medium
Staphorsius et al[24]	Medium	High	Medium
Burke et al[23]	Medium	Medium	Medium
Schagen et al[21]	High	High	Medium
Tack et al[30]	High	High	Medium
Vlot et al[31]	Medium	High	Medium
Jarin et al[32]	High	High	Medium
Tack et al[22]	Medium	High	Medium

A modified version of the QUIPS tool was used to assess risk of bias according to 3 domains of bias, with each domain having 3 potential ratings of low, medium, or high.[18] These domains of bias included study participation (study sample adequately represents population of interest), study attrition (available study data adequately represents the study sample), and outcome measurement (outcomes of interest are measured in a similar way for all participants). Use of the QUIPS tool has been described previously.[17]

revealed nonsignificant decreases in absolute and *z* scores for BMD.[19,31] However, the duration of treatment varied significantly in these studies, being unknown in 1 study[31] and at least 1 year[19] and 2 years[29] in the others.

GnRHas in Transmale Adolescents

There was a greater reduction in BMD in transmale adolescents treated with GnRHas than transfemale adolescents. Two studies revealed a significant decrease in absolute and *z* scores for lumbar spine BMD,[19,31] whereas another study revealed a significant reduction in only *z* scores.[29] In 1 study, researchers quantified the reduction in BMD *z* scores as being 0.79 for individuals with a bone age <14 years and 0.56 for individuals with bone ages ≥14 years.[31] Two studies also revealed statistically significant reductions in BMD *z* scores at the hip and femoral regions in transmale adolescents.[19,31]

Estrogen

Estrogen monotherapy was associated with significant increases in both absolute BMD and *z* scores in the lumbar spine,[29,31] but not the hip,[31] of transfemale adolescents previously treated with GnRHas. Furthermore, their *z* scores after 2 years of estrogen were still below that of age- and birth-assigned sex-matched norms.[31] Specifically, *z* scores in the spine were −1.10 and −0.66 in those with younger (<15 years) and older (≥15 years) bone ages, respectively.

Testosterone

Testosterone monotherapy led to a significant increase in both absolute BMD and *z* scores in the lumbar spine[29,31] and hip[31] of transmale adolescents, who had previously been on GnRHas. However, their *z* scores did not reach that of age- and birth-assigned sex-matched controls, aside from the *z* scores in the hip of individuals with older bone ages. Specifically, *z* scores in the spine and hip were −0.15 and −0.37, respectively, in those with younger (<15 years old) bone ages and −0.06 and 0.02, respectively, in those with older (≥15 years old) bone ages.

Growth and Body Composition

GnRHas

Growth velocity decreased during treatment with GnRHas[29] in all transgender youth compared with pubertal-matched peers.[21] In particular, younger individuals, who had greater growth potential, had significantly lower height standard deviation scores (SDSs) after treatment.[21,29] One study revealed significantly lower height standardized values for transfemale adolescents only.[19] No researchers have examined whether individuals given GnRHas achieved their predicted final height after GAHs. After 1 year on GnRHas, individuals had a significant increase in body fat percentage[29] and BMI,[19,21] which was accompanied by a decrease in lean body mass.[29]

Progestins

Lynestrenol resulted in significant increases in weight and BMI absolute and *z* scores during the first 6 months with a return to baseline after 12 months of treatment.[30]

Antiandrogens

Cyproterone acetate resulted in a decrease in growth velocity compared with age-matched peers,[22] with a final height after 12 months of treatment also being significantly lower than age-matched peers with a mean standardized score of −0.309. There were no clinically significant changes in body weight and BMI after 12 months.

Estrogen

It is unclear whether differences in the pubertal stage and bone age at which estrogen was commenced contributed to the variable outcomes found because these data were not collected.[29] Estrogen in combination with cyproterone acetate resulted in reduced growth compared with age-matched peers in 1 study,[22] whereas another study revealed no change in growth velocity after estrogen.[29] Total BMI was significantly increased after estrogen in 1 study,[22,32] although another revealed that total BMI did not change after 6 months.[32]

Testosterone

Testosterone monotherapy resulted in increased growth velocity compared with age-matched peers in 1 study,[29] but the impact on final

height (nor the age and pubertal stage at commencement) was not specified. Testosterone was also associated with weight gain,[30] resulting in a significantly raised absolute BMI[20,30] from an average baseline of 20.7 to 22.4 within 6 months.[20] This increase in BMI was less than that of age-matched male adolescents.[32]

Other Physical Effects

GnRHas

After 1 year of GnRHa, there were no changes in carbohydrate or lipid metabolism as measured by fasting glucose, insulin, cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels.[29] In 1 study, researchers observed that alkaline phosphatase (ALP) was decreased as a likely secondary result of decreased bone turnover, whereas all other liver enzymes were unchanged.[21] In this same study, researchers also reported lower levels of creatinine and hypothesized that this might be due to reduced muscle mass but found that there was no correlation between change in muscle mass and creatinine.[21]

Progestin

Progestins were associated with an adverse lipid profile, with a significant decrease in HDL cholesterol by an average of 0.46 mmol/L and an elevation of LDL cholesterol by 0.37 mmol/L after 1 year.[30] There were no significant changes in hemoglobin A1c (HbA1c), glucose levels, insulin levels, or homeostasis model assessment (HOMA) index.[30] Alanine aminotransferase (ALT) increased after 12 months, but this was not clinically significant.[30] Mean hemoglobin (Hb) and hematocrit (Hct) levels increased in the first 6 months and subsequently remained stable.[30]

Antiandrogens

Cyproterone acetate was associated with a significant reduction in only triglycerides, but total cholesterol, LDL cholesterol, HDL cholesterol, HbA1c, glucose, insulin, and HOMA index were unaffected.[22] There was no change in liver enzymes or thyrotropin.[22] There was a slight decrease in Hb and Hct after 12 months, but this was not clinically significant.[22]

Estrogen

Apart from 1 study in which a significant decrease in HDL after 4 to 6 months was observed,[32] estrogen had no effect on carbohydrate and lipid metabolism.[22,29,32] Similarly, no significant changes in liver enzymes,[22,32] thyrotropin, or free thyroxine (fT4)[22] were noted with estrogen treatment. A significant increase in serum creatinine was seen after 12 months with combined estrogen and cyproterone acetate treatment.[22] Hb and Hct were found to have decreased initially but returned to baseline after approximately 6—12 months.[32] However, when estrogen was used in combination with a progestin, Hb and Hct levels did not change any further after 12 months.[22] Blood pressure (BP) was unchanged after 6 months of estrogen.[32]

Testosterone

Testosterone had no significant effect on carbohydrate and lipid metabolism.[29,30,32] Although in 1 study researchers observed raised liver enzymes (aspartate aminotransferase [AST] and ALT) after a year,[30] another study revealed no significant change in AST and a decrease in ALT after 4 to 6 months.[32] Testosterone treatment decreased thyrotropin and fT4 to be outside of the normal reference ranges, although these changes were not clinically relevant because there was no clinical or biochemical hypo- or hyperthyroidism in participants.[30] Serum creatinine increased after 6 months of testosterone with no subsequent change thereafter and was thought to reflect an increase in muscle mass.[30] Hb[20] and Hct[30] were increased after 6 months but remained stable during the next 6 months within the male reference ranges,[20,30] whereas another study revealed no significant change in these parameters at any stage.[32] Systolic BP was elevated in treated individuals, with an average rise of 5 mm Hg after 6 months.[20]

PSYCHOSOCIAL EFFECTS

All relevant results are shown in Table 3.

GnRHas

GnRHa treatment was associated with significant improvements in multiple psychological measures, including global functioning,[25–27] depression,[26,27] and overall behavioral and/or emotional problems.[26,27] The effects of GnRHas on anger and anxiety remain unclear with conflicting results.[26,27] Moreover, GnRHa treatment had no significant effect on symptoms of GD,[26,27] with researchers in 1 study observing a nonsignificant increase in GD and body image difficulties.[26]

Progestin, Antiandrogens, Estrogen, and Testosterone

Critically, no researchers have examined the psychosocial effects of these hormonal therapy types in transgender youth.

COGNITIVE EFFECTS

All relevant results are shown in Table 4.

GnRHas

In one study, researchers examined the effect of GnRHas on executive functioning using the Tower of London test, which is used to assess mental planning ability.[24]

After GnRHa treatment, there was significantly reduced accuracy in transfemale adolescents.[24] There was also exaggerated regional brain activation typical of birth-assigned sex on functional magnetic resonance imaging (fMRI).[24] However, given the small sample size (8 participants), these results should be interpreted cautiously.

In another study, researchers examined the effect of GnRHa treatment on mental rotation in transmale adolescents,[23] exploring whether rotated pairs of three-dimensional shapes were identical images of each other.[35,36] Because men significantly perform better on this task compared with women, this result has also previously been suggested as evidence for the classic theory of the organizational and activational effects of sex hormones on the brain.[37,38] Interestingly, GnRHa suppression in transmale adolescents was associated with male brain activation patterns, with reduced activity in the right frontal area.[23]

Progestin, Antiandrogens, and Estrogen

No researchers have examined the cognitive effects of these treatments.

Testosterone

In the same study, researchers also examined the effects of testosterone in transmale adolescents on mental rotation tasks, in which they observed moderate to strong improvements in accuracy and reaction time.[23] Similar to control boys, treated transmale adolescents also demonstrated increased activation of brain regions implicated in mental rotation on fMRI.[23]

DISCUSSION

This is the first systematic review of the effects of hormonal treatment in transgender youth; authors of previous systematic reviews in this field, including those commissioned by the recent Endocrine Society Clinical Practice Guidelines, focused on the use of GAHs in adults.[8–11,15]

GnRHas successfully suppressed endogenous puberty, consistent with the primary objective of this treatment, although there was only a single study in which researchers actually recorded these data.[29] GnRHas were observed to be associated with significant improvements in global functioning,[25–27] depression,[26,27] and overall behavioral and/or emotional problems[26,27] but had no significant effect on symptoms of GD. The latter is probably not surprising, because GnRHas cannot be expected to lessen the dislike of existing physical sex characteristics associated with an individual's birth-assigned sex nor satisfy their desire for the physical sex characteristics of their preferred gender. Like GnRHas, the antiandrogen cyproterone acetate effectively suppressed testosterone in transfemale adolescents,[22] but its potential psychosocial benefits remain unclear. Meanwhile, GAHs increased estrogen and testosterone levels and thus induced feminization and masculinization, respectively, of secondary sex characteristics.[22,29] However, in the case of breast development, the outcomes were subjectively less in size than expected in the majority of recipients,[22] and the potential psychosocial benefits of GAHs remain unknown. Finally, although the use of the progestin (lynestrenol) has been studied in transmale adolescents,[30] its effects were predominantly examined in the context of potential adverse effects, so the therapeutic impact of progestins for menses suppression and psychosocial outcomes cannot be understood from the current literature.

Overall, hormonal treatments for transgender youth were observed to be relatively safe but not without potential adverse effects. For GnRHas, a significant concern in clinical practice is their potential effects on BMD accrual; their use was associated with a significant reduction in BMD,[19,29,31] which appeared to be worse for transmale adolescents[19,31] and is consistent with previous studies of nontransgender youth[39,40] and adults[41] who received GnRHas. However, given the relatively short follow-up duration of the studies reviewed here, it will be important for future researchers to better establish if this reduction in bone density is long-lasting or transient, as observed in nontransgender youth after GnRHa cessation.[39,40] It is notable that BMD increased after estrogen and testosterone, which suggests potential compensation by GAHs. However, for estrogen treatment, the BMD of those who had previously received GnRHas still remained lower than age-matched peers 2 years after estrogen treatment,[31] so compensation may only be partial. Furthermore, there is a lack of reporting of pubertal stage at treatment commencement, which makes interpretation of some changes difficult, especially BMD.

Clinically, patients who receive GnRHas and still have significant growth potential are counseled about the risk of the treatment affecting their final height. Although researchers in 2 studies have now examined growth and height characteristics in transgender youth receiving GnRHas,[21,29] their relatively short follow-up times (≤3 years) precluded determination of the effects of GnRHas on final height, and future researchers should address this knowledge gap. Another clinical concern in the use of GnRHas is the induction of menopausal-like symptoms due to the withdrawal of sex steroids, especially in postpubertal individuals. GnRHas were commonly observed to cause hot flashes in transmale adolescents in late puberty, but these decreased in frequency over time.[29] For

potentially similar reasons, one of the main complaints after cyproterone acetate administration in transmale adolescents was fatigue.

Hormonal treatment of transgender adults is known to be associated with various metabolic and cardiovascular effects.[10–12] GnRHas significantly increased both body fat percentage[29] and BMI[19,21] while decreasing lean body mass.[29] Similarly, testosterone significantly increased both body fat and BMI.[20,29] Although lynestrenol also increased BMI, this was transient, with BMI returning to baseline after 12 months.[30] Cyproterone acetate was not associated with any changes in BMI.[22] In terms of lipid metabolism, neither testosterone nor estrogen had any observable impact, but lynestrenol was associated with lower HDL and higher LDL cholesterol after 1 year,[30] whereas cyproterone acetate significantly reduced triglycerides.[22]

The findings from this review are subject to limitations. Firstly, the current literature has a limited number of studies in which the different hormonal treatments in transgender youth is examined. Secondly, for any given class of hormonal treatments, there is a variety of different agents, formulations, and administration routes that are being used clinically in transgender youth. For example, the physical effects of 1 antiandrogen and 1 progestin have been studied in only 1 study each, with no confirmation of results or further exploration. Thirdly, in existing studies there is a medium to high risk of bias, given small sample sizes, retrospective nature, and lack of long-term follow-up. In this regard, although randomized controlled trials are often considered gold standard evidence for judging clinical interventions, it should be noted that, in the context of GD in which current guidelines highlight the important role of hormonal treatments,[15] conducting such trials would raise significant ethical and feasibility concerns. Fourthly, authors of existing studies have neglected several key outcomes. These include the following: psychological symptoms related to GD, which is a critical knowledge gap given the high rates of mental health problems observed in transgender youth and justification of these treatments as treating GD[42]; the impact of hormonal treatments on fertility, which is an integral part of the counseling recommended by current guidelines[15]; and potential adverse effects such as arterial hypertension, which was reported in a recent case series in association with GnRHas.[43] Finally, there are no known studies to date in which researchers have reported the rates and circumstances under which transgender youth cease their hormonal therapy in an unplanned manner or the risk of subsequent regret, which would be of great clinical utility.

Notwithstanding these limitations, collectively, the studies reviewed provide qualified support for the use of GnRHas, GAHs, cyproterone acetate and, to a lesser extent, lynestrenol in transgender youth. Overall, these hormonal treatments appear to provide some therapeutic benefits in terms of physical effects and are generally well-tolerated on the basis of current evidence.

CONCLUSIONS

Looking ahead, it will be essential for future researchers to reassess and expand on the findings of the existing studies. Large, prospective longitudinal studies, such as have been recently initiated,[44] with sufficient follow-up time and statistical power and the inclusion of well-matched controls will be important, as will the inclusion of outcome measures that investigate beyond the physical manifestations.

ABBREVIATIONS

ALT: alanine aminotransferase
AST: aspartate aminotransferase
BMD: bone mineral density
BP: blood pressure
fMRI: functional magnetic resonance imaging
FSH: follicle-stimulating hormone
fT: free testosterone
fT4: free thyroxine
GAH: gender-affirming hormone
GD: gender dysphoria
GID: gender identity disorder
GnRHa: gonadotropin-releasing hormone analog
Hb: hemoglobin
HbA1c: hemoglobin A1c
Hct: hematocrit
HDL: high-density lipoprotein
HOMA: homeostasis model assessment
LDL: low-density lipoprotein
LH: luteinizing hormone
QUIPS: Quality in Prognosis Studies
SDS: standard deviation score
SHBG: sex-hormone binding globulin

Ms Chew screened studies for inclusion and exclusion, conducted the data extraction, conducted the analyses, drafted the initial manuscript, and revised the manuscript; Dr May screened studies for inclusion and exclusion, conceptualized and designed the study, and reviewed and revised the manuscript; Dr Anderson conducted the data extraction, conducted the analyses, and revised the manuscript; Prof Williams reviewed and revised the protocol and manuscript; Dr Pang conceptualized and designed the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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