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Approach to the Patient

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Pharmacological Management of Trans and Gender-Diverse Adolescents

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Abbreviations: BMI, body mass index; BMD, bone mineral density; CPA, cyproterone acetate; GAH, gender-affirming hormone; GD, gender dysphoria; GnRHa, GnRH agonist; GV, growth velocity; PS, pubertal suppression; TGD, trans and gender-diverse.

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Abstract

Internationally, increasing numbers of children and adolescents with gender dysphoria are presenting for care. In response, gender-affirming therapeutic interventions that seek to align bodily characteristics with an individual's gender identity are more commonly being used. Depending on a young person's circumstances and goals, hormonal interventions may aim to achieve full pubertal suppression, modulation of endogenous pubertal sex hormone effects, and/or development of secondary sex characteristics congruent with their affirmed gender. This is a relatively novel therapeutic area and, although short-term outcomes are encouraging, longer term data from prospective longitudinal adolescent cohorts are still lacking, which may create clinical and ethical decision-making challenges. Here, we review current treatment options, reported outcomes, and clinical challenges in the pharmacological management of trans and gender-diverse adolescents.

Key Words: transgender, gender dysphoria, gender diverse, hormone therapy, adolescents

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Case Presentations

Case 1

R.C. is 12 years old. Her female gender expression commenced in early childhood when she began to describe herself as a girl, express that her body was "wrong," and ask for her penis to be removed. At the age of 8 years, she socially transitioned to living as a girl, with improvement in her wellbeing and psychological distress, and her female gender identity has been consistent and persistent for many years. In recent months, she started puberty and is now experiencing distressing erections as well as an intense fear of developing a deeper voice, facial hair, and an Adam's apple. She has been assessed by mental health clinicians as meeting Diagnostic and Statistical of Manual of Mental Disorders, 5th edition criteria for Gender Dysphoria (GD) (1) (Table 1). R.C. is keen to access pubertal suppression (PS) to prevent further masculinizing changes. She also expresses a longer term goal to feminize her body and therefore envisages progression not only to gender-affirming hormone (GAH) therapy with estrogen but also feminizing surgery. Baseline examination and investigation findings are shown in Table 2.

Case 2

H.G. is a 15-year-old adolescent. He describes not thinking much about gender as a young child, but reports feeling different from age ~10 years of age in the context of early pubertal changes; thereafter, he reported increasing discomfort in relation to his body, with significant escalation in distress in the past 2 to 3 years. He describes his gender identity as "definitely not female," with progression to consistent feelings of a more masculine identity over time. Menarche occurred at age 12.5 years. His chest, voice, menstruation, and misgendering as female are the predominant sources of his GD. In the past 2 years, his mental health has deteriorated with heightened anxiety around school and social engagements. His mood is low, with intermittent deliberate self-harm. He has been assessed as meeting Diagnostic and Statistical of Manual of Mental Disorders, 5th edition, criteria for GD (1) and is seeking hormonal intervention. His gender-affirming goals are to "pass" as male with a deeper voice, flat chest appearance, and facial hair. He reports no desire for future pregnancy or parenting but recognizes that his views on this may change over time and has been counselled on the potential effects of testosterone on fertility. Baseline examination and investigation findings are shown in Table 2.

Introduction

Internationally, presentations of trans and gender-diverse (TGD) children and adolescents seeking support and therapeutic intervention from specialist clinics have significantly increased in recent decades (2-4), consistent with recent population-based surveys suggesting that TGD individuals comprise 1.2% to 2.7% of all young people (5, 6). Key terminology continues to evolve in this area and is summarized in Table 3. Gender incongruence is characterized by a marked and persistent mismatch between an individual's experienced gender and their assigned sex (7).

Table 1. Definition and criteria for a diagnosis of gender dysphoria

The Diagnostic and Statistical of Manual of Mental Disorders, 5th edition (1) defines gender dysphoria as a marked incongruence between an individual's experienced/expressed gender and their assigned gender that has been present for at least 6 months *and* is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

In adolescents and adults, this is manifested by at least 2 of the following:

- A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics
- A strong desire to be rid of one's primary and/or secondary sex characteristics (or in young adolescents, a desire to prevent the development of anticipated secondary sex characteristics)
- A strong desire for the primary and/or secondary sex characteristics of the other gender
- A strong desire to be of the other gender
- A strong desire to be treated as the other gender
- A strong conviction that one has the typical feelings and reactions of the other gender

In children, gender dysphoria is manifested by at least 6 of the following (one of which *must* be the first criterion):

- A strong desire to be of the other gender or an insistence that one is the other gender
- A strong preference for wearing clothes typical of the opposite gender
- A strong preference for cross-gender roles in make-believe play or fantasy play
- A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender
- A strong preference for playmates of the other gender
- A strong rejection of toys, games, and activities typical of one's assigned gender
- A strong dislike of one's sexual anatomy
- A strong desire for the physical sex characteristics that match one's experienced gender

Table 2. Clinical details of case illustrations

	Case 1			Case 2		
Sex assigned at birth	Male			Female		
Gender identity	Female			Masculine		
Current age	12 y, 2 mo			15 y, 3 mo		
Pubertal development	Testicular volumes: 6-8 mL Stretched penile length: 6.5 cm Tanner staging: G2,PH 2-3			Tanner staging: B5 Age of menarche: 12.5 y		
Blood pressure	104/58			138/84		
		Centile			Centile	
		Assigned	Affirmed		Assigned	Affirmed
Height	161.4 cm	93.0	89.4	158.4 cm	28.5	6.0
Weight	52.1 kg	86.0	82.8	71.9 kg	92.4	87.6
Body mass index	20.0 kg/m^2	77.2	72.2	28.7 kg/m^2	95.4	96.9
Baseline index		Reference [a]:			Reference[a]:	
LH	1.7 IU/L	1.0-10.0 IU/L		8.3 IU/L	0.8-15.5 IU/L	
FSH	3.9 IU/L	0.0-6.0 IU/L		6.5 IU/L	0.0-15.0 IU/L	
Testosterone	3.4 nmol/L			0.6 nmol/L	0.4-2.5 nmol/L	
Estradiol	<18 pmol/L			330 pmol/L	70-936 pmol/L	
LFT	Normal			ALT 52; others normal	ALT < 35	
Lipid profile	Normal			Normal	1.0–3.0 nmol/L	
FBE	Normal			Normal		
HbA_{1C}	4.7%	4.5%-5.7%		5.4%	4.5%-5.7%	
25(OH) vitamin D	28 nmol/L	50-150 nmol/L		38 nmol/L	50-150 nmol/L	
Bone age[a,b]	12 y			16 y		
DXA[a]	L-spine: -1.4 SD			N/A		
	Hip: -1.8 SD			N/A		

Abbreviations: ALT, alanine transaminase; DXA, dual energy X-ray absorptiometry; FBE, full blood examination; FSH, follicle stimulating hormone; HbA1c, glycated hemoglobin; LFT, liver function tests; LH, luteinising hormone; N/A, not available.
[a]Relative to birth-assigned sex reference.
[b]Greulich and Pyle assessment.

This may be associated with GD (1), although not all TGD individuals experience dysphoria. TGD youth are a vulnerable population, with a higher prevalence of social isolation, harassment, mental health problems (notably mood and anxiety disorders), self-harm, and suicidality compared with the general population (2, 3, 8-12).

Therapeutic interventions that aim to more closely align bodily features with an individual's gender identity have evolved over the past few decades. Gender-affirming hormonal interventions were first initiated for TGD adolescents by clinicians in the Netherlands >30 years ago (13). Today, various clinical guidelines (3, 14-16) recommend hormonal interventions for adolescents with GD who meet defined criteria (Table 4). A multidisciplinary approach to management is important (3, 14, 15), and the involvement of an experienced mental health clinician is critical, not just to assess GD but also to determine readiness for, and provide monitoring during, hormonal therapy.

A range of different pharmacological options exist for the management of adolescents with GD (Table 5) and are described next.

Pubertal Suppression

Although dysphoria is not universal, the development and progression of secondary sex characteristics incongruent with one's gender identity are recognized precipitants of increasing GD and worsening mental health in TGD adolescents (3, 17, 18). PS aims to temporarily suspend sex hormone production and the development of secondary sex characteristics incongruent with an individual's gender identity. GnRH agonists (GnRHa) are the recommended means of PS for those in early or mid-puberty (14, 15), reflecting their efficacy in achieving biochemical and clinical PS (19).

GnRHa agents act via reversible desensitization of the GnRH receptor, with spontaneous resumption of the hypothalamic-pituitary-gonadal axis expected within months if therapy is discontinued (15, 20, 21). Treatment temporarily prevents further pubertal progression, allowing TGD adolescents more time to explore their gender identity without experiencing ongoing incongruent pubertal development. As such, PS with GnRHa is a therapeutic intervention in its own right and, although recent data indicate that

Table 3. Commonly used terminology in transgender health

Affirmed gender	The gender with which one identifies (which may or may not match that assigned at birth).
Birth-assigned male	A person who was recorded as male at birth (typically based on external genital appearance) and initially raised as a boy.
Birth-assigned female	A person who was recorded as female at birth (typically based on external genital appearance) and initially raised as a girl.
Cisgender	A term for someone whose gender identity aligns with the sex they were assigned at birth.
Gender-affirming hormone therapy	A term used to describe hormonal interventions that aim to reduce endogenous pubertal sex hormone production and induce secondary sex and physical characteristics congruent with gender identity.
Gender-affirming surgery	A term that describes surgical procedures that may be undertaken by individuals who want to adapt their bodies to better align with their gender identity. Current international guidelines recommend genital surgery is delayed until age 18 years or older, whereas chest surgery may be appropriate at a younger age (assessed individually).
Gender diverse	A term to describe people whose gender identity differs from culturally defined expectations of masculine or feminine "norms." Being transgender is 1 way of being gender diverse, but not all gender diverse people are transgender.
Gender dysphoria	Clinically and/or functionally significant distress arising from the incongruence between one's birth-assigned sex and gender identity.
Gender expression	The outward presentation of a person's gender, which may include name, pronouns, clothing, hairstyle, behavior, or voice. Gender expression may or may not reflect a person's inner gender identity based on traditional and cultural expectations.
Gender identity	A person's innermost concept of self as male, female, a blend of both, or neither. One's gender identity is not visible to others and can be the same or different from the sex assigned at birth.
Gender incongruence	A term used for a marked and persistent incongruence between an individual's experienced gender and their assigned sex. Diagnostic term in International Classification of Diseases, 11th revision.
Gender nonbinary	A term to describe someone who does not identify exclusively as male or female, but whose identity falls in between or outside of this typical gender binary.
Medical transition	The process by which a person uses hormonal intervention(s) and/or surgery to change their physical appearance and sex characteristics to more closely align with their gender identity.
Puberty suppression/"blockers"	The process of temporarily inhibiting endogenous pubertal sex hormone production to prevent progression of secondary sex characteristics.
Sex assigned at birth	Refers to the sex designated and recorded at birth (typically based on external genital appearance).
Sexual orientation	An individual's physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of gender identity, an individual may be attracted to women or men, both, or neither.
Social transition	The process by which a person changes their gender expression to more closely align with their gender identity.
Transfemale	A person who was assigned male at birth but identifies as female.
Transfeminine	A person who was assigned male at birth but identifies as feminine or gender nonbinary but closer to the female end of the gender spectrum.
Transmale	A person who was assigned female at birth but identifies as male.
Transmasculine	A person who was assigned female at birth and who identifies as masculine or gender nonbinary but closer to the male end of the gender spectrum.

a majority of TGD adolescents who undergo PS proceed to GAH or surgery in due course (22, 23), these subsequent treatment pathways should not be regarded as a fait accompli once PS has been initiated. TGD young people on GnRHa should continue to be counselled, with ongoing assessment and discussion of their desire to continue to PS as well as their longer term therapeutic goals.

A variety of GnRHa agents and formulations are currently available and there are no reported differences in efficacy in the context of treating TGD adolescents (24). Formulations differ predominantly in their mode of administration and duration of effect, with depot preparations that afford longer suppression often being preferred. Choice of a particular GnRHa agent depends on patient and physician preference, local therapeutic agency approval, and cost. In practice, effective PS may extend beyond the approved dosing schedule (25). Given the high cost of GnRHa therapy and need for removal/replacement procedures with implants, it is not uncommon for clinicians to monitor for pubertal reawakening before administering the subsequent dose.

Table 4. Typical criteria for hormonal interventions in TGD adolescents[a]

- Confirmation of diagnosis of GD by an experienced mental health professional
- Adolescent is in established puberty and experiencing heightened symptoms of dysphoria with onset of puberty (for GnRHa therapy)
- Adolescent has been given comprehensive information as to the expected, possible, and unknown effects of the proposed therapy (including implications for fertility and options to preserve fertility)
- Psychological, social, and medical circumstances are stable enough to commence treatment and no medical contraindications exist
- The adolescent, their parent/guardian(s), and treating clinicians (both medical and mental health) agree that the proposed treatment is in the adolescent's best interests
- Informed consent has been given for treatment to commence[b]

Abbreviations: GD, gender dysphoria; GnRHa, GnRH agonist; TGD, trans and gender-diverse.
[a]The exact criteria that appear in various published guidelines and position statements (3, 14-16) differ. Those listed here are a representative amalgam. Clinicians should be aware that where reimbursement for gender-affirming therapy may be accessed through private health insurance, the insurance company may require that particular criteria be met or that particular guidelines (eg, World Professional Association for Transgender Health) be used for treatment to be covered.
[b]Many older adolescents may have the capacity to give their own consent to treatment and indeed this is often considered preferable, particularly for estrogen and testosterone where effects are partially irreversible; however, issues pertaining to consent differ in different jurisdictions.

Modulation of Endogenous Pubertal Hormone Effects

A number of other agents are used in TGD adolescents to modulate the effects of endogenous pubertal hormones. Agents with antiandrogenic properties may have beneficial effects for TGD individuals with a feminine identity, whereas high-dose progestogens can achieve menstrual suppression in transmasculine or gender nonbinary youth. These agents modulate potentially distressing symptoms of incongruent puberty without causing full PS, and therefore are not typically considered first-line if PS is indicated. They may however be used when affirming care is sought at Tanner 4+ (when the higher likelihood of adverse effects from abrupt hormonal withdrawal (23) arguably outweighs the more marginal effects on physical development) or where GnRHa therapy is unavailable, precluded by cost, or undesirable (eg, needle phobia) (15).

Antiandrogens with reported use in TGD populations include cyproterone acetate (CPA), spironolactone, medroxyprogesterone acetate, and bicalutamide (26). Of these, spironolactone and CPA are most commonly used (27, 28), although outcome data specific to TGD adolescents are limited. Spironolactone has well documented antiandrogenic effects (29, 30). CPA has been found to effectively reduce facial and body hair in a majority of late pubertal transgirls, with fewer spontaneous erections also reported by some (31). Choice of agent may be influenced by availability (CPA is not available in the United States because of safety concerns), clinician experience, cost, patient preference, and tolerability. Some antiandrogens contribute to breast development (26, 31, 32). This may arise because of lower testosterone levels (hence altered circulating estrogen:testosterone ratio), as a progestogenic effect or a combination of mechanisms; however, the relative roles of different hormones or agents in promoting breast growth are not well established in TGD populations (33). Optimal dosing strategies are unknown but much lower doses of agents such as CPA (eg,12.5 mg daily or alternate daily) than were initially studied (up to 100 mg daily) are currently used.

For transmasculine youth, suppression of menses is often desired, not only to help relieve menstruation-associated GD, but also given prevalent safety concerns in accessing bathrooms (34). Options include a progestogen, such as medroxyprogesterone (orally or injectable depot), oral lynestrenol, or norethisterone, either alone or in a continuous combined oral contraceptive pill (although many transmasculine youth may decline this because of concerns regarding estrogen use) (35, 36). Highest rates of amenorrhoea are reported with depot medroxyprogesterone (35), although concerns regarding adverse impacts on bone health limit its use as a first-line choice. The levonorgestrel-containing intrauterine device is another option, particularly if contraception is desired. Pelvic ultrasound to confirm sufficient uterine cavity size may be beneficial in such cases, especially in individuals presenting soon after menarche, and some TGD adolescents will require light sedation or a short anesthetic to tolerate insertion. Irregular, unpredictable bleeding may occur with all progestogens, which may lead to discontinuation (36). Ultimately, for those who use testosterone as masculinizing GAH therapy, circulating testosterone levels in the adult male range will induce menstrual suppression in >90% of cases (35). Involvement of pediatric gynecology services is very useful for gynecological, reproductive, and sexual health aspects of TGD care.

Gender-affirming Hormone Therapy

Exogenous estrogen or testosterone may be prescribed to adolescents wishing to feminize or masculinize, respectively (3, 14, 15). The principal goal of GAH therapy is to induce desired secondary sex characteristics congruent with an individual's identity; however, specific goals and priorities for gender affirmation vary between individuals.

Table 5. Gender-affirming pharmacological interventions—examples of agents used, mechanism of action, effects, and suggested monitoring

Indication	Examples of agents and dosing[a]	Mode and frequency of administration[a]	Mechanism(s) of action	Effects considered reversible[b]	Potentially irreversible effects[b]	Monitoring[c]
Puberty suppression	**GnRHa** *Leuprolide* 7.5/22.5/30/45 mg *Triptorelin* 11.25/22.5 mg *Goserelin* 3.6/10.8 mg *Histrelin* 5 mg	 IM 4/12/16/24 weekly IM 3/6 monthly SC 4/12 weekly SC annually	Central suppression of HPG axis	Suppression of HPG axis	Bone health: reduced BMD accrual may not fully revert; long term effect unclear.	3-6 monthly: Growth: height, weight BP, puberty 6-12 monthly: LH, E2/T, 25OHD Annual DXA
Modulation of androgen effect	*Cyproterone acetate (CPA)* 50-100 mg[d] *Spironolactone (S)* 50-100 mg *Bicalutamide (B)* 50 mg	PO; daily (or less frequently[d]) PO; daily or bd PO: daily	AR antagonist: B, CPA, S PR agonist: CPA, S HPG suppression: CPA Inhibition of steroidogenic pathway (T production): S	Reduction of body and facial hair Decreased oiliness of skin Reduced libido	Unclear If it arises, breast development (B, S) may not fully revert	Electrolytes (S) LFT (B)
Suppression of menstruation	**Progestogens** *Medroxyprogesterone (M):* 150-mg implant/104 mg injection/10-20 mg tablet *Lynestrenol* 5 mg *Norethisterone* 5-20 mg *Levonorgestrel* **Combined OCP**[g] **Testosterone** (see next section)	 IM/SC 12-14 weekly or PO od-bd PO od PO od-tds[f] IUD ~5 yearly PO—daily	Altered endometrial angiogenesis; inhibition of endometrial proliferation Central GnRH inhibition (higher dose M) IU levonorgestrel—local inhibitory effects on endometrium	Suppression of menses	Unclear: reduced BMD accrual (with depot M implant) may not fully revert	Depot M: bone health[e] BP
Feminization	**17ß estradiol/estradiol valerate** Oral: 5 µcg/kg/day-2 mg/day; up to 6 mg/day reported Transdermal: 6.25 mcg-100 mcg **Estradiol valerate/cypionate** 5-30 mg	 PO daily Patch: apply once-twice per week IM every 14 days	Stimulation of estrogen receptor Central suppression of HPG axis[i]	Softening of skin Body fat redistribution Decreased libido; decreased erections Reduction of body and facial hair	Breast tissue Epiphyseal fusion/growth Fertility effects (spermatogenesis)	3-6 monthly[b]: Growth: height, weight BP, reported feminization 6-12 monthly: Prolactin, E2 25OHD 1-2 yearly: BMD with DXA

Table 5. Continued

Indication	Examples of agents and dosing[a]	Mode and frequency of administration[a]	Mechanism(s) of action	Effects considered reversible[b]	Potentially irreversible effects[b]	Monitoring[c]
Masculinization	*Testosterone cypionate* or *Testosterone enanthate* 12.5-50 mg increasing to 200-250 mg (higher dose less frequently)	SC: 1-4 weekly or IM 2-4 weekly	Stimulation of androgen receptor Central suppression of HPG axis[i]	Acne skin changes Increased libido; increased muscle mass	Voice lowering Alopecia	3-6 monthly: FBE (hematocrit); lipids; T Growth: height, weight
	Testosterone undecanoate[j]	IM 1000 mg 12 weekly (once adult dosing established)		Menstrual suppression	Facial hair; genital changes/clitoral growth	BP, reported virilization
	Testosterone gel 1% (12.5-50 mg) *Testosterone pellets*[j] (2-4 mg pellets)	Topical daily		Body fat redistribution	Vaginal mucosal thinning	6-12 monthly: T, FBE, lipids, 25OHD 1-2 yearly: BMD with DXA

Abbreviations: 25OHD, 25-hydroxyvitamin D; AR, androgen receptor; B, bicalutamide; bd, twice daily; BMD, bone mineral density; BP, blood pressure; CPA, cyproterone acetate; DXA, dual energy X-ray absorptiometry; E2/T, estrogen/testosterone; FBE, full blood examination; GnRHa, Gonadotropin releasing hormone agonist; HPG, hypothalamic-pituitary-gonadal; IM, intramuscular; IUD, intrauterine device; LFT, liver function tests; LH, luteinising hormone; od, once daily; od-bd, once-twice daily; PBM, peak bone mass; PO, by mouth; PR, progestogen receptor; S, spironolactone; SC, subcutaneous; T, testosterone; tds, three times daily; TGD, trans and gender-diverse

[a]Relates to reports in the literature in TGD populations; note—use in this context may be off-label and not all agents have reported data in adolescent TGD populations.

[b]Either gender-affirming or potentially unwanted effects.

[c]Ongoing monitoring of potential unwanted/ adverse effects (eg, drug reaction, mood effects, fatigue/altered energy, fluid retention, headaches).

[d]Optimal dosing of antiandrogenic agents is unknown; studies of smaller and less frequent doses of agents such as CPA are under way.

[e]Consider DXA if additional bone health risk factors (eg, low 25-OHD, history of low impact fracture).

[f]Titrate to response—may need 5-10 mg bd-tds to achieve amenorrhoea; use lowest effective dose.

[g]Numerous combined oral contraceptive pills are available, commonly containing a synthetic estrogen and progestogen. First- or second-generation oral contraceptive pills contain more androgenic progestins, which may be more acceptable in TGD youth; however, they also have a higher thromboembolic risk profile.

[h]Reiteration of need for preventive measures to reduce thromboembolic risks. Need for prolactin monitoring can be individualized (eg, if also on CPA).

[i]Through negative feedback—greater effect when used in supraphysiological doses.

[j]Limited data in adolescent TGD cohorts.

Where PS is commenced in early puberty and the adolescent is relatively naïve to sex hormone, GAH is conventionally introduced at a low dose with gradual incremental dose increases timed to mimic the tempo of typical puberty. For adolescents already in well-established puberty (Tanner 4+), introduction and escalation of GAH therapy can be more rapid (3, 15).

Medications that contain 17 ß-estradiol are most commonly recommended for feminization. Use of ethinyl estradiol-containing medications should be avoided because of higher thromboembolic risks (15, 37). Oral and transdermal agents are the most commonly used routes in many countries, with injectable and sublingual options available in some jurisdictions. Published dosing strategies (15) are largely based on experience and expert opinion, and prospective controlled studies comparing different regimens are lacking (37, 38).

Although exogenous estrogen therapy will provide some hypothalamic-pituitary-testicular axis suppression, experience in adult cohorts indicates that estrogen alone is unlikely to provide sufficient suppression without use of supraphysiological doses (and attendant increase in risk of adverse effects). Concomitant GnRHa therapy can therefore be beneficial, but use of an antiandrogen is a common alternative if GnRHa is not available (15, 37). Ultimately, some transfeminine individuals elect to undergo gender-affirming surgery including orchiectomy, which will remove the need for GnRHa or an antiandrogen; however, this is generally not performed until age >18 years (3, 14, 15).

Testosterone regimens in TGD adolescents seeking to masculinize reflect those used in hypogonadal cisgender males. International guidelines recommend use of short-acting injectable preparations (2-4 weekly) and these are the most commonly reported agents in adolescent cohorts (3, 15, 37, 38). However, if unavailable or unacceptable (eg, because of frequent injections), alternative regimens and routes may also be used (3, 15). Longer acting injectable testosterone preparations are more typically reserved for use in those with well-established pubertal hormone exposure. Dose modulation is more easily undertaken with short-acting injectable testosterone esters or topical preparations. PS or alternative therapies to modulate the effects of endogenous pubertal hormones (eg, progestogens) are typically continued until adult testosterone levels are consistently established.

Therapeutic Effects of Hormonal Intervention

Gender-affirming Physical Changes

Physical outcomes more congruent with gender identity have also been reported among TGD adults who received PS compared with those who completed endogenous puberty (39, 40). Desired masculinizing effects reported in testosterone-treated TGD cohorts include voice deepening, increased facial and body hair growth, clitoral growth, and cessation of menses (9, 15, 41). Many of these effects become established within 6 to 12 months and continue to develop thereafter (15). In transfeminine adolescents treated with estrogen, the main gender-affirming physical changes include breast development (starting within 3-6 months and continuing to Tanner 4+ in >80% at 3 years (42)) and feminization of body shape and fat distribution (42-44). Studies comparing different GAH regimens head-to-head are currently unavailable. Because many gender-affirming physical effects are gradual and may take years to become fully established, open discussion of the estimated timelines involved (see Endocrine Society Guidelines 2017 (15)) is important to ensure realistic expectations, especially for adolescents whose long-term and abstract thinking is still developing.

Mental Health

Most empirical studies have reported improved mental health outcomes in TGD youth using hormonal therapies; however, the overall quality of evidence is low with studies limited by small sample sizes which may preclude the ability to determine statistically significant effects in some outcomes (23, 45-50). Suboptimal study design (eg, cross-sectional (51), retrospective (45, 52), lacking a well-matched control group (23, 45-48, 50, 52-54)), and use of various nondiagnostic screening tools (23, 47, 50, 51, 53) are additional methodological limitations. Although studies with prospective/ longitudinal designs (23, 46-51, 53, 54) have emerged, randomized controlled trials are lacking. Studies assessing outcomes in socioeconomic and ethnically diverse populations or gender nonbinary adolescents are also scarce. Despite these limitations, as outlined here, improvements have been noted across most empirical studies following use of both PS alone and GAH (either alone or with PS) in the outcomes of overall psychological functioning, depressive symptoms, self-harm, and suicidal ideation. Additionally, improvements in GD and body image with use of GAH have been reported.

Overall psychological functioning

General psychological wellbeing, assessed using Youth Self Report (23, 47, 49-51), the Child behavior checklist (23, 47, 49, 50), or the Children's Global Assessment scale (47, 50, 53), significantly improved from baseline following PS alone in 3 studies (50, 51, 53) but was unchanged in

another cohort, where notably, 57% were Tanner 4+ before PS (23).

Improved psychological functioning, with follow-up outcomes comparable to the general population, has also been reported following use of PS (53) and GAH and/or gender-affirming surgery (47, 49).

GD and body image

GnRHa therapy alone has not been associated with a subsequent change in GD or body dissatisfaction in adolescents (17, 23); however, as neither one's incongruent primary sex characteristics nor the absence of desired secondary sex characteristics are influenced by GnRHa therapy, this is not unexpected (38). Complete resolution of GD and significant improvements in body satisfaction with subsequent introduction of GAH and/or surgery have been documented (47, 54).

Depression and anxiety

Depressive symptoms decreased significantly from baseline after PS in a prospective longitudinal study of Dutch TGD adolescents (50), with no further significant change in symptoms noted after GAH/surgery (47). Two additional longitudinal studies also found self-reported depressive symptoms decreased from baseline in TGD youth receiving endocrine interventions (PS and/or GAH) (48, 54).

Longitudinal studies have shown anxiety is largely unchanged with PS alone (50, 54). Anxiety symptoms improved significantly among those who received either PS or GAH in 1 study (n = 102), whereas the decreases seen in another study (n = 32) were not statistically significant (47).

Self-harm and suicidal ideation

Five studies of PS and GAH documented significantly reduced rates of self-harm and suicidal ideation (45, 46, 48, 51, 52) and, importantly, in one of these, TGD adolescents undergoing PS had similar rates of self-harm/suicidality as cisgender controls (51). Another study (n = 44) reported no significant effect of PS alone (23).

Potential Side Effects of Hormonal Intervention

Available data indicate that hormonal treatments for TGD adolescents are generally safe (19, 42, 43). Nonetheless, it is important to consider the possibility of unwanted effects.

General physical, Hematological, and Biochemical Effects

GnRHa agents are typically well-tolerated (55), although hot flashes, headaches, emotional lability, and mood changes are described (15, 19, 23, 45), particularly early in treatment (56) and in those in more advanced puberty at GnRHa initiation (23). Similar symptoms have been described with CPA use (31). Transmasculine adolescents should also be counselled that the transient stimulatory effects of GnRHa may induce a menstrual bleed in the initial weeks after the first dose.

Electrolyte monitoring is recommended with spironolactone use but hyperkalemia has not been documented in TGD youth (57). CPA is not approved for use in United States because of concerns regarding hepatoxicity and meningioma (37); additional reported side effects include low mood, hyperprolactinemia, and less favorable cardiovascular profiles (15, 27, 58).

Testosterone therapy is commonly associated with acne, particularly in the first year (41, 45, 59). Erythrocytosis in association with exogenous testosterone use is also recognized (37, 60), with higher hemoglobin and hematocrit levels observed in adolescents on testosterone (43). Evaluation and attention to concomitant secondary causes (eg, smoking, obstructive sleep apnea) is important. Data from adult cis (61) and TGD (62) cohorts suggest erythrocytosis is highest with short-acting injectable preparations and lower with transdermal preparations. Therapeutic phlebotomy or change of testosterone dose, interval, or preparation may also be considered. Androgenic alopecia (45), higher blood pressure (63), and mild reductions in high-density lipoprotein (63, 64) have also been documented in some TGD adolescents using testosterone; a higher prevalence of obesity before and during testosterone therapy is also reported (64).

Estrogen-specific health risks relate predominantly to prothrombotic effects (37), although reports in adolescents are rare (65). To reduce this risk, use of 17ß-containing estrogens is recommended, whereas ethinylestradiol should be avoided (15). Transdermal delivery may also be helpful (66-68). Elevation in prolactin following estrogen therapy is also recognized (15, 37), likely exacerbated by CPA (27, 58, 69). Current guidelines recommend prolactin monitoring (15), but clinically relevant hyperprolactinemia has not been found in adolescent cohorts (42) and an individualized approach based on additional risk factors and medications is taken by many.

To date, no significant differences in cardiovascular risk factors have been observed in association with hormonal therapies in TGD youth treated from adolescence to early adulthood (64). Nonetheless, encouraging universally endorsed lifestyle measures that promote cardiovascular health—such as physical activity, healthy body mass index (BMI), and avoidance of smoking and prolonged immobility—and ongoing clinical monitoring are recommended.

Long-term assessment of cumulative risk in those who commence hormonal therapies in adolescence will be important.

Bone Health

Sex hormones drive the significant pubertal increase in bone mineral density (BMD) accrual, which is critical for optimizing peak bone mass in early adulthood and mitigating against osteoporosis and fractures later in life (70, 71). Unsurprisingly, PS affects BMD accrual and monitoring of bone health is recommended for all GnRHa-treated TGD adolescents (3, 14, 15). Interestingly, low BMD including high rates of BMD <2 SD below the median (72-75) have been reported in TGD adolescents even before commencement of PS. The underlying reasons are unclear but may reflect low rates of physical activity. Although longitudinal assessment in GnRHa-treated youth has documented either stable (72, 74) and/or slightly reduced mean group BMD (23, 73) relative to peers, approximately one-half of reported GnRHa-treated subjects appear to have lost absolute BMD during PS, which is concerning (76). Longitudinal data indicate improvement with GAH therapy, albeit with incomplete catch-up (73) and persistently low bone mineral apparent density *z*-scores in transfeminine individuals (77). Additional longer term follow-up studies will be required to assess the impact, if any, on functional outcomes such as fracture risk. In the meantime, promoting measures that optimize bone health, such as weight-bearing exercise and vitamin D sufficiency, is encouraged.

Fertility

Clinical guidelines underscore the importance of fertility counselling for TGD adolescents considering hormonal interventions, given their potential impact on reproductive function (3, 14, 15). In particular, concerns relate to the adverse effects of prolonged GAH on spermatogenesis and oocyte development (15, 78), and the reader is referred to comprehensive recent reviews for more details on this subject (79, 80). Nonetheless, counselling should address both the option of gamete cryopreservation before hormone commencement as well as the alternative (with documented success) of interrupting GAH treatment for a sustained period in the future to restore reproductive function (81-85). The associated implications of an interruption in GAH—which might include the development of undesired physical characteristics and an exacerbation of GD—may, however, be unacceptable to many TGD individuals (86). Although use of GnRHa therapy is not expected to permanently affect fertility, the high rates of progression from PS to GAH (22, 23) mean fertility counselling is recommended before PS (3, 14, 15). Oocyte cryopreservation from a transmale adolescent using GnRHa therapy from early puberty has also been reported (87). Additionally, transmasculine young people should be counselled that although it may induce amenorrhea, testosterone does not provide reliable contraception, and, in the event of a pregnancy, is teratogenic (15, 35). The need for an alternative means of effective contraception if engaging in vaginal intercourse should be emphasized (88).

Growth

In TGD adolescents with open epiphyses, GnRHa therapy will delay the pubertal sex hormone-dependent increase in growth velocity (GV) and prolong overall duration of growth. Subsequently, additional growth is expected following GAH initiation, with a higher GV than during PS. The cumulative impact of hormonal interventions on final height will vary depending on an individual's genetic height potential, bone age at the initiation of therapy, duration of PS and tempo of GAH dose escalation (15). Modulation of estrogen regimens to prevent excessive height in transfeminine adolescents has been attempted, albeit with unclear success and safety (42).

Impact on Feminizing Surgery Options

By limiting genital growth, the use of PS in early-mid puberty may restrict future feminizing surgical options, in particular penile inversion techniques for neovaginal formation (89, 90). Consequently, alternative surgical methods, such as peritoneal flaps or intestinal grafts, may be required but are surgically more complex and can be problematic (eg, because of unwanted intestinal tissue mucus production (91, 92)). A recent Dutch study found that among those deemed to have insufficient genital skin for penile inversion, stretched penile length was <8 cm (91). Counselling before GnRHa therapy should include discussion of locally available surgical options when considering optimal timing to initiate PS, while bearing in mind that surgical techniques are continuing to evolve as greater numbers of people treated with GnRHa seek feminizing surgery.

Cognition

Adolescence is associated with increasing maturity, cognitive gains, and ongoing neurodevelopment; however, the precise roles of sex hormones in these processes are not well established. Available data have not demonstrated

any adverse impact of PS on executive function in TGD youth; however, the sample size of this study was small and likely underpowered (93). A recent systematic review and meta-analysis of data in postpubertal TGD young adults reported no adverse impact of GAH on any cognitive domain assessed and significant improvement in visuospatial abilities following testosterone treatment (94).

Unwanted Psychosocial Impacts

A common concern when discussing gender-affirming interventions is the potential for future regret in the face of irreversible physical effects. To date, the largest study to systematically examine regret comes from the Netherlands and followed 6793 TGD individuals who attended a single gender identity clinic from 1972 to 2015 (4). Regret rate among those 5433 individuals who first presented as adults was 0.5%, and no cases of regret were observed among the 1360 individuals who were first seen before the age of 18 years. Although duration of follow-up varied, the cohort included adolescents aged 12 to 18 years and children <12 years from 1981 and 1984 onwards, respectively; overall numbers of both children and adolescents increased significantly from 2003. Ongoing, long-term follow-up of this and other adolescent cohorts who receive hormonal interventions in adolescence is required. Although GAS is uncommonly performed in adolescents aged <18 years, regret rates in those who undergo GAH in the presence or absence of subsequent GAS may also differ, and it will be important for future studies to assess this.

Data in adults also suggest testosterone may have a short-term impact on increasing aggression (95) but not anger (96, 97); however, these effects have not been well-studied in adolescent TGD cohorts. Ongoing review with an experienced mental health clinician over the course of medical transition is therefore important (3, 15).

Although GAH can assist with development of desired secondary sex characteristics, they will not reverse established anatomical features (eg, phenotypically male external genitalia). Ensuring realistic expectations and acceptance of the limitations of hormonal interventions before commencement is a critical part of counselling.

Sexual Function and Wellbeing

Sexual maturation is one of the hallmarks of adolescence, and the use of hormonal interventions in TGD young people can potentially affect sexual function and satisfaction.

Psychologically, the unwanted changes of a TGD adolescent's endogenous puberty can increase body and genital aversion, and thus influence their approach to sexual experiences and satisfaction (47). TGD adolescents have lower self-esteem and poorer body image, and are less romantically and sexually experienced than their cisgender peers (98). Because body image, self-esteem, psychological wellbeing, and sexual anxiety are all critical aspects of sexual health and satisfaction (99, 100), hormonal interventions have the potential to positively influence sexual wellbeing by improving GD (101, 102).

Physically, vaginal atrophy and dryness are common in postmenopausal women and other hypoestrogenic states (103), and might therefore be expected with GnRHa therapy in transmasculine individuals (104), but to date have not been reported. Testosterone can increase libido, induce clitoral growth, and cause vulvovaginal atrophy and dryness (that usually respond well to topical estrogen or lubricant therapy), whereas antiandrogens and estrogen typically reduce libido, erections, semen production, and ejaculate volume (15).

Taken together, hormonal interventions for TGD adolescents can be expected to affect desire, arousal, and/or sexual interest as well as the ability to orgasm (105). However, it is important to note that some of the apparent disturbances or changes in sexual function do not necessarily translate to sexual dysfunction because they may not be accompanied by distress. For example, TGD individuals may interpret increased or decreased sexual desire differently. Thus, heightened libido is welcomed by some transmasculine people, but perceived by others as stressful (100); similarly, reduced libido is undesirable for some transfeminine individuals, but is a reported relief for the majority (106, 107).

Data systematically assessing sexual function and wellbeing in TGD adults, let alone adolescents, are sparse. To date, the few studies have focused on outcomes in adults following both GAH and gender-affirming surgery and, although they report improved sexual function and satisfaction (101, 108), the relative contribution of hormonal or surgical interventions is not known. Longitudinal studies assessing sexual function before and after hormone treatment in TGD individuals, including adolescents, are therefore needed.

Challenges, Areas of Uncertainty, and Future Directions

A number of controversies exist in this field, most of which are driven by understandable concerns that individuals may come to regret decisions they made about hormonal treatments as adolescents and be left with unwanted irreversible effects (109, 110). As mentioned previously, existing evidence suggests low rates of regret, but further studies are required to further establish or refute these findings.

A principal challenge centers on the capacity of an adolescent to fully understand the implications of hormonal treatment as well as related decisions regarding the optimal timing of hormonal therapies. Internationally, practices pertaining to both the age and/or developmental stage at which these treatments might be prescribed, as well as circumstances relating to obtaining consent for their use from legal minors, differ. On one hand, some advocate for earlier introduction of GAH for younger adolescents to avoid being physically "out of sync" with their age-matched peers and have started GAH in individuals as young as 11 years (111). Conversely, others argue that hormonal treatments in minors require greater restrictions. Indeed, in countries such as Australia (112, 113) and the United Kingdom (114), concerns relating to the capacity of adolescents to give fully informed consent have resulted in judicial oversights that limit the ability of minors to consent autonomously to GnRHa and GAH therapies. The specific situations in which this applies differ between jurisdictions, but in such scenarios either parents may give consent on the adolescent's behalf or court authorization may be required.

Such legal restrictions appear to be based on various concerns. For example, an important goal of PS is to allow additional time for a TGD young person to further explore decisions about potential GAH use without the associated distress of ongoing incongruent pubertal development. Whether typical cognitive maturity and decision-making capacity is achieved in TGD adolescents in the absence of pubertal sex hormones (115) is unclear, although no impact of PS on cognition has been demonstrated in cisgender cohorts treated with GnRHa for either precocious puberty (116) or short stature (117). Another concern relates to the perception that hormonal interventions reflect the start of a "pathway" that an adolescent may find it difficult to get off (118). Specifically, some worry that early PS may change the trajectory of gender-diverse adolescents by limiting the potential for their endogenous pubertal hormones to reinforce their assigned gender identity (110). Potentially consistent with this, older reports suggested low rates of persistence of gender incongruity from childhood into adolescence (119, 120) and these studies seemingly conflict with more recent data indicating that the vast majority of TGD young people who commence PS progress onto further GAH or surgery (22, 23). However, this discrepancy most likely reflects methodological issues (121), including changes in diagnostic criteria over this timeframe. Previously, gender nonconforming behavior alone was sufficient to warrant a diagnosis without requiring actual distress as is now the case, with the implication being that earlier reports were based on subjects who were not actually transgender (121). Consistent with this, "persistence" of GD has been most closely linked to the intensity of the GD in childhood and the amount of reported "cross-gendered behavior" (122).

It is also important to recognize that terms such as "persistence" and "desistence" tend to imply binary male/female outcomes in relation to gender identity (123). However, for many young people, gender identity is fluid, dynamic, and/or not exclusively male or female (ie, nonbinary) (124). Thus, some may elect not to have hormonal therapies in adolescence but to pursue this later in life (123). Equally, some adolescents may choose to discontinue GAH therapy, not because they regret using these therapies but because they are satisfied with the physical changes already attained (124). Future studies of "desistence" should therefore take into account possible gender fluidity and nonbinary identities. Similarly, when "de-transition" is assessed as an outcome, this does not necessarily imply a change of gender identity or indeed regret. Indeed, in the US Transgender study 2015, only 5% of those who had ever de-transitioned (0.4% of the overall sample) reported that they had done so because they realized gender transition was not for them; in contrast, the vast majority (82.5%) reported that the decision to de-transition was driven by external pressures (most commonly family pressure and social stigma) (125).

Looking ahead, it is essential that more research be conducted to improve the available evidence base and better guide the hormonal treatment of TGD adolescents. Although existing data indicate positive outcomes, the overall quality of evidence relating to hormonal therapies in TGD youth is low (37, 38). In particular, questions remain regarding optimal pharmacological strategies (eg, timing, dose, agent) to maximize psychological and physical benefit while minimizing unwanted effects; studies specifically assessing regret as well as interventions/outcomes for gender nonbinary youth are also required. Ethical concerns regarding the withholding of hormonal therapy have precluded randomized controlled trials in TGD adolescents, and studies with relevant control groups (eg, those unable to access hormones, matched for existing mental health problems) are challenging to perform. Nonetheless, further studies directly assessing different hormonal treatment strategies are necessary and feasible, as are large prospective cohort studies comparing long-term physical and mental health outcomes (including bone health, fracture risk, cardiovascular outcomes, depression, anxiety, self-harm, and suicidality) between TGD adolescents who access hormonal treatments and contemporaneous age-matched, population-based samples (111, 126).

Back to Our Cases

Case 1

Given her puberty-related distress, R.C. expressed a strong desire for GnRHa therapy; all her clinicians and family members supported this. However, R.C. and her parents opted to initially defer PS for several reasons. First, R.C. indicated a desire to access feminizing surgery as an adult

and therefore wished to delay initiation of PS to optimize her chances of having penile inversion surgery, although she was aware that this could not be guaranteed. Second, R.C.'s parents saw potential benefits in delaying PS to minimize adverse bone health effects. Third, although R.C. was unsure about her future parenting desires, she and her parents were keen to preserve her fertility by cryopreserving sperm, and delaying PS increased the likelihood of this being successful. Finally, because R.C. was already quite tall and concerned about excessive final female height, although height outcomes were more difficult to predict, it was agreed that delaying PS (but introducing before peak GV) was a reasonable approach.

Initiation of PS was therefore deferred with planned commencement at a stretched penile length of ~9 to 10 cm and testicular volumes of ~10 mL. However, the option of starting PS earlier was also provided should R.C.'s distress regarding her endogenous pubertal development become intolerable. In the meantime, vitamin D supplementation and lifestyle advice were provided to optimize her bone health, and regular mental health, medical, and hormonal monitoring continue.

Case 2

H.G.'s principal gender affirmation goals were "passing" as male, altering his chest appearance, masculinizing his body, and achieving menstrual suppression. Potential options (either alone or in combination) that were discussed with H.G. and his parents included: (1) chest binding and eventually reconstruction surgery; (2) hormonal modulation for menstrual suppression; and (3) testosterone for masculinization. Although GnRHa therapy might induce some minor reduction in breast volume (23), a female chest appearance would nonetheless remain and the potential for adverse effects was felt likely to outweigh any positive impact of PS at Tanner 5. In the first instance, H.G. trialed the oral progestogen norethisterone (commencing 5 mg twice daily) for menstrual suppression, with good response. H.G. was keen to pursue chest surgery but this was not available locally until >18 years of age, so options and resources for safe chest binding were discussed as an interim measure. Finally, information in relation to the potential affirming, unwanted, and unknown effects of testosterone—as well as its limitations—was shared with H.G. and his parents, with further detailed discussions planned for future sessions.

H.G., whose current (likely final) height is more than -2 SD below the median for adult males in the general population, was also counselled that his bone age indicated no capacity for further linear growth; this was frustrating for him because of the likelihood it would negatively affect his "passing" as male. In light of his high BMI, dietary and lifestyle modification with a view to weight loss and stabilization were also encouraged. He continues to see both medical and mental health clinicians, who are further evaluating his potential desire for and capacity to consent to testosterone.

Conclusion

The increasing use of hormone therapies for TGD adolescents reflects a significant increase in demand for services from TGD youth that has occurred in the broader context of improved understanding and community support for gender diversity. Endocrine practice in this area remains relatively new with sparse medium- and long-term outcome data. Clinicians can therefore face many moral and ethical challenges when providing such care (109, 110). For example, choosing not to provide hormonal interventions to a young person with GD may itself cause harm, especially given previous observations that lack of access to hormonal therapies is a known predictor of adverse mental health among TGD adults (18). Clinicians must act in the best interests of the young person, while armed with the best available evidence. That the evidence base is still emerging and not yet robust is not an adequate rationale to withhold treatment from TGD adolescents. Instead, in direct consultation with community stakeholders, evaluation of the effectiveness and safety of current treatment approaches should be considered an essential part of clinical service provision moving forwards. TGD adolescents are marginalized and vulnerable in many ways and ongoing efforts to optimize their wellbeing and physical and mental health outcomes must continue to be a priority.

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Additional Information

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