Journal of the Endocrine Society, 2021, Vol. 5, No. 1, 1–14
doi:10.1210/jendso/bvaa161
Mini-Review

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Testosterone Use in Adolescent Males: Current Practice and Unmet Needs

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Abbreviations: BMD, bone mineral density; CDGP, constitutional delay of growth and puberty; DMD, Duchenne muscular dystrophy; FDA, US Food and Drug Administration; HH, hypogonadotropic hypogonadism; IBD, inflammatory bowel disease; IM, intramuscular; T, testosterone; TRT, testosterone replacement therapy; TE, testosterone enanthate; TU, testosterone undecanoate.

Received: 14 August 2020; Editorial Decision: 19 October 2020; First Published Online: 2 November 2020; Corrected and Typeset: 1 December 2020.

Abstract

Testosterone replacement therapy (TRT) is routinely prescribed in adolescent males with constitutional delay of growth and puberty (CDGP) or hypogonadism. With many new testosterone (T) formulations entering the market targeted for adults, we review current evidence and TRT options for adolescents and identify areas of unmet needs. We searched PubMed for articles (in English) on testosterone therapy, androgens, adolescence, and puberty in humans. The results indicate that short-term use of T enanthate (TE) or oral T undecanoate is safe and effective in inducing puberty and increasing growth in males with CDGP. Reassuring evidence is emerging on the use of transdermal T to induce and maintain puberty. The long-term safety and efficacy of TRT for puberty completion and maintenance have not been established. Current TRT regimens are based on consensus and expert opinion, but evidence-based guidelines are lacking. Limited guidance exists on when and how T should be administered and optimal strategies for monitoring therapy once it is initiated. Only TE and T pellets are US Food and Drug Administration approved for use in adolescent males in the United States. Despite the introduction of a wide variety of new T formulations, they are designed for adults, and their metered doses are difficult to titrate in adolescents. In conclusion, TRT in adolescent males is hindered by lack of long-term safety and efficacy data and limited options approved for use in this population. Additional research is needed to identify the route, dose, duration, and optimal timing for TRT in adolescents requiring androgen therapy.

Key Words: testosterone, testosterone therapy, adolescent male, puberty, hypogonadism

ISSN 2472-1972

Testosterone (T) therapy is routinely prescribed in adolescent males with constitutional delay of growth and puberty (CDGP) or hypogonadism. T plays a critical role in male sexual development and function, beginning in utero and continuing through infancy, adolescence, and beyond [1]. In addition, T has numerous effects on various tissues and systems. These include the acceleration of linear growth during adolescence, a positive effect on bone mass and accretion [1-3], and changes in body composition associated with an increase in lean mass and a reduction and redistribution of fat mass [1, 4]. Recent evidence indicates that T and other androgens are involved in sexually dimorphic differences in certain brain regions, such as the amygdala [1, 5, 6], while their effects on neurocognition and behaviors are being actively investigated [7, 8].

T therapy in boys with CDGP is applied for a limited time, typically 3 to 6 months [1, 9]. The goals are to initiate sexual changes, increase growth, and ameliorate the negative psychosocial aspects associated with CDGP [1, 10-21]. Testosterone replacement in adolescents with primary or secondary hypogonadism is a long-term therapy. By using escalating T doses, such therapy induces progressive pubertal changes that mimic the physiologic course of puberty in healthy males [1, 22]. Despite the importance and routine administration of T to these populations, there has been marked variation in its use and little consensus on proper procedures [1, 22]. To add to the complexity, T therapy in boys and adolescent males is largely given "off label" [23]. T enanthate (TE) and T pellets are the only formulations approved by the US Food and Drug Administration (FDA) for the treatment of males with delayed puberty [23-25]. No preparation is FDA approved for long-term use in adolescents. Additional pediatric uses of exogenous T, which are not FDA approved, but have been suggested, include the treatment of microphallus in infants and the management of diminished or absent minipuberty, as well as its rapidly emerging use as cross-sex hormone therapy for transgender males [1, 26-30].

T replacement therapy (TRT) has recently expanded in adults because of its increased use among men with functional hypogonadism [31]. A number of new T preparations have entered the market, with improved pharmacokinetics, ease of administration, and likely increased adherence [22, 32]. However, all focus on adult males, and dose formulations are frequently not metered for pediatric use. The Endocrine Society and multiple other medical societies have developed practice guidelines for the care of adult patients, with little or no reference to adolescents [32-35]. This review summarizes the T options available to adolescent males and the evidence that supports current TRT practice in this population. We will use the results of this analysis to address the unmet needs and challenges related to TRT in adolescents and highlight areas for investigation likely to lead to improved care in these patients.

1. Materials and Methods

We searched PubMed using the search terms (testosterone [mesh] AND testosterone [ti] or androgen*[ti]) AND ((therapy[ti] OR treatment[ti]) OR (pubert*[ti] OR adolescen*[ti]) OR (sexual maturation[mesh]) using the filters "English, Humans, All Child, Male." The initial search yielded 606 references. Redundant or irrelevant material was eliminated. Additional references were identified by searching the reference lists of remaining articles, and relevant articles from those lists were added and included in the review.

2. Quantitating the Need for Testosterone Therapy in Adolescence

The precise prevalence of hypogonadism in adolescent males is difficult to calculate because it can be difficult to distinguish true hypogonadism from CDGP until puberty is initiated. Hypogonadism is classified as primary or secondary. Primary or hypergonadotropic hypogonadism is caused by testicular failure and is associated with elevated gonadotropin levels. Secondary hypogonadism or hypogonadotropic hypogonadism (HH) is caused by a hypothalamic or pituitary defect or injury and is thus characterized by low or seemingly normal gonadotropin levels, but in concert with low T concentrations. Both primary and secondary hypogonadism can be congenital or acquired. Functional HH is caused by the delayed maturation of the hypothalamic-pituitary-gonadal axis due to a variety of underlying conditions [36, 37].

The differential diagnosis of delayed puberty and hypogonadism in children is complex, and the reader can refer to recent reviews for a detailed description of involved conditions [1, 22, 37]. Klinefelter syndrome, the most common cause of congenital primary hypogonadism, occurs approximately in 1 of 660 males [23, 38]. The US estimate of affected adults was approximately 250 000 in 2008 [23]. Congenital causes of HH include Kallmann syndrome and other causes of isolated HH, with a combined prevalence of 1 in 10 000 [23, 39]. This prevalence translates to approximately 1275 affected boys, age 12 to 17 years, in the United States, based on government estimates (US government estimates for 2017, www.census.gov and www.childstats.gov).

Pediatric cancers and their treatments are frequent causes of hypogonadism. The risk of hypogonadism in patients with pediatric cancer is related to the patient's age and pubertal maturation at the time the cancer is diagnosed and the type,

dose, and duration of treatment [40]. Current estimates suggest that the rate of hypogonadism in pediatric cancer survivors is between 11% and 56% [41-43]. Mumps orchitis, a traditionally low-incidence cause of primary hypogonadism in developed countries, appears to be increasing in the United States, with reported cases exceeding 6000, both for 2017 and 2018 [23]. It is estimated that approximately 33% of affected adolescents will develop orchitis [23]. Additional frequent causes of hypogonadism in pediatric patients include intracranial tumors and traumatic brain injury. Although the exact incidence and prevalence are difficult to calculate, hypogonadism occurs in 20% to 80% of children treated for intracranial tumors [23, 44-46]. Given the multiple other disorders that may lead to permanent hypogonadism in pediatric patients, it is reasonable to estimate that the number of boys requiring TRT for induction and maintenance of puberty could rise into the tens of thousands.

The most frequent cause of delayed puberty is CDGP, which affects 2% of the population [22, 47]. Although most will do well with "watchful waiting," there is a substantial subgroup who will benefit from TRT. The specific numbers are, however, lacking. Similarly, it is difficult to estimate the number of adolescent boys with functional hypogonadism, who would also benefit from TRT. Functional hypogonadism is found in association with a chronic illness, such as inflammatory bowel disease (IBD), end-stage renal disease, or some genetic diseases such as cystic fibrosis, with those affected now living into their fourth and fifth decades [48, 49]. With advances in pediatric care, the number of adolescents with chronic illnesses requiring TRT is rising sharply. Chronic glucocorticoid therapy, such as in boys with Duchenne muscular dystrophy (DMD), leads to hypogonadism. Although no clinical trial has specifically assessed TRT use in these adolescents, the most recent guidelines call for an endocrine evaluation and appropriate therapy [22, 50, 51]. Eating disorders and excessive exercise may result in decreased activity of the hypothalamic-pituitary-gonadal axis and hypogonadism [52, 53]. Finally, the number of adolescent males who experience hypogonadism because of opioid addiction or androgen abuse, although uncertain, is likely significant [54].

In 2019, the FDA provided information on TRT prescriptions in adolescent males [23]. Outpatient retail pharmacy data were used to determine the number who received T prescriptions. In the year ending August 2010, approximately 7400 boys younger than 19 years received T prescriptions [23]. This number increased over time, and in the year ending August 2017, approximately 11 000 males of this age-group received prescriptions. In a sample of 9696 boys younger than 19 years who received T prescriptions, only 17% met the definition for chronic use. Although the reported numbers involved only commercial insurance and did not capture patients on Medicaid or without health care or pharmacy coverage, these numbers raise concerns that not all pediatric patients with permanent hypogonadism are appropriately treated.

3. Testosterone Formulations: Pediatric Applications and Regulatory Perspectives

Since the initial reports of T synthesis in the 1930s [55], numerous T formulations have been introduced, but the only products that currently have a pediatric indication in the United States are intramuscular (IM) TE injections and implantable subcutaneous T pellets [23-25]. Both are approved to stimulate puberty in "carefully selected males with clear evidence of delayed puberty" [23]. TE and T pellets were approved in 1953 and 1942, respectively, before the passage of the 1962 Kefauver-Harris Drug Control Act, which requires that approved drugs be both efficacious and safe [23]. Although both formulations remain approved, it is unlikely that evidence supporting their efficacy and safety aligns with current standards for FDA approval of drugs for children and adolescents.

Additional IM formulations (T propionate and cypionate) were introduced in the 1950s, oral testosterone undecanoate (TU) was developed in the 1980s, transdermal patches were first marketed in the 1990s, and topical gels, buccal patches, and a long-acting IM preparation of TU were initially marketed in the 2000s [22, 55]. More recent introductions include a nasal T preparation in 2016 [22, 56], a weekly TE depot delivered subcutaneously via an autoinjector in 2018, and an oral TU formulation in 2019 [22, 57].

All TRT products approved after 1953 target adults, and their safety and efficacy in boys younger than 18 have not been established [23]. For newer agents, the labeling warns that improper use of T in adolescents has been associated with bone age acceleration and premature closure of epiphyses [23]. Because these formulations were designed for adults, dosing is not flexible or easily titrated, which is essential for therapy in adolescents, especially to initiate pubertal maturation. Certain preparations are not available globally [58]. For example, oral TU, which has been used successfully in boys with CDGP [59, 60], is available in Europe. TU was not available in the United States until 2019, when it was FDA approved for men [61], whereas T pellets are still available in the United States and Australia.

4. Current Options for Testosterone Therapy in Adolescents and Evidence From Pediatric Studies

The current TRT options for adolescent males with CDGP and hypogonadism, and information on dosing, or lack thereof, are summarized in Table 1 [1, 15, 22, 25, 32, 36, 59, 60, 62-82].

A. Injectable Testosterone Esters

IM TE is the most frequently used formulation for induction and progression of puberty in adolescent males. The practice is supported by limited numbers of studies, primarily in those with CDGP. Two prospective controlled trials, published in 1995 or earlier, evaluated 2 regimens for pubertal induction in adolescents with CDGP [11, 83]. The first involved TE administration at the dose of 200 mg every 3 weeks for 4 times in 8 boys, while 8 boys served as controls [83]. The second trial used TE 100 mg IM monthly for 6 months in 148 treated boys and 50 controls [11]. Both reported increases in height velocity compared to controls, with no adverse bone age advancement. Testicular size and serum T concentrations were greater in boys treated with TE vs their respective controls 1 year after initiation of therapy [11]. Greater satisfaction with growth and increased muscle mass was reported in those treated [11].

An additional small number of uncontrolled or retrospective studies confirmed a positive effect of TE on growth and pubertal maturation in boys with CDGP [14, 17, 21, 84]. Those studies also used alternative regimens, such as TE 125 mg once every 6 weeks for 3 doses [84], while Bergadá reported on TE administered at 33 to 50 mg monthly for 20 months [17]. All confirmed an increase of height velocity without an adverse effect on bone age in boys with CDGP [14, 17, 21, 84]. Overall, these studies indicate that various regimens of T esters administered for a short time period can safely induce virilization in boys with delayed puberty, with some evidence of a psychosocial benefit. None tested a titration regimen to adult T doses and the long-term safety and efficacy of this type of treatment. Furthermore, the effect of therapy on bone mass, insulin sensitivity, and other metabolic parameters was not examined.

TE and T cypionate are ester derivatives of T. They both have suboptimal pharmacokinetic profiles and reach supraphysiological T concentrations a few days after injection that gradually decrease to subphysiologic levels within the following 2 to 3 weeks [58, 85]. To overcome this limitation, additional T esters were developed by modification of the esterified fatty acid molecule that is attached to the 17β carbon of natural T [58, 86]. T propionate results in wide T fluctuations, requires frequent injections, and was therefore deemed unsuitable for treatment of male hypogonadism [87]. IM-injected TU has the longest duration of action [88]. However, its use is restricted because of rare associated cases of pulmonary oil microembolism [89]. Furthermore, its use in pediatrics is limited because of dosing and its long washout period, should complications arise. Finally, to improve pharmacokinetics, formulations that include mixtures of short- and longer-acting T esters, such as Sustanon, which is a mixture of 4 esters, have been used for induction of puberty in adolescent males and treatment of male hypogonadism in Europe [1, 22, 62, 90, 91]. The clinical advantages of these preparations over TE are uncertain [62].

B. Oral Testosterone Undecanoate

Natural T taken orally is ineffective as TRT because of its first-pass metabolism by the liver and rapid inactivation. Earlier forms of oral testosterone (methyltestosterone and 17α derivatives) led to hepatic dysfunction and are no longer marketed [86]. Oral TU is absorbed into the lymphatic system [86], and therefore bypasses rapid inactivation by the liver. However, it has a short, unpredictable half-life, requiring multiple daily doses in adults, and its absorption can be unreliable and particularly sensitive to food intake, especially the lipid content of meals [1, 92]. Still, oral TU is effective in inducing pubertal maturation in boys with delayed puberty. Two double-blind, randomized, placebo-controlled trials tested 2 different doses of TU (20 mg daily for 6 months in one vs 40 mg daily for 3 months in another) in small numbers of boys with CDGP [59, 60]. Results from these studies indicated that TU increased height velocity and circulating T levels compared to controls. Similar effects on growth and pubertal maturation were observed in a larger, retrospective study of 96 Danish boys treated with TU daily (40-mg daily doses escalated up to 80 mg twice daily) for an average of 0.8 years and 63 untreated controls [66]. In another randomized trial, oral TU at the dose of 40 mg daily was equally effective as oxandrolone 2.5 mg daily in terms of growth, pubertal maturation, and bone age advancement in boys with CDGP [67]. In addition, oral TU (40 mg daily for 8 weeks) had an effect on growth similar to an IM T ester mixture (Sustanon 50; Aspen Pharma Trading Limited, Dublin, Ireland) in a randomized crossover comparison study in boys with CDGP [68]. These studies provide significant evidence that short-term use of oral TU at 40 mg daily is safe and effective to promote growth and pubertal changes without an adverse effect on bone age in adolescent males with CDGP [22]. Little is published about the long-term efficacy of oral TU [69] and titration regimens for pubertal progression and completion [70]. To overcome the erratic absorption of oral TU, a new oral formulation that is less affected by the lipid content of meals was approved by the FDA for hypogonadism in men [93]. This formulation has not been studied in adolescents.

C. Transdermal Testosterone

Transdermal preparations of T (patches or gel) are appealing options for TRT because they combine ease of administration with physiological and constant T levels.

Table 1. Commonly used or previously reported regimens of various testosterone formulations and options for adolescent males with constitutional delay of growth and puberty or with hypogonadism [1, 22]

Formulation		Commonly used regimens			Comments
		Induction of puberty	Hypogonadism: puberty progression	Adult doses	
Intramuscular	TE or T cypionate	25-50 mg monthly for 3-6 mos; not to exceed 100 mg monthly [36, 62]	Escalating regimens[a] [36] 100 mg monthly for 6 mos 150 mg monthly for 6 mos 100 mg every 2 wks for 6 mos 150 mg every 2 wks	150-200 mg [32] every 2 wks	• Most data and clinical experience in adolescents • TE is only FDA-approved formulation for adolescent males in US
	Short-acting: combination T esters (Sustanon) [63]	25 mg monthly [64]	Similar dose escalation as TE	250 mg every 3-4 wks	• Not available in US
	Long-acting: TU (AVEED) [65]	ND	ND	750 mg (3 mL) injected at initiation, at 4 wks, and every 10 wks thereafter	• Lack of data in adolescents • Has been used for puberty induction in young men
Oral	TU	20-40 mg daily; not to exceed 80 mg twice daily [59, 60, 66-69]	40 mg daily for 1 y followed by 80 mg for 1 y [70]	40-80 mg 2-3 times daily [32]	• Erratic absorption, needs to be taken with meals (fat content important) • Pubertal progression based on single case series presented as letter to the editor [70]
	TU (JATENZO) [71]	ND	ND	158-396 mg twice daily	• Lack of data in adolescents • Approved in US for adults in 2019
Transdermal	T gel	1 or 2% T gel (5-10 mg gel daily containing 50-100 mg T) [15, 72]	ND	1 or 2% gel (5-10 mg gel daily containing 50-100 mg T) [32]	Data supported by 2 studies and case series [72-74]
	T patch (nonscrotal)	2.5 mg every 12 h daily, or 5 mg every 8-12 h daily for 6 mos [75, 76]	Limited experience to a single case series in hypogonadal males with β thalassemia [77] • Age 14-16 y: 2.5 mg every 12 h • Age 17-19 y: 2.5 mg every 24 h • Age > 20 y: 5 mg every 24 h	1 or 2 patches (5-10 mg T) over 24 h applied daily [32]	Induction regimens according to small case series or short-term use [75-77]
	T patch (scrotal)	ND	ND	4-6 mg daily	• Lack of data in adolescents • Patch too large for immature scrotum

Table 1. Continued

Formulation		Commonly used regimens			Comments
		Induction of puberty	Hypogonadism: puberty progression	Adult doses	
Subcutaneous	TE (XYOSTED [78]	ND	ND	50-100 mg weekly	• Lack of data in adolescents
	T pellets	ND	600-800 mg (8-10 mg/kg) of T pellet implants every 6 mos	150 to 450 mg every 3-6 mos (TESTOPEL) [25]	Case series in adolescents for completion and maintenance of puberty [79, 80]
Miscellaneous	Nasal T gel	ND	ND	3 daily doses of 1 actuation per nostril, 33 mg daily (NATESTO) [81]	• Lack of data in adolescents
	Buccal T mucoadhesives	ND	ND	30 mg twice daily (STRIANT) [82]	• Lack of data in adolescents • Altered taste/gum irritation

Abbreviations: FDA, US Food and Drug Administration; ND, no data; T, testosterone, TE, testosterone enanthate; TU, testosterone undecanoate; US, United States of America.
[a]Supported by consensus, not trials. Based on Mason and Stancampiano [1, 22].

For T gel, the pediatric experience is limited to a single prospective study, a few retrospective analyses, and a case series. Rogol et al retrospectively evaluated the clinical response to T gel 1% in a subgroup from a prospective, open-label, observational study of 86 adolescent boys (age 12-17 years) with primary hypogonadism due to Klinefelter syndrome or anorchia. Administration at starting doses of 0.5 g daily for 6 months or less increased serum T concentrations to normal, age-matched levels [72]. No clinically meaningful changes were observed on physical examination, and no significant safety concerns were raised. In this study, proper dosing became an issue, given the variable responses in individual adolescents [72]. In a retrospective study in adolescent males with CDGP, 10 mg daily of 2% testosterone gel for 3 months had a similar effect on height velocity as TE 50 mg monthly for 3 months [15]. In a case series of 3 males with hepatic dysfunction, T gel 2% (Fortesta; Endo Pharmaceuticals Inc., Malvern, Pennsylvania, USA) and 1% (Androgel; AbbVie Inc., North Chicago, Illinois, USA) were safe and effective for pubertal induction and progression of puberty [73]. Finally, treatment with T gel resulted in appropriate and adequate increases in serum T concentrations in 104 boys with Klinefelter syndrome, although specific doses and regimens were not described [74].

The experience with transdermal T patches to induce puberty is sparse. Patches are designed to deliver adult TRT doses and cannot be fractionated. For this reason, the few available studies in adolescent males applied patches for a shorter time (usually for 12 hours daily) instead of the 24-hour recommended adult application [76, 77]. In a case series, puberty was induced in 3 adolescents with IBD by using 2.5-mg or 5-mg patches for 12 hours daily for 4 to 6 months. However, only 2 participants responded [75]. In a prospective, randomized, crossover study, overnight application of a 5-mg patch in 8 boys simulated physiologic T secretion and increased short-term growth [76]. In a final retrospective study of 9 adolescents and young adult males with β thalassemia major, therapy with T patches at various doses induced virilization, promoted growth, and increased bone mineral density (BMD) [77]. Skin reactions and poor skin adherence both occur with this formulation.

D. Testosterone Pellets

T pellets are implanted subcutaneously and are designed for consistent and prolonged release [79, 80]. Two reports on adolescent males observed that completion and maintenance of puberty were successful with this formulation [79, 80]. Both were uncontrolled and had a small sample

size [79, 80]. Zacharin and Warne treated 16 boys with hypogonadism and 2 males with tall stature using doses of 8 to 10 mg/kg every 6 months for 18 months [79], while Moskovic and colleagues treated 4 males with Klinefelter syndrome with implantations every 3 to 4 months for 2 to 3 years [80]. Wide variability in circulating T levels was noted, but overall, the therapy was well tolerated and associated with improvements in patients' mood, emotional well-being, and self-esteem [79, 80]. The need for a minor surgical procedure every 3 to 6 months and the associated cost make this formulation appropriate for select patients who have compliance difficulties with other forms of TRT. Pellet extrusion was not observed in these series, although it has been reported to occur in approximately 12% of implants [94]. T pellets have not been evaluated for the induction of puberty.

E. More Recent Testosterone Formulations

TE for weekly subcutaneous injection has been recently approved in the United States for treating adults with hypogonadism. It has been also successfully used for managing sex transition in transgender males, although its use for pubertal induction has yet to be formally evaluated [95]. Likely advantages for adolescents include its potential for self-administration, reduced peak-to-trough T-concentration variability, and ability to accurately titrate to approximately physiologic T levels [96]. Buccal T in the form of mucoadhesive tablets, and more recently, a nasal T gel formulation have been introduced for adult TRT [22, 56]. Lately, a new formulation of TU that fosters more consistent absorption and allows for twice-daily dosing (JATENZO; Clarus Therapeutics) has entered the market for treatment in adult men [93]. None of these formulations have been tested in adolescent males. They all face concerns about metered doses and ease of titration for pubertal induction and progression.

5. Unmet Needs

A body of pediatric literature supports that short-term use of intermediate-duration T esters, such as TE, and oral TU are effective and safe in puberty induction in adolescents with CDGP [11, 59, 60, 83]. Their use is associated with increased patient satisfaction [11]. Various regimens of TE and oral TU increase growth rate and lead to pubertal progression without reducing adult height [11, 59, 60, 83]. Although there is encouraging evidence for the efficacy of transdermal T therapy (gels and patches), the data are limited [22, 75-77]. No pediatric studies have been published with the most recent T formulations.

Data on TRT management of adolescent males with hypogonadism are sparse. After initiation of puberty, T doses are gradually increased to mimic normal pubertal physiology over the course of 2 to 3 years until puberty is clinically completed and adult doses are reached. Various T-titration regimens for pubertal progression and completion have been reported. However, they are all based on expert opinion or consensus rather than evidence provided by carefully designed studies [10, 22, 37, 62]. Although decades of clinical practice suggest that these regimens are largely successful in achieving full virilization, various questions remain. For example, there is little concrete evidence to guide the optimal timing for initiating T therapy in adolescents with either CDGP or hypogonadism [1]. Moreover, questions remain with regard to the appropriate tempo of introducing pubertal changes or how rapidly T doses should be escalated. Once pubertal maturation is complete, the ideal range of serum T concentrations for TRT continuation in a young hypogonadal male is poorly defined. Addressing such questions is likely to improve the outcomes of the multiple physiological processes occurring during puberty, such as growth and bone accrual, and affect the psychosocial well-being of the treated adolescent.

Hypogonadism is linked to low bone mass and an unfavorable metabolic profile characterized by increased visceral adiposity, insulin resistance, and dyslipidemia [97]. The TRT literature on adolescent males is limited on T-induced pubertal changes and growth. There is little reported on changes in body composition due to T administration. The literature on young males with hypogonadism, such as those with Klinefelter syndrome, describes associations between TRT and body composition, bone mass, and metabolic parameters. However, results are mixed and specific TRT regimens are not precisely reported. Furthermore, these studies are observational, with no controlled trials available. Additional TRT studies on the maintenance and completion of puberty that include monitoring of bone mass, body composition, and various cardiometabolic parameters and risk biomarkers are greatly needed.

Finally, the current literature does not provide sufficient guidance for the increasing needs of the many adolescent males with functional hypogonadism, such as those affected with eating disorders, IBD, cystic fibrosis, or DMD [36, 98]. It is likely that TRT regimens will require individualization for these different patient groups. Although detailed reviews of each of the disorders is beyond the scope of this work, we will use DMD as an example to highlight some of the multiple unanswered questions relevant to these boys. Hypogonadism affects most adolescents and emerging adults with DMD, likely the result of the

underlying condition and high-dose, chronic glucocorticoid treatment [50, 99]. Recent DMD guidelines call for assessment of puberty as part of a complete exam and appropriate endocrine referral, despite a lack of relevant clinical trials [51, 100]. For these affected adolescents, ethical questions related to quality of life, issues around sexuality, and concerns about bone and cardiometabolic health remain [51, 100]. Similar challenges face other adolescents with chronic illnesses resulting in hypogonadism [100, 101].

6. The Current Practice of Testosterone Therapy in Adolescent Boys

The current TRT practice in adolescent males is captured in published consensus or expert opinion statements and reviews [10, 22, 37, 62, 102], but official guidelines are lacking. Frequently used therapeutic regimens and proposed monitoring schemes, adopted by recent reviews, use TE for induction and escalation of puberty and are depicted in Fig. 1. This figure also lists oral TU and transdermal T as alternative T formulations that can be used for puberty induction. Experience with puberty progression has concentrated on TE [1, 22].

A. Therapeutic Regimens and Their Challenges

T therapy in males with delayed puberty is hindered by the lack of reliable biomarkers differentiating between CDGP and HH. These 2 entities can be indistinguishable at presentation [1, 102]. Functional hypogonadism can be particularly difficult to differentiate from CDGP [36]. Because CDGP is by far the most common diagnosis, most physicians adopt an approach of watchful waiting, monitoring for signs of spontaneous puberty, especially testicular enlargement. In a recent review of a pediatric endocrine practice, only 13% of the referred boys with delayed puberty were treated with T at the mean age of 14.2 years (range, 12.1-17.7 years) [103]. The treated boys included those with CDGP and all types of hypogonadism. The data may suggest a high threshold for starting TRT. What is unclear is for how long clinical monitoring without initiating TRT is prudent. Whereas the psychosocial sequelae of untreated hypogonadism and delayed puberty are well documented [1, 104-109], there is emerging evidence that the timing of exposure to sex steroids in adolescents may affect various physiological parameters in adulthood, including skeletal and cardiometabolic health [1, 108, 110]. An optimal age window to introduce sex steroids has been proposed [111]. As it stands, many adolescents with

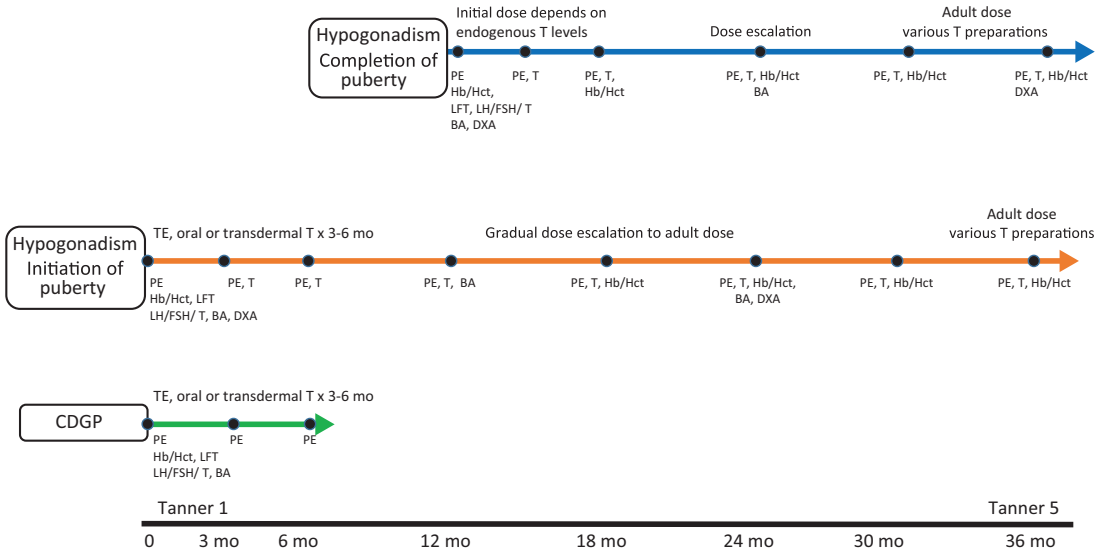

Figure 1. An illustration describing testosterone (T) therapy for initiation and completion of puberty in males with hypogonadism (orange and blue arrows, respectively) and for induction of puberty in adolescent males with constitutional delay of growth and puberty (CDGP; green arrow). Specifically, frequently used therapeutic regimens and proposed monitoring schedules, adopted by recent reviews, are depicted in the figure. Briefly, in males with delayed puberty and suspected CDGP, puberty is initiated by using small T doses such as intramuscular testosterone enanthate (TE) 50 mg monthly or oral testosterone undecanoate (TU) 40 mg daily for 3 to 6 months. Transdermal T (1 or 2% gel providing 10 mg of T daily or 5-mg testosterone patch worn for 12 hours daily) can be used, although experience is limited. An increase in testicular volume, typically up to 6 to 8 mL, heralds the presence of central puberty, and T replacement therapy can be discontinued. If sexual maturation is not induced, therapy can be extended to a year or more. Lack of hypothalamic-pituitary-gonadal axis activation is likely to indicate hypogonadism. In boys with permanent hypogonadism, T doses should be gradually increased to mimic normal pubertal physiology over the course of 2 to 3 years until adult doses are reached. Experience with puberty progression has concentrated on TE. T doses are increased by 50 mg per month at 4- to 6-month intervals until the monthly dose reaches 150 mg. At this point, transitioning to 100 mg twice monthly may help patients maintain more steady serum T concentrations. Patients may then be able to transition to a newer T formulation, such as a testosterone gel, beginning at 1.25 or 2.5 g per day, if desired. BA, bone age; DXA, dual-energy X-ray absorptiometry; FSH, follicle-stimulating hormone; Hb, hemoglobin; Hct, hematocrit; LFT, liver function testing; LH; luteinizing hormone; PE, physical examination. Based on Mason and Stancampiano [1, 22].

delayed puberty start TRT much later than age 14 years, an age set to define delayed puberty in males [73, 111, 112].

The biochemical distinction between CGDP and HH can be challenging with the current diagnostic modalities. Basal gonadotropin and gonadotropin-releasing hormone stimulation tests have limited diagnostic specificity, with an overlap in gonadotropin levels between CDGP and HH [113]. Measurements of inhibin B and antimüllerian hormone, both markers of Sertoli cell number, and insulin-like factor 3, a marker of Leydig cell function, have been proposed as diagnostic tools [102, 113, 114]. Indeed, whereas very low serum concentrations are indicative of congenital HH, there is considerable overlap between adolescents with CDGP and other causes of HH [102, 114, 115]. The diagnostic dilemma between CDGP and HH may be addressed clinically with 3 to 6 months of T therapy to induce pubertal maturation. If physiologic puberty does not ensue, clinical monitoring can be extended and T can be administered for an additional 3 to 6 months [22]. Failure to progress in central puberty, as signaled by lack of testicular enlargement, is likely to support the diagnosis of HH [22].

Males with Klinefelter syndrome represent the most common genetic category of primary or hypergonadotropic hypogonadism among adolescents [1, 116]. TRT is routinely prescribed, although the most appropriate time to initiate therapy varies significantly among practices [117, 118]. In these individuals, onset of puberty is age-appropriate. The first stages of puberty are usually normal and characterized by some virilization and an increase in serum T concentrations into the pubertal range, followed by a rise in gonadotropin levels and a plateau in circulating T [119]. Most of these adolescents and young adults are actually able to maintain a spontaneous serum T concentration in the low-normal adult range, despite markedly elevated gonadotropin levels [119]. Early TRT is advocated by some investigators, but is not universally adopted [118]. The differences in practice stem from the lack of controlled studies linking TRT to health outcomes. Beyond the well-described concerns of untreated hypogonadism on sexual development, bone, and cardiometabolic health, questions regarding the impact of sex steroids on neurocognition and executive function in these adolescents remain [7].

B. Monitoring Therapy

The goals of monitoring during therapy are to ensure appropriate growth and virilization and screen for potential adverse effects. For hypogonadal individuals, monitoring entails additional surveillance for associated comorbidities, such as low bone mass and cardiometabolic risk factors. A proposed monitoring plan is shown in Fig. 1. Similar to TRT regimens for adolescent males, this monitoring plan is driven by consensus [22, 62] and by adoption of adult guidelines. For example, the Endocrine Society recommends screening adults for polycythemia 3 and 6 months after therapy initiation. Because the response of hemoglobin to T administration is dose-dependent [32], monitoring for polycythemia is applicable to adolescent males as they reach adult T doses but not during the initial steps of T-dose titration.

While surveillance for low bone mass, dyslipidemia, and metabolic syndrome has been suggested for hypogonadal adolescents on TRT, there is no clear consensus when such screening should be initiated and how frequently it should be performed [22, 62, 102]. Research confirms the multiple anabolic effects of T, including those on bone [1, 3, 4, 22, 120]. Some reports have suggested an association between low BMD and delayed puberty, but findings have not been consistent enough to recommend the routine adoption of bone mass measurement in adolescent males with CDGP [22, 121-127]. For hypogonadal adolescents, measurement of BMD may influence decisions concerning TRT initiation and titration [22]; however, there are no specific pediatric data to guide such decisions.

7. Patient Satisfaction and Adherence to Therapy

TE appears to be the predominant T formulation used to induce puberty. Treated adolescents express satisfaction with how TRT affects pubertal maturation and growth [11]. With respect to satisfaction with TE itself, many manuscripts and reviews refer to the inconvenience and discomfort related to IM injections [128, 129], but there are no specific data describing the degree of dissatisfaction associated with this inconvenience and discomfort and/or how it may affect compliance. Remarkably, there is documented dissatisfaction with the daily application of T gel. Mehta et al documented a 25% rate of dissatisfaction among young men with Klinefelter syndrome. Five percent switched to IM injections or to pellets [74]. Rogol and colleagues documented a 72% compliance with T gel [72]. Clearly, more studies with better designs are required to determine the rate and reasons for dissatisfaction with current TRT options in adolescents.

8. Conclusions

Tens of thousands of adolescent males require TRT annually. In this review we have identified 2 broad areas of unmet needs for these patients. The first involves the absence of data on the impact of TRT, as it is currently implemented, on various health parameters, including quality of life and adult health outcomes. Although androgens have a positive influence on the multiple physiologic processes

that mature during puberty, from bone accrual and changes in body composition to cardiometabolic and mental health, the specific TRT regimen that will optimize these parameters and ameliorate the long-term comorbidities associated with hypogonadism for an individual is uncertain and requires assessment in controlled, prospective studies. Lack of TRT guidelines for adolescent males reflects the lack of appropriate data to guide recommendations. The specific needs of adolescent males with chronic illnesses and functional hypogonadism should also be addressed.

The second area of unmet needs involves the scarcity of T formulations that are suitable for use in adolescent males. Many new T formulations have entered the market recently, but all are designed for adults. As a result, their dosing is not very flexible and does not permit easy titration, which is essential for therapy in adolescents. According to World Health Organization guidelines, the ideal formulation should be safe, effective, affordable, convenient, and flexible in dosing, and it should possess a pharmacokinetic profile similar to that observed in pubertal physiology [130]. With TE being the main T option for adolescents, TRT practice in this patient population remains far from this ideal recommendation.

Acknowledgments

The authors thank Nicole Cooper of MedVal Scientific Information Services, LLC (Princeton, New Jersey), for medical writing and editorial assistance, which were funded by Antares Pharma, Inc. This manuscript was prepared according to the International Society for Medical Publication Professionals' "Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3."

Financial Support: The authors received no financial support for the research, authorship, and/or publication of this article.

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Disclosure Summary: M.V. has served as a consultant for Antares Pharma, Inc, and has not received honoraria or reimbursement for this manuscript. J.P.T. is a former employee of Antares Pharma, Inc. J.S.J. is an employee of Antares Pharma, Inc. S.H. is a former employee of Antares Pharma, Inc. A.D.R. is a consultant for Clarus Therapeutics, Lumos Pharma, Tolmar Pharmaceuticals, and Antares Pharma, Inc, and has not received honoraria or reimbursement for this manuscript.

Data Availability: All data analyzed during this study are included in this published article or in the data listed in "References."

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