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Chioma L, Cappa M

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Review Article

Hypogonadism in male infants and adolescents: new androgen formulations

Laura Chioma^a, Marco Cappa^a

^a Endocrinology Unit, University Pediatric Department, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Short Title: New androgen formulations in pediatric and adolescent populations

Corresponding Author:

Marco Cappa

Endocrinology Unit, University Pediatric Department

Bambino Gesù Children's Hospital, IRCCS

L.go S.Onofrio, 4

00165 Rome, Italy.

Telephone number: +39 0668594727

E-mail: marco.cappa@opbg.net

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Abstract

Background

Male hypogonadism may be associated with micropenis and cryptorchidism in newborn, absent or incomplete pubertal development when it occurs during childhood. During puberty, androgen replacement therapy plays a pivotal role in subjects with hypogonadism to induce sexual maturation, growth acceleration, anabolic effects on fat-free mass growth increasing muscle strength, directly and indirectly on the attainment of peak bone mass in young men. Moreover, in newborns with congenital hypogonadism, androgen therapy could be effective to increase genital size.

Summary

Testosterone replacement therapy (TRT) represents the cornerstone of the management of hypogonadism in boys. During puberty, replacement therapy needs to be modulated with gradual dosing increase to better mimic the physiologic pubertal development. Currently, intramuscular testosterone esters (in particular testosterone enanthate, TE) and subcutaneous testosterone pellets are the only formulations approved by the US Food and Drug Administration (FDA) for delayed puberty, while no preparation is approved for long-term use in the adolescent age. Several new testosterone (T) formulations (as transdermal, nasal, subcutaneous, and oral formulation) are recently developed to improve the pharmacokinetic profile and to ease the administration route increasing patient compliance in adult males with hypogonadism. All these formulations are not approved for pediatric age, although some of them are used as “off-label” regimens. This special issue is aimed to illustrate new T formulations and their potential role as replacement therapy in the pediatric population, as well as to highlight investigational areas to contribute to health care improvement in these patients.

Key Messages.

Despite the lack of evidence-based guidelines regarding the choice of T formulation in the pediatric population, new formulations appear to have a potential role for TRT in adolescent age. They have been designed for adult age with a little flexibility of dosage, although a few formulations may be attractive for pubertal induction and penile enlargement thanks to their greater flexibility and easing of administration. On the other hand, long-acting and stable formulations could meet post-pubertal needs, increasing TRT compliance in a critical phase as the adolescent age. Further controlled, long-term safety, and efficacy studies for all these new T formulations within the pediatric population are needed.

Introduction

Hypogonadism in males refers to a decrease in sperm and testosterone (T) production. It may be related to gonadal failure (primary hypogonadism) or hypothalamus-pituitary disease (secondary hypogonadism). Primary hypogonadism is characterized by low serum T and elevated FSH and LH levels (hypergonadotropic hypogonadism, HeH), while secondary hypogonadism presents both T and gonadotropin hormone deficiency (hypogonadotropic hypogonadism, HoH).

Clinical features of hypogonadism may vary greatly, depending upon when this occurs. Congenital androgen defects during the first trimester of intrauterine time result in uncompleted virilization of male fetuses, while later decreased T production, during the third trimester in fetuses and the mini-puberty in newborns, is associated with small penis (so-called micropenis) and cryptorchidism. Lastly, when hypogonadism occurs during childhood or peri-pubertal time, it is associated with absent or incomplete pubertal development. Hypogonadism can also cause short- and long-term consequences such as secondary osteoporosis [1], increased risk for metabolic syndrome [2, 3], and depression with consequent impaired psychosexual health [4-6].

Both hypergonadotropic and hypogonadotropic forms of hypogonadism may be either due to congenital or acquired disease. The most frequent causes are summarized in Table 1.

Androgen replacement therapy should be aimed to reproduce the physiological effect of T on many different tissues and systems. In newborns with the absence of mini-puberty, a short-term therapy with androgens (both T and 5 α -dihydrotestosterone) could be effective to correct micropenis [7-11]. In infants with HoH, combined gonadotropin (FSH plus LH recombinant) or GnRH injective therapy seems to be able to restore the hormonal pathway of mini-puberty allowing the descent of retractile testis, as well as Sertoli and germ cell proliferation and initial maturation [12-15]. This suggests that early gonadotropin therapy may improve the fertility potential and the response to gonadotropin therapy during adolescence and adult life [15-17]. These therapies represent a valid alternative to androgens therapy, although they are more invasive, and their therapeutic use is beyond the scope of this review. During puberty, beyond inducing sexual maturation, androgens play an anabolic role on bone mass, both directly and through their conversion to estrogen by aromatase, contributing to the attainment of peak bone mass in young men [18, 19]. Sex steroids are able to induce growth acceleration, defined also pubertal “spurt”, thanks to their synergic effects on GH-IGF1 secretion, through estrogen conversion, and directly interacting with androgen receptor localized in the growth plate cartilage [20-22]. T has also anabolic effects on muscle mass and body composition [23-25]. Several studies have demonstrated the effects of testosterone replacement therapy (TRT) in hypogonadal men to increase fat-free mass, muscle strength and to reduce fat mass [2, 25-27]. Finally, young men with untreated hypogonadism have lower HDL cholesterol levels and increased cardiometabolic risk, compared to healthy controls [28].

For all these reasons, T therapy represents the cornerstone of the management of hypogonadism in boys. Although testosterone enanthate (TE) and subcutaneous testosterone pellets are the only formulations approved by the US Food and Drug Administration (FDA) for adolescent males [29-31], a number of new formulations are currently used as “off-label” regimens. This report is aimed to illustrate new T formulations and their *potential* role as replacement therapy in newborn, child and adolescent males with hypogonadism.

Main Text

The most common use of T therapy in childhood is related to pubertal induction in boys with constitutional delay in growth and puberty (CDGP), the most frequent and self-limited form of HoH. In boys with delayed puberty, a short-term therapy with low dose of T may be proposed as an alternative to expectant observation for psychological reason. Furthermore, it could be useful to differentiate CDGP to permanent HoH, often indiscernible prior to the T therapy. In adolescents with persistent hypogonadism, TRT is a long-term therapy with the peculiarity of the need to be modulated with a gradual increase of the dose to mimic the physiologic pubertal maturation. Since mid-20th century, several T formulations have been developed to improve their pharmacokinetics and to reduce potential adverse effects. The first available formulations,

introduced between the 1940s and 1950s, included subcutaneous pellets and intramuscular injection of T esters (propionate, enanthate, and cypionate). Current TRT formulations and their pediatric dosing regimens are summarized in Table 2.

Pellets, available only in USA, UK, and Australia, are implanted subcutaneously every 3 to 6 months, requiring a minor surgical procedure for the implantation. This formulation was well tolerated when used in adolescent males, even if few cases have been described [32, 33]. In addition, it was reported wide variability in circulating T levels, with excessively high serum T values for the early stage of puberty. No reports are available upon the use of pellets for pubertal induction.

Despite the limited number of prospective studies involving adolescent males [34, 35], intramuscular TE is the most frequently used therapy for induction and progression of puberty in boys. Different regimens have been reported with a positive effect on pubertal maturation in boys with delayed puberty [36-39], while no data are available concerning titration schemes to adult T doses and long-term safety and efficacy. Some escalation schemes from pubertal induction to adulthood doses have been proposed [40-42]. During the neonatal period, short-term low-dose injective T esters therapy could also be used to increase penile size in hypogonadal boys [43, 44], although a standardized dosing regimen has not been established.

Intramuscular T therapy presents some pitfalls. Indeed, both enanthate and cypionate esters are unable to mimic the physiological testosterone levels due to their pharmacokinetic profiles. T rises to supraphysiological concentrations a few days after injection, with a gradual decrease to subphysiological levels within the following 2 to 3 weeks [45]. Propionate ester is uncommonly used for hypogonadism treatment, due to its short-term formulation and wide T fluctuations. A possible inconvenience of T esters is related to intramuscular injections and relative discomfort, although no specific data upon its influence on compliance are available.

Oral T undecanoate (TU) was developed in the 1980s to avoid the liver inactivation of earlier natural oral T formulation. It is absorbed into the lymphatic system, bypassing liver inactivation, even if oral bioavailability is unreliable depending upon the lipid content of meals [46, 47]. Some authors have reported oral TU use in pediatric population [48-50], although the short half-life and the requirement of multiple daily doses make it difficult to use in long-term replacement therapy.

Transdermal T patches introduced in the 1990s were designed for adult doses and cannot be divided. For this reason, their use in males during childhood and adolescence is extremely limited [51, 52]. From the 2000s novel testosterone formulations have become available with the introduction of topical gels, oral soft gel, nasal preparation, subcutaneous depot, and a long-acting intramuscular formulation. New T formulations, their relative advantages or disadvantages and their possible use in the pediatric population are summarized in Table 3.

Transdermal gel formulations

T transdermal gel formulations represent an upcoming option for hormonal replacement therapy. Their appeal is related both to the daily self-administration, avoiding the injection discomfort, and to a more physiological pharmacokinetics. Population pharmacokinetic analysis has demonstrated that 1% or 2% hydroalcoholic gel application allows a rapid rise of serum testosterone levels in hypogonadal males, reaching the steady-state level at the end of the first day [53]. Thereafter, serum T levels may undergo very small peak to trough fluctuations because T absorbed is likely stored as a skin reservoir and then slowly release to the circulation as a sustained release delivery system [53]. Gel formulations may provide therefore a more physiological TRT in hypogonadal males. At present, gel formulations have been extensively studied in adults and are approved as TRT only in men with hypogonadism. Their pediatric experience is still limited, lacking randomized controlled trials.

Short-term induction therapy with gel formulation has been proposed in boys with constitutional delay in growth and puberty (CDGP), as a valid alternative to intramuscular TE [54]. The advantages of gels consist in the non-invasive formulation and low dose availability for a few of them with a minimum dose equivalent to about one-quarter to one-six of adult dosage, useful for a more physiological pubertal induction. In addition, transdermal absorption allows to avoid first-pass metabolism and potential hepatic toxicity of injected T formulations, as reported in some case

reports regarding high dose self-administration of anabolic androgen steroids in bodybuilders [55-57]. Therefore, transdermal gel T may be used also in subjects with hepatic dysfunction [58]. Few data are available on gel formulations for long-term TRT in boys with hypogonadism. Rogol et al. [59] evaluated the safety and clinical outcomes of 6-month treatment with T gel 1% therapy in adolescents with hypogonadism related to Klinefelter syndrome (21 subjects) or anorchia (8 subjects). The authors had retrospectively analyzed data from a multicenter open-label observational study carried out in adolescent boys with primary or secondary hypogonadism, or with constitutional delay in growth and puberty treated with a starting dose of 0.5 g T gel (Androgen 1%; AbbVie, North Chicago, IL, USA) once daily with a dose titration up to 5.0 g daily, based on investigator clinical judgment. The authors had demonstrated as the gel TRT was able to increase serum testosterone and relative metabolites to normal age-matched values, with mild adverse effects like cough, acne, and headache. No significant safety concerns were reported, while treatment compliance was suboptimal (72%) [59]. In a larger retrospective analysis [60], gel formulation was administered in 104 boys with Klinefelter syndrome, with a dose titration to reach high-normal serum T levels. The study aim was to investigate the safety and tolerability of a prolonged TRT (average of TRT duration was almost 24 months) in these subjects followed up to 5 years. The authors reported no severe adverse event associated with T therapy. In particular, neither behavior modification nor deep vein thrombosis was reported, while a small percentage (8%) of patients complained of acne requiring medical treatment. The gel administration did not suppress gonadotropin levels in the study population, suggesting the more physiological pharmacokinetics of topical T formulations. It should be noted that the majority of boys with Klinefelter syndrome presents a spontaneous puberty onset with a subsequent gonadal failure, often requiring a TRT from mid puberty onwards. For this reason, T supplementation appears to be easier to set at the appropriate dosage in adolescents with Klinefelter syndrome than in other boys with hypogonadism. During the extended observation period, the gel formulation was well tolerated, and patient compliance was high, despite a small proportion of the subjects reported to have forgotten to apply the gel on occasion [60]. The advantages of gel formulation for long-term TRT in adolescents are similar to those in adulthood and include the flexibility of dosing, the easy self-application, and the small number of adverse events reported [26]. The availability of very low dosing could suggest gel formulation particularly useful for newborn micropenis treatment, although no data are available in these patients. A potential disadvantage may consist in the daily administration and its compliance in a critical phase of life as the adolescent age. An extensive counseling of patients and their parents on TRT benefits and the active involvement of patients in the management of T therapy may increase subject motivation favoring higher TRT compliance. Finally, gel preparations may lead an unintentional T transference to patients' family members. The potential risk of secondary exposure to androgens could represent an important disadvantage of transdermal gels in adolescents with behavioral difficulties as Klinefelter syndrome population.

New oral Testosterone undecanoate soft capsule

Recently, a Phase 3 Clinical Trial has investigated a new formulation of oral TU dissolved in a combination of lipids and hydrophilic surfactant, encapsulated in soft gelatin capsules in 18-65 years man with hypogonadism [61]. This formulation enables TU solubilization and consequently its absorption with meals without requiring high fat content [62]. No clinically significant difference in serum T levels was observed among different meal fat compositions. Twice-daily oral TU administration immediately before a breakfast and dinner meal was demonstrated to be effective to restore eugonadal T levels in hypogonadal men, avoiding excessive peak concentrations. This dosing regimen has been adopted because plasma T concentration decline under eugonadal T range about 8 to 12 hours after oral TU dose, with a mild within-day fluctuation. The overall safety profile was similar to other approved TRT products. Gastro-intestinal side effects were reported (nausea, diarrhea, and burping), but these were minor in severity, transient, and did not request discontinuation of oral TU therapy [61].

At present, no studies are available on the pediatric population. In our opinion, this novel formulation presents some weaknesses as long-term TRT in adolescents, since twice-daily oral dosing

could reduce subject adherence to the therapy. In addition, oral administration with food requires a minimum fat content (15 gr) in breakfast meals not always guaranteed in all types of diets, as sweet breakfast of the Mediterranean diet. Finally, the availability of a single dosage (150 mg of unesterified T equivalents for capsule) equal to adult TRT dose reduces its use only in post-pubertal boys with hypogonadism after completing the pubertal induction.

Nasal Testosterone gel

In the last years, the intranasal route has been increasingly investigated for systemic drug delivery thanks to the high permeability and high drug bioavailability of the nasal mucosa, avoiding first-pass metabolism [63, 64]. Nasal T gel formulation has been also explored to overcome some undesired properties of transdermal gel formulations, as skin absorption or irritation problems and unintentional T transference to patients' family members. Multiple daily doses were required to achieve appropriate T circulating levels. In addition, the intranasal route seems to be a simple, non-invasive, safe, and rapid administration via, requiring only a few seconds per day for the drug assumption [65].

A multicenter phase 3 randomized open-label study showed that T nasal gel restores T levels to eugonadal ranges in males aged 18 to 80 years with hypogonadism [66]. A 4.5% T gel was administered from a non-pressurized, manual pump dispenser with a specific nasal applicator. The single dose was 125 μ L (equivalent to 5.5 mg of T) for each nostril (total dose 11 mg of T). After each nasal dose, it was observed a short-acting peak of plasma T level, declining to baseline values about two to four hours after administration. Peak values were consistently below safety upper-limit ranges, while the peaks-and-troughs serum T profile did not appear to have a negative impact on sexual function and energy-related symptoms. Twice daily and three-time daily nasal gel administration were well tolerated, restoring T levels into eugonadal ranges in the majority of study subjects. Active allergic rhinitis or the use of a symptomatic decongestant drug did not affect the absorption and bioavailability of T from nasal formulation [67]. The short-acting pharmacokinetic property of nasal gel seems to be responsible of a more physiological T release, allowing the maintenance of gonadotropin levels within normal limits and preserving a normal spermatogenesis in nearly all men with hypogonadism observed [68].

The most commonly reported adverse effects were of mild severity with low incidence in both dosing regimens. They were related to local nasal side effects, as nasopharyngitis, rhinorrhea, or epistaxis. A recent retrospective cross-sectional analysis reported no cases of polycythemia, the most frequent adverse effect of TRT, in patients treated with nasal gel therapy [69].

The nasal gel formulation was well tolerated by most subjects. Nearly half of interviewed men remarked the beneficial property of not touching the gel preparation, that probably outweighs the necessity of multiple daily dosing regimens [66].

Nasal gel T is approved as TRT in men with hypogonadism over 18 years, while its safety and effectiveness have not been established in the pediatric population. The potential use of nasal gel may be promising also in adolescents with hypogonadism, although the limited availability of dose titration makes its role less usable for pubertal induction.

Subcutaneous formulation

From the beginning of the 2000s, some preliminary reports have investigated weekly subcutaneous (SC) T administration as an alternative route for TRT to currently available options [70, 71]. More recent phase II and III pharmacokinetic studies have demonstrated that administration of TE in oil SC formulations through an autoinjector device was effective to restore physiologic T levels in patients with hypogonadism [72, 73]. Serum T level achieves normal values within a few hours after the first dose, with a lower peak to trough variability compared to IM TE. SC administration of TE appeared to be safe and well-tolerated by subjects. A different study has investigated the use of T cypionate SC formulation as TRT in female-to-male transgender patients [74]. Weekly SC self-administrated T cypionate in cottonseed oil solution resulted to be effective, safe and well accepted by transgender subjects, preferring SC to IM formulations. No serious local reactions at the injection sites were reported in all of the above mentioned studies [72-73].

No data are available regarding the use of SC T formulation in the pediatric population. Weekly SC preparations appear to have a potential role in TRT in adolescent age, thanks to the painless and self-administrated SC injections, avoiding recurrent physician office visits. In addition, the availability of different dosages of SC T may be useful for dose titration during pubertal induction therapy.

Long-acting intramuscular formulation.

From the beginning of the 2000s, a novel injectable TU formulation was available. The semisynthetic androgen TU is dissolved in castor oil solvent and benzyl benzoate as cosolvent agent. This component combination provides a prolonged intramuscular reservoir, thus enabling a continuous release of T from the ester into the bloodstream. Long-acting IM TU is administered with a 6-week interval for the first two injections (loading dose), and then every 10-14 weeks according to pre-injection serum T levels. This dosing regimen results in a significant reduction of injection frequency (4 to 5 per year) with a consequent increase in patient compliance. In addition, this novel injective formulation does not result in supraphysiological serum T levels. Indeed, pharmacokinetic analysis revealed stable T levels within the normal range, with a steady peak to trough profile after the third injection [75-78]. IM TU was approved by FDA in 2014 as a safe and effective form of TRT for adult males with hypogonadism. Pulmonary oil microembolism (POME) has been reported as a rare adverse event of IM TU formulations, related to its castor oil compound. A recent postmarketing safety analysis demonstrated that POME events related to IM TU therapy were rare and resolved quickly without medical intervention in the majority of cases reported. The most severe cases were associated with non-label adherent injection techniques or dosing errors [79].

No data are available on IM TU use in children. Its use seems to be limited in pubertal age due to only adult dosage availability and its long-acting release. On the contrary, this formulation could be useful as long-term TRT in adolescents with hypogonadism after the pubertal induction period.

Conclusion

New T formulations are demonstrated to be safe, effective, and well-accepted as TRT in males with hypogonadism. Unfortunately, these formulations are approved only for adults due to the lack of randomized controlled trials in the pediatric population. However emerging data support safety, efficacy, and high compliance of transdermal formulation for TRT also in adolescent age [59, 60]. At present, pubertal induction is typically enabled with IM testosterone esters, given the major clinical experience with this preparation, and then switched to newer formulation with “off-label” regimens once adult dosing is reached. Many fewer data are available upon T use during minipuberty in newborns with micropenis and hypogonadism, with only a few schemes therapy based on expert opinions [8].

Despite no evidence-based guidelines regarding pubertal induction dosing regimens or optimal T formulation, TRT should be individualized to the patient’s age and needs. It would be desirable to use a slow titration dosing regimen during pubertal induction, up to adult dosage when adult height is reached. In this direction, the flexibility of dosing and easing of administration of some formulations, as a few transdermal gels or subcutaneous TE, could make them attractive for pubertal induction in adolescent age. In this respect, it should be noted that the majority of new T formulation may be used in pediatric population only from mid puberty onwards, due to their little flexibility of dosing. On the other hand, long-acting and stable formulations, as IM UT, could meet post-pubertal needs of the adolescent population, increasing TRT compliance in a critical phase for acceptance of chronic diseases. Finally, nasal gel and oral soft capsule daily formulation may represent a good pain-less and non-invasive choice for after-pubertal long-term TRT of male hypogonadism also in children. Further controlled, long-term safety and efficacy studies for all these new T formulations on the pediatric population are needed.

Statements**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by LC and MC. The first draft of the manuscript was written by LC. MC reviewed and commented the manuscript. All authors read and approved the final manuscript.

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Table 1

Hypogonadotropic Hypogonadism	Hypergonadotropic Hypogonadism
<ul style="list-style-type: none"> • Transient (Constitutional Delay in Growth and Puberty) • Congenital <ul style="list-style-type: none"> - Isolated (Kallmann syndrome, LHRH receptor mutation, congenital adrenal hypoplasia [DAX1 mutation], isolated LH deficiency, isolated FSH deficiency) - Multiple pituitary hormone deficiency (PROP1 mutation) - Syndrome associated (Prader-Willi, Laurence-Moon and Bardet-Biedl syndrome) • Functional gonadotropin deficiency <ul style="list-style-type: none"> - Chronic systemic disease (cystic fibrosis, AIDS, chronic gastroenteric disease, chronic renal disease, sickle cell disease) - Malnutrition (eating disorders, intense physical exercise) - Associated with other endocrine diseases (hypothyroidism, diabetes mellitus, Cushing disease, hyperprolactinemia) • Acquired gonadotropin deficiency <ul style="list-style-type: none"> - CNS Tumors and infiltrative causes (craniopharyngiomas, germinomas, hypothalamic and optic gliomas, astrocytomas, Langerhans histiocytosis) - Post CNS surgery or radiation therapy - Other causes: postinfectious lesion of CNS, head trauma, lymphocytic hypophysitis, congenital midline anomalies (as holoprosencephaly) 	<ul style="list-style-type: none"> • Congenital <ul style="list-style-type: none"> - Klinefelter syndrome - Testicular steroid biosynthetic defects - Sertoli-only syndrome - LH receptor mutation - Testicular dysgenesis - Anorchia/Vanishing testis • Acquired testicular failure <ul style="list-style-type: none"> - Chemotherapy - Testicular radiation therapy - Cryptorchidism - Testicular trauma, torsion - Orchitis - Orchiectomy

Table 1 Classification of hypogonadism in males. CNS: central nervous system

Table 2

Formulation	Commonly used regimens in pediatric population	Advantage/Disadvantage
Subcutaneous T pellets	Puberty induction: ND Adult dose: 8-10 mg/kg every 6 months [26] or 150-450 mg every 3-6 months [25]	A: good compliance; well tolerated by adolescents D: Wide variability of serum T levels; need to repeat surgical implantations
Intramuscular T esters (enanthate and cypionate)	Newborn micropenis: 25 mg every 3 weeks for 3 months [8, 37] Pubertal induction: starting dose of 25 to 50 mg every 4 weeks for 6 months. Titration scheme: increase of 50 mg every 6-12 months until the dose of 150-200 mg every 4 weeks, then decrease interval to every 2 weeks as adult dose [34-36] Adult dose: 150-200 mg every 2 weeks [20]	A: low cost, most clinical experience in childhood D: non-physiological serum T fluctuations, painful injections, behavior disturbances; recurrent physician office visits requirement
Oral TU	Pubertal induction: 20-40 mg daily [42-44] Adult dose: 40-80 mg twice daily [20]	A: painless administration D: erratic oral bioavailability depending upon the lipid content of meals; twice daily administration
Transdermal T patch	Pubertal induction: 2.5 mg for 12 h daily, or 5 mg for 8-12 h daily application for 6 months [45, 46] Adult dose: 5-10 mg over 24 h daily [20]	A: painless administration, easy application D: skin irritation, indivisible formulation

Table 2 Current testosterone replacement therapy with pediatric dosing regimens and relative advantage or disadvantage formulation. T: testosterone; TU: testosterone undecanoate; A: advantage; D: disadvantage; ND: no data.

Table 3

Formulation	Adult dose	Pediatric use	Advantage/Disadvantage
Transdermal gel (1% or 2%)	1% gel: 50-100 mg daily [20] 2% gel: 40-70 mg daily [20]	Pubertal induction in delayed puberty: 2% gel 10 mg daily for 3 months [48] Replacement therapy in boys with hypogonadism: 1% gel 0.5 g up to 5 g daily [53]	A: extreme flexibility of dosing; self-application; painless formulation; physiological pharmacokinetics; avoid of hepatic first-pass metabolism; mild adverse effects; good skin tolerability D: adherence to daily formulation; unintentional drug transference to other persons
Nasal gel	11 mg (5.5 mg for each nostril) twice or three-time daily [20]	ND	A: high drug bioavailability; avoid of first-pass metabolism; stable serum T profile; noninvasive, rapid and self-application; mild local adverse effects D: multiple daily formulation; limited availability of dosing
Oral TU soft capsule	1 capsule (equivalent to 150 mg of T unesterified) twice daily [55]	ND	A: noninvasive formulation; mild within-day serum T fluctuation D: multiple daily formulation; mild gastro-intestinal side effects; requirement of minimum fat content in meals; single adult dose availability
Subcutaneous T esters	50-100 mg weekly [20, 66]	ND	A: painless and self-administrated SC injections; avoid of recurrent physician office visits; stable serum T profile D: limited availability of dosing
Long-acting injective TU	750 mg IM, followed by 750 mg at 4 week, then 750 mg every 10-14 weeks [20]	ND	A: prolonged intramuscular reservoir with continuous release of T; stable serum T levels; high

			adherence to long-term administration D: single adult dosage; long-term effect; local adverse effects
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Table 3 New testosterone formulations, adult dosage, pediatric application, and relative advantages or disadvantages. T: testosterone; TU: testosterone undecanoate; IM: intramuscular; SC: subcutaneous; A: advantage; D: disadvantage; ND: no data.