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REVIEW

An update on the available and emerging pharmacotherapy for adults with testosterone deficiency available in the USA

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ABSTRACT

Introduction: Testosterone deficiency (TD) is defined as low serum testosterone associated with symptoms and signs. There has been an increasing prevalence of TD in recent decades, especially in males aged 15–39. Many of these men will require long-term testosterone therapy (TT). Although the end-goals for all treatments are essentially the same, strategies for increasing serum testosterone should be decided individually.

Areas covered: This review focuses on the pharmacological management of TD in adults which includes TT with different routes of administration, such as transdermal, buccal, intramuscular and subcutaneous injections, pellets, nasal gel, and oral (pills). The authors review the options for TT available in the USA with emphasis on newer therapies. Furthermore, they examine the efficacy of these therapies with comparison between potential advantages or disadvantages related to dosing, administration method, and adverse events.

Expert opinion: Treating TD can be difficult due to the wide range of available medications, diverse side effects related to testosterone replacement and route-of-administration, and necessity for long-term therapy. The combination of pharmacological and non-pharmacological therapies can improve symptoms of TD and patient satisfaction. Each patient should be managed individually, and clinicians should consider available treatment regimens based on the route-of-administration, efficacy, safety, and cost based on a shared decision-making approach.

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Testosterone therapy; testosterone deficiency; hypogonadism

1. Introduction

Testosterone is the primary male sex hormone which plays an integral role in many facets of physiology including embryologic development, spermatogenesis, and development and maintenance of secondary sexual characteristics throughout puberty and adulthood. Testosterone deficiency (TD) is defined as insufficient production of testosterone combined with symptoms of low serum total testosterone such as decreased muscle mass, osteoporosis, poor erythropoiesis, diminished energy, low libido, and erectile function [1–6]. Etiologically, TD can be separated into primary and secondary TD. Primary TD occurs when there are problems with testosterone production at the level of the testes, whereas secondary TD involves defects in the production of gonadotropin hormones from the hypothalamus or pituitary [7]. Although this review focuses mainly on the treatment of TD from a primary etiology, the principles and medications can be used with any patient that presents with TD. Diagnosing TD can be challenging because of the heterogeneity of symptoms experienced by different individuals but the current definition relies on two criteria: having a low serum testosterone defined by two separate early morning testosterone levels <300 ng/dL as well as manifestations of the aforementioned symptoms.

TD is incredibly common among the general population. A recent study estimated the prevalence of TD in the elderly population to be as high as 2.1% [8]. Another study examining testosterone levels from 2000 to 2016 also demonstrated an increasing prevalence of decreasing serum levels in adolescents and young males over time [9]. This can possibly be due to the increasing prevalence of obesity and elevated BMI which are associated with low testosterone levels [8]. As such, physicians are now frequently seeing patients with this pathology. TD is treated with various forms of testosterone therapy (TT) with the goals of improving symptoms and increasing serum testosterone to physiologic levels in the range of 450–600 ng/dL [10]. Many options for TT have been approved by the FDA with each formulation having unique advantages and disadvantages. Available routes of administration include transdermal, buccal, nasal, IM injections, implants and, most recently, oral pills. This article will review treatment options available in the USA for TT in adult men with an emphasis on novel, more recently developed medications.

2. Non-exogenous TT options

While the majority of TT options involve direct exogenous testosterone replacement, other medications aimed at increasing serum testosterone include selective estrogen receptor

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Article highlights

- Testosterone deficiency is a common diagnosis among males with an increasing number of patients seeking treatment.
- There are many options for testosterone therapy with various routes of administration including transdermal, buccal, nasal, IM and subcutaneous injections, subcutaneous implants, and oral formulations.
- For those seeking fertility preservation, forms of TT other than exogenous testosterone replacement are available.
- Different formulations will allow patients to reach normal testosterone levels, but each has unique advantages and disadvantages.
- Each patient should be treated individually, and clinicians should discuss the route of administration, side effects, benefits, safety, dosing, and costs prior to making a decision on the appropriate medication.

This box summarizes key points contained in the article.

modulators (SERMs), human chorionic gonadotropin (hCG), and aromatase inhibitors (AIs). SERMs such as clomiphene citrate function by decreasing the negative feedback of estrogen on the hypothalamic-pituitary-gonadal axis (HPG) axis. In turn, this results in an increase in gonadotropin-releasing hormone (GnRH) from the hypothalamus which stimulates release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. LH subsequently acts on Leydig cells in the testicle to accelerate native production of testosterone while FSH acts on Sertoli cells to promote spermatogenesis. While primarily given for male factor infertility, SERMs have the ability to raise testosterone levels. A retrospective review of 69 men with testosterone levels below 300 ng/dL who received 25 mg of clomiphene citrate every other day showed an average testosterone level of 389 ng/dL after treatment [11]. hCG also has the ability to increase serum testosterone levels. This medication shares a very similar chemical structure with LH allowing it to act directly on Leydig cells and stimulate testosterone production. In addition to treating male infertility, hCG has been useful in men who experience symptoms of TD [12]. A retrospective analysis of 20 men showed that treatment with hCG raised average testosterone levels from 362 ng/dL to 519.8 ng/dL. Perhaps more importantly, 50% of the patients reported symptomatic improvement including increased libido, erectile function, and energy. AIs are another method of increasing testosterone levels that act by blocking aromatase, an enzyme that converts testosterone to estrodiol. By increasing testosterone levels through this mechanism, AIs have been shown to improve semen parameters in subfertile men. In an analysis of 86 sub-fertile men with low testosterone:estradiol ratios

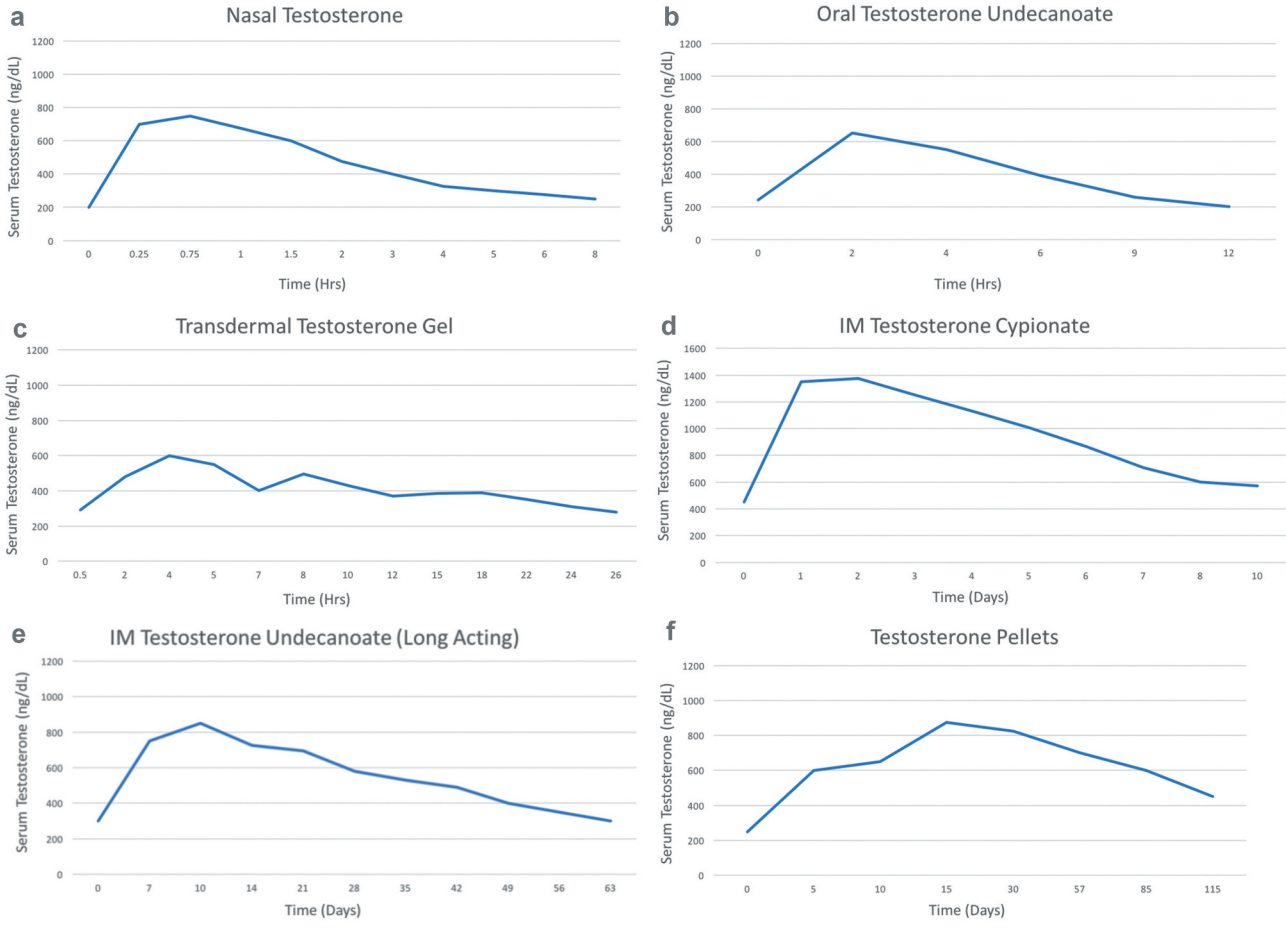

Figure 1. A schematic representation of serum testosterone levels over time for various of routes of administration of exogenous testosterone therapy based on reported peak concentrations and half-life. (A) Testosterone gels [serum testosterone vs. time (hours)]. (B) IM testosterone cypionate [serum testosterone vs. time (days)]. (C) IM testosterone undecanoate [serum testosterone vs. time (days)]. (D) Subdermal testosterone pellets [serum testosterone vs. time (days)]. (E) Nasal testosterone gel [serum T vs. time (hours)]. (F) Oral testosterone undecanoate [serum T vs. time (hours)] [21,40,49,55,59,73].

Table 1. **Summary of testosterone therapy available in the USA**: A summary of the various formulations of testosterone therapy with information on their route of administration, time until peak concentration, starting dose, titration range, recommended follow-up, advantages, and disadvantages [19,21,24,26,28,30–32,34,40,44,46,49,54,59,73].

Therapy	ROA	Time to peak	Starting dose	Titration range	Follow up	Advantages	Disadvantages
Androderm®	Patch	8 hours	4 mg/day or 2.5 BID	2 mg–6 mg/day or 2.5 mg–7.5 mg/day	2 weeks	Noninvasive Easy to use	High risk of skin reaction Less efficacious than other therapies
Androgel® 1%	Gel	4 hours	50 mg/day	25 mg–100 mg/day	Physician Discretion	Noninvasive Easy to use	High risk of transference
Androgel® 1.62%	Gel	2–4 hours	40.5 mg/day	20.25 mg–81 mg/day	14 days and 28 days	Noninvasive Easy to use	High risk of transference
Testim®	Gel	4 hours	50 mg/day	50 mg–100 mg/day	14 days	Noninvasive Easy to use	High risk of transference Inflexible dosing
Vogelxo®	Gel	4–8 hours	50 mg/day	50 mg–100 mg/day	14 days	Noninvasive Easy to use	High risk of transference Inflexible dosing
Fortesta®	Gel	2 hours	40 mg/day	10 mg–70 mg/day	2 hours, 14 days, and ~35 days	Noninvasive Easy to use Flexible dosing	High risk of transference
Testavan	Gel	2–4 hours	23 mg/day	23 mg–69 mg/day	2–4 hours	Noninvasive Easy to use Less gel used per dose	High risk of transference
Axiron®	Liquid Solution	2–8 hours	60 mg/day	30 mg–120 mg/day	2–8 hours and 14 days	Noninvasive Easy to use	High risk of transference
Testosterone Cypionate	IM injection	2–5 days	75–100 mg/week or 150–200 mg/bimonthly	-	Physician Discretion	Less frequent dosing	Injection discomfort Rapid fluctuations Highest risk for Erythrocytosis
Testosterone EnanThate	IM injection	1–2 days	50–400 mg/bimonthly or monthly	-	Physician Discretion	Less frequent dosing	Injection discomfort Rapid fluctuations Highest risk for Erythrocytosis
Xyosted™	Subcutaneous injection	1–2 days	75 mg/week	50 mg–100 mg/week	7 days	Less frequent dosing Relatively less invasive	Rapid fluctuations Highest risk for Erythrocytosis
Testosterone Undecanoate	IM injection	7 days	2 × 750 mg/month then 750 mg/10 weeks	-	-	Less frequent dosing	Pulmonary oil micro-embolism
Testopel®	Subdermal Pellet	1–2 weeks	150 mg–450 mg/3–6 months	Physician discretion/patient preference	Physician Discretion	Less frequent dosing Higher compliance	Requires procedure under local anesthesia
Natesto®	Intranasal Gel	<1 hour	11 mg TID	-	1 month	Noninvasive Easy to use No risk of transference	Inflexible dosing options Nasal irritation/bad taste
Striant®	Buccal Tablet	10 hours	30 mg BID	-	Physician Discretion	Noninvasive Easy to use	Gum inflammation/Gingivitis Inflexible dosing
Jatenzo®	Oral Capsule	4 hours	237 mg BID	158 mg BID–396 mg BID	7 days	Least invasive Easiest to use	GI side effect Increase in systolic BP

treated with anastrazole, average serum testosterone increased from a baseline of 258.4 ng/dL to 449.9 ng/dL after 4 months [13]. These non-exogenous forms of TT rely on adequate testicular function to produce natural testosterone. Through this mechanism, however, they have the added benefit of physiologic intratesticular testosterone concentrations capable of maintaining or triggering spermatogenesis. This effect can be measured using the serum 17-Hydroxyprogesterone as an indicator for intratesticular testosterone concentrations [14–16]. Unlike exogenous forms of TT, this allows for preservation and/or treatment of male infertility. While these medications all have the ability to treat TD, most TT in patients not focused on fertility will act through exogenous testosterone replacement which we discuss throughout this review.

3. Transdermal

Transdermal formulations depend on testosterone reaching systemic circulation directly through the skin, bypassing potentially detrimental first-pass metabolism in the liver. All transdermal delivery methods of testosterone rely on hydroalcoholic vehicles that quickly dry after application, creating a reservoir of testosterone on the skin. Some formulations are combined with penetration enhancers which disrupt the stratum corneum layer of the skin to increase delivery into circulation [17]. Transdermal formulations of testosterone come in varying mediums and concentrations ranging from gels and patches to liquid sprays.

In general, the advantages of transdermal systems are their lack of invasive application, ease of use, and ability to sustain testosterone levels without significant fluctuations [18]. Disadvantages include potential skin irritation (especially in the case of patches) and the potential for transference (unique to gels and solutions). Due to the risk of transference, especially with children, testosterone gels carry an FDA boxed warning. For this reason, patients on gels are recommended to wash their hands after each application and apply the medication on areas that are usually covered with clothing.

3.1. Androderm®

The first transdermal systems were developed in the form of adhesive patches. Currently, one of the only patches approved in the United States is Androderm (AbbVie, North Chicago, IL, USA) [19]. The patch consists of a microporous membrane with a peripheral mucoadhesive layer and a central reservoir with the entire system contained by an impermeable backing film. The contents of the reservoir include testosterone, the only active ingredient dissolved in hydroalcoholic gel. Patches are available in dosages of 2, 2.5, 4, and 5 mg of testosterone. The recommended starting dose is one 4 mg patch per day, one 5 mg patch per day, or two 2.5 mg patches per day, applied centrally to the back, abdomen, arms, or thighs. Maximum testosterone levels are reached at 8 hours after application. Testosterone levels should be checked 2 weeks after starting treatment to allow for proper titration.

The pharmacokinetics, efficacy, and safety of Androderm have been studied in a comparison to IM testosterone enanthate [20]. Androderm was initiated at a starting dose of 5 mg in 33 patients and titrated up or down based on adverse events or testosterone levels. The average testosterone levels of the Androderm group were 517±176 ng/dL by the end of the study, with maximum levels of 765 ± 277 ng/dL reached at around 8 hours after application. Testosterone was absorbed continuously throughout the 24-hour period and decreased after removal of the patch with a half-life of about 70 minutes. Sixty percent of patients experienced transient skin irritation in the study, however, only three patients discontinued treatment for this reason.

3.2. Androgel®

More recently, transdermal testosterones were developed in gel form with the introduction of Androgel 1% (AbbVie, North Chicago, IL, USA). The hydroalcoholic gel consists of the only active ingredient, testosterone [21]. Androgel can be applied using two mechanisms: non-aerosol, metered-dose pumps or unit-dose aluminum foil packets. The pump system delivers 12.5 mg of testosterone dissolved in 1.25 g of gel per pump actuation, while the packets contain 25 or 50 mg of testosterone dissolved in 2.5 g and 5 g of gel, respectively. The dosing starts at 50 mg of testosterone applied bilaterally on the upper arms/shoulders or abdomen applied once every 24 hours. Titrations can be made to increase up to 75 mg or 100 mg or decrease to 25 mg depending on testosterone concentrations after initial treatment. After application, Androgel dries and the skin serves as a reservoir for testosterone delivery. Only 10% of the testosterone dose applied enters systemic circulation. Concentrations reach the normal range within 4 hours after application, and testosterone continues to be absorbed over the 24-hour period [22]. Once Androgel is discontinued after reaching steady state, testosterone levels remain stable for 1–2 days and stay within the normal range until the fifth day after the last application [21].

A 180-day clinical trial was conducted in which patients were randomized to Androgel 1% (50 mg or 100 mg) and an alternative 5 mg non-scrotal transdermal system [23]. In the Androgel group, men were titrated up to 75 mg based on testosterone concentration at day 60. As long as Androgel continued to be properly applied, testosterone concentrations were maintained. Across all three Androgel groups, average testosterone concentrations were 555 ± 225 ng/dL, 601 ± 309 ng/dL, and 713 ± 209 ng/dL for 50 mg, 75 mg, and 100 mg, respectively. Of the patients who had been titrated to 75 mg on day 60, 87% of them reached testosterone concentration within the normal range by the 180th day. In contrast, steady-state levels of testosterone concentration well into the normal range were never reached for the non-scrotal transdermal system. Furthermore, dropout rates were also higher for the alternative transdermal system compared to Androgel.

Androgel is also offered in a 1.62% gel. Although it has a list of identical ingredients to that of the 1% formulation, it has a unique set of dosing recommendations and is more specific with its application site [24]. Similar to the 1% gel, Androgel 1.62% comes in the form of a metered-dose pump with 1 pump actuation releasing 20.25 mg and aluminum foil packets with 40.5 mg and 20.25 mg packets available. The

recommended starting dose is 40.5 mg of gel (2 pump actuations or one 40.5 mg packet). Serum testosterone concentrations should be assessed at 14 and 28 days after the start of treatment. The dosages can be adjusted to a minimum of 20.25 mg (1 pump actuation or one 20.25 packet) if testosterone levels exceed 750 ng/dL and a maximum of 81 mg (4 pump actuations or two 40.5 mg packets) if levels fall short of 350 ng/dL. In terms of application, Androgel 1.62% is only recommended to be applied on the shoulders in contrast to 1% which can also be applied to the abdomen. Maximum testosterone concentrations are reached within 2–4 hours in a 24-hour period and on discontinuation, serum testosterone decreases to baseline within 48–72 hours after the last dose.

3.3. Testim®

Testim 1% (Endo pharmaceuticals, Malvern, PA, USA) was the second commercially available testosterone gel to be produced after Androgel. The ingredient list differs from Androgel, most notably by the presence of a penetration enhancer called pentadecalactone that is widely used as a controlled-release drug carrier [25]. Testim 1% is available in unit-dose tubes each containing 5 g of gel with 50 mg of testosterone. The starting dose is 50 mg of testosterone (one tube) daily with peak testosterone levels reached at 4 hours after application. Testim can be titrated up to 100 mg (two tubes) daily based on testosterone concentrations following treatment. Concentrations should be checked at 14 days after administration to ensure proper titration. Testim 1% should be administered to the shoulders and/or upper arms [26].

A 406-patient clinical trial was used to evaluate Testim 1% over the course of 90 days [27]. Patients were given either Testim 1% 50 mg, Testim 1% 100 mg, placebo, or non-scrotal transdermal system (testosterone patch). At day 60, patients were titrated up or down based on their 24-hour average testosterone concentrations of testosterone. By the 90th day, 74% of the patients titrated appropriately had average serum testosterone levels within the normal range. All treatments, including the patch, showed significant elevations compared to the placebo treated group. By the end of the study, only those treated with 100 mg showed significant elevation of average testosterone concentrations compared to all other groups. Although the 50-mg group did not show significant changes in average testosterone concentrations, the minimum testosterone concentration of 50 mg was significantly elevated from the minimum testosterone concentration of the patch.

3.4. Fortesta®

Fortesta is an another testosterone gel with a 2% concentration (Endo Pharmaceuticals, Malvern, PA, USA). Similar to Testim 1%, it contains a penetration enhancer in the form of oleic acid [28]. Fortesta comes as a metered dose pump with each pump actuation delivering 10 mg of testosterone. The starting dose is four pump actuations (40 mg of testosterone) daily which can be titrated to a minimum of 10 mg or a maximum of 70 mg. Peak levels are reached at about 2 hours after application. Levels should be checked 2 hours, 14 days, and ~35 days after applications to ensure proper titration. Fortesta is relatively unique because of its high testosterone concentration. This allows for more precise dosing as small amounts of gel can be used to titrate into the optimal range. Specifically, starting from 40 mg, dosages can be decreased by 20 mg or 10 mg if serum testosterone is higher than 2500 ng/dL or between 1250 and 2500 ng/dL, respectively. If serum testosterone is less than 500 ng/dL, 10 mg of Fortesta can be added until the optimal level is reached. Fortesta is applied exclusively to the front and inner thighs, in contrast to other gels which focus more on the upper body.

A non-comparative trial evaluated 149 men using Fortesta over 90 days to determine the percentage of patients with average testosterone concentrations within the normal range by the 90th day of the study [29]. The patients were started on a 40 mg dose and titrated to a maximum of 70 mg and a minimum of 10 mg based on the aforementioned dosing scheme. At day 90, 77.5% of the patients had average testosterone concentrations in the normal range. Patients were also evaluated for maximum testosterone concentrations greater than 1500 ng/dL or between 1800 and 2499 ng/dL with only 5.4% and 1.6% in those categories, respectively.

3.5. Vogelxo®

Another recently developed 1% testosterone gel is Vogelxo (Upsher-Smith Laboratories, Maple Grove, MN, USA). Although other gels are also available at this concentration, Vogelxo is unique in that it contains multiple known penetration enhancers such as diisopropyl adipate, oleyl acid, and methyl laurate [30]. The gel comes in either unit-dose tubes, packets, or metered-dose pumps. The starting dose is 50 mg (one tube/packet or 4 pump actuations) and can be titrated up to a maximum dose of 100 mg. The gel is applied to the shoulders and upper arms and should be limited to the area covered by a shirt. Clinical trials evaluating Vogelxo (50 mg and 100 mg) compared to a placebo and a non-scrotal testosterone transdermal system showed that 74% of the patients had average testosterone concentrations of testosterone in the normal range by day 90 [27].

3.6. Testavan®

Testavan (Ferring Pharmaceuticals, Saint Prex, Switzerland) is a novel 2% gel with a novel hydroalcoholic and highly viscous formulation [31]. Testavan comes in a meter-dose dispenser which includes a hands-free cap applicator. The starting dose is 23 mg of testosterone delivered in 1.15 g of gel (one pump actuation) and the highest dose is 69 mg of testosterone in 3.45 g of gel. The dose is titrated based on peak testosterone concentration measured 2–4 hours after application. Testavan is unique in that relatively less gel must be applied compared to other products. This feature is attributed to its increased bioavailability from a proprietary topical gel technology called Ferring Advanced Skin Technology (FAST) which uses a unique combination of penetration enhancers. Although Testavan also has a risk of transference similar to other gels, its hands-free cap applicator provides a possible means of decreasing

this risk. One study demonstrated that 87% of the patients felt a reduced risk of secondary exposure when using the applicator [31].

3.7. Axiron®

Axiron (Eli Lilly, Indianapolis, IN, USA) comes in the form of a liquid solution with 30 mg of testosterone for every 1.5 mL of hydroalcoholic solution containing the penetration enhancer octyl salicylate [32]. Axiron comes in a pump or twist actuated metered-dose pump. Each pump or twist delivers 30 mg of testosterone into an applicator cup which is then applied exclusively to the axilla. The starting dose is 60 mg (two pumps or twist actuations) daily with peak levels reached at 2–8 hours, and can be titrated up to 120 mg or down to 30 mg depending on subsequent testosterone measurements. Titrations can be made based on levels at 2–8 hours after application and at least 14 days after starting treatment.

Clinical trials done with Axiron showed that 84.8% of patients had average testosterone concentrations within the normal limits over 60 days [33]. During the study, it took 14 days to reach steady-state concentration and 7–10 days for testosterone levels to decrease to baseline after discontinuation. As with other transdermal routes of administration, the most common adverse event was application site irritation/erythema [33]. Furthermore, similar to gels, this formulation demonstrates a risk of transference, necessitating thorough handwashing and coverage of the administration site with clothing [32].

4. Buccal

Buccal testosterone developed as Striant® (Endo Pharmaceuticals, Malvern, PA, USA) is available in the form of a mucoadhesive tablet that adheres to the gums and provides a controlled release of testosterone as saliva hydrates the system. The testosterone is absorbed directly into systemic circulation via the mucosa, bypassing first-pass metabolism in the liver [34]. Striant tablets contain 30 mg testosterone and are dosed with one tablet twice daily. After application, serum testosterone reaches maximum levels within the normal physiologic range in 10–12 hours. Upon removal, testosterone levels decrease back to baseline in 2–4 hours.

Two clinical trials were conducted to evaluate the pharmacokinetic profiles of Striant. At 7 days and 12 weeks, 84% and 76% of the participants reached testosterone levels within the normal range, respectively, with steady-state concentrations of 550±169 ng/dL and 520±205 ng/dL [35,36]. The most common adverse effects were related to gum or mouth irritation and taste perversion. Despite these unique side effects, however, long-term studies indicate that these symptoms did not worsen over time and only resulted in a 4.3% overall discontinuation rate [37]. Striant provides an easy-to-use, noninvasive option to treat hypogonadism with relatively few side effects.

5. Intramuscular depot

Unmodified injected testosterone has an inconsistent half-life of around 30 minutes, and thus modifications have been made to provide a slower sustained release [38]. The addition of an ester group increases the solubility of the testosterone molecule in hydrophobic environments which causes a slower release of bioactive testosterone from the muscle into systemic circulation. Therapeutic intramuscular testosterone currently comes in three forms: testosterone cypionate (TC), testosterone enanthate (TE), and testosterone undecanoate (TU), each of which differs in the length of the ester chain on the 17-beta position carbon molecule. The testosterone esters have carbon chain lengths of seven, eight, and eleven molecules for TE, TC, and TU, respectively. Generally, a longer chain provides a longer duration with TC and TE having similar durations of action and TU lasting longer [39].

One unique disadvantage of intramuscular formulations is that they necessitate frequent injections which can cause pain, injection site reactions, and distress to the patients. Furthermore, IM testosterone is associated with more rapid testosterone fluctuations which can cause mood swings and changes in libido along with an increasing chance of developing dependence [40]. Injectable testosterone is also associated with a greater risk of erythrocytosis compared to other forms of testosterone therapy [41].

5.1. Testosterone cypionate

Testosterone cypionate or Depo-Testosterone© was developed by Pharmacia and Upjohn Company (New York, NY, USA) but is also available in a generic form. Both options provide doses of 100 mg/mL (10 mL vial) and 200 mg/mL (1 or 10 mL vial) with cottonseed oil as the vehicle. While the FDA recommends a starting dose with a wide range of 50 to 400 mg every 2–4 weeks, the Endocrine Society Clinical Practice Guidelines suggest an alternative dosing scheme at 75–100 mg weekly or 150–200 mg every 2 weeks [40,42].

A study analyzing the pharmacokinetics of TC over a 14 day period after administration of 200 mg in 11 hypogonadal men demonstrated that mean testosterone levels rose to supratherapeutic levels peaking at 1112 ± 297 ng/dL around post-injection day 4–5 [43]. Afterward, levels slowly declined and approached 400 ng/dL by day 14. In addition, elevations in testosterone were associated with a threefold increase in estradiol levels. These wide fluctuations throughout the 2-week period likely account for mood swings and changes in libido that are commonly reported.

5.2. Testosterone enanthate

Testosterone enanthate, developed by Endo Pharmaceuticals and Antares Pharma (Malvern, PA, USA), is available as a generic intramuscular injection as well as a new subcutaneous injector. Its chemical structure contains an ester heptanoate side chain at the 17-(beta) carbon. For IM TE, dosing guidelines are similar to those recommended by the FDA and Endocrine Society for TC [44].

The pharmacokinetics of IM TE was evaluated in a trial of various dosages [45]. During the trial, 100 mg was given every week, 200 mg every 2 weeks, 300 mg every 3 weeks, and 400 mg every 4 weeks. Average serum concentrations of testosterone remained in the normal range for all groups. Although the 100 mg and 200 mg groups both maintained

minimum concentrations within the normal range throughout the dosing period, both the 300 mg and 400 mg groups had testosterone concentrations that plateaued below the lower limit. Furthermore, each dosage group reached peak levels above 1,200 ng/dL 24–48 hours after administration, demonstrating the wide variation in levels between doses.

5.2.1. Xyosted™

Xyosted, a new form of TE developed by Antares Pharma (Malvern, PA, USA), is available in the form of a subcutaneous auto-injector. The injector is available in three dosage forms: 50 mg, 75 mg, and 100 mg, all dissolved in a 0.5 mL solution. The recommended starting dose is 75 mg administered in the abdominal region once a week. Concentrations can be titrated up or down depending on trough levels at the end of the dosing interval [46].

The efficacy and safety of Xyosted was evaluated in a 150-patient, 52-week clinical trial [47]. Each patient was started off at 75 mg weekly and titrated 25 mg up or down based on trough levels at week 6. Endpoints included 7-day average serum testosterone concentrations within the normal range at week 12 and percentage of patients with maximum testosterone levels above 1500, between 1800 and 2500 and above 2500 ng/dL. By week 12, average serum testosterone concentrations were in the normal range for 90% of the patients with no patients having maximum levels greater than 1500 ng/dL. Xyosted offers a less painful, easy-to-use alternative to IM injections while still maintaining the ability to raise testosterone levels over a relatively long period of time [48]. Due to a mean increase of 4 mmHg increase in systolic blood pressure during the trial, Xyosted also includes an FDA boxed warning for an increase in blood pressure that raises the risk of major adverse cardiovascular events [47].

5.3. Testosterone undecanoate

Injectable testosterone undecanoate, or Aveed®, was developed by Endo Pharmaceuticals (Malvern, PA, USA) and is the longest acting IM injection available. The starting dose of IM TU is two injections in the gluteus medius of 750 mg (3 mL) spaced 4 weeks apart and one 750 mg injection every 10 weeks thereafter. There are no dosage titrations for IM TU [49]. Administration of IM TU can only be done in-office as there is a risk of intravascular injection which can lead to pulmonary oil microembolism (POME) [50]. Patients must be observed in the clinic for a half-hour to observe for symptoms such as urge to cough, shortness of breath, throat tightening, chest pain, dizziness, and syncope [49]. Due to this significant side effect, the use of Aveed® is restricted and only available through the Aveed REMS (Risk Evaluation and Mitigation Strategy) Program.

IM TU was evaluated for efficacy by an 84 week trial including 130 hypogonadal patients [51]. The primary and secondary endpoints were the percentage of patients who reached steady state average testosterone concentrations within the normal range and significantly increased maximum testosterone levels (>1500, 1800–2499, and >2500 ng/dL). Of the 130 men, 117 completed the study with 94% reaching normal steady state concentrations and only 5.1% below the normal range. Only 7.7% of the patients had maximum levels above 1500 ng/dL but none had levels greater than 1800 ng/dL.

Another study analyzed the pharmacokinetics of IM TU and compared them to other testosterone esters with respect to time to maximum levels and elimination half-life. Overall, IM TU rises more slowly compared to TE (7 days to maximum concentration versus 1–2 days) and has greatly increased elimination half-life compared to TE (18–24 days versus 4.5 days). This may help prevent unwanted side effects related to the rapidly changing levels of testosterone [47,52].

6. Subdermal pellets

The earliest form of testosterone replacement comes in the form of long-acting subcutaneous pellets made of crystalline testosterone formulated to allow for a slow release within extracellular fluid [53]. Implantation requires an in-office procedure under local anesthetic in which a small incision is made on the hip (or another fatty area) and the pellets are placed with the aid of a trocar. The recommended starting dose is 150–450 mg every 3–6 months. Dosage adjustments are made depending on the patient's response and the appearance of adverse events [54]. Despite these recommendations, clinical studies and experience over the years have demonstrated that more pellets are needed to achieve satisfactory results [55]. Pharmacokinetic studies have been performed using 100 mg or 200 mg pellets at 600 mg doses (6 ×100 mg or 3 × 200 mg) and 1200 mg (6 × 200 mg). Testosterone levels were maintained at physiological levels for 4–5 months with 600 mg and 6 months in the 1200 mg group with a half-life duration of 2.5 months [56].

The most common unique adverse related to testosterone pellets is extrusion (8.5%) with less common side effects of bleeding (2.3%) and infection (0.6%) [57]. Other common adverse effects include pain, bruising, and fibrosis. Although pellets may seem like an unnecessarily invasive option compared to other forms of TRT, potential advantages include long duration of action with uniform levels, reliable patient compliance, and no risk of transference. Testosterone pellets are currently available as Testopel® (75 mg) (Endo Pharmaceuticals, Malvern, PA, USA) or as a generic pellet (12.5 mg, 25 mg, 37.5 mg, and 50 mg). A clinical trial is under way to evaluate the efficacy of Testopel compared to a generic 100 mg and 200 mg pellets [58].

7. Nasal gel

One of the more recent forms of TRT comes in the form of Natesto® (Acerus Pharmaceuticals, Mississauga, ON, Canada), a nasal testosterone gel. The gel comes in a 4.5% metered-dose pump with each pump actuation delivering 5.5 mg of testosterone [59]. Natesto is dosed with one pump actuation in each nostril, with three applications per day spaced 6–8 hours apart for a total of 33 mg/day. Testosterone concentrations should be checked as soon as 1 month following the beginning of treatment. Application to the nasal mucosa allows for testosterone absorption to bypass first-pass liver metabolism.

Studies assessing the pharmacokinetic profile of nasal testosterone showed that peak levels in the normal physiologic range were reached within 40 minutes after administration in doses ranging from 7.6 mg to 22.8 mg [60]. Levels dipped back to baseline around 8 hours after administration across all study dosages. Another study found that the optimal dosage pattern was three administrations spaced 6 hours apart and produced steady state levels completely within the physiologic range [61]. Clinical trials have shown that 90% of the patients taking Natesto three times daily had average testosterone levels within the normal range (300–1050 ng/dL) after 90 days with roughly 10% of the patients remaining below the physiologic range [60].

In contrast to other testosterone gels, Natesto has no risk of transference as it is solely applied to the nasal mucosa. In addition, the short acting nature of Natesto allows the body to potentially restore the hypothalamic-pituitary-gonadal axis. A recent clinical trial demonstrated that Natesto® dosed twice daily allowed for preservation of gonadotropin levels and maintenance of spermatogenesis at 6 months [62]. Relatively common adverse events specific to Natesto included symptoms related to nasopharyngitis, rhinorrhea, epistaxis, and upper respiratory infection [61]. Overall, Natesto provides a noninvasive, reliable method to raise testosterone levels in hypogonadal men with the added benefit of maintaining spermatogenesis.

8. Oral formulations

Oral formulations of testosterone offer the benefit of convenience, ease of use, and avoidance of transference and painful injections. Despite these advantages, early oral formulations have not been widely adopted as a viable treatment option due to high-dose requirements as a result of significant inactivation by first-pass liver metabolism [63]. Initial attempts at a viable oral testosterone option lead to the development of 17 α-methyltestosterone; however, this medication led to significant hepatotoxicity [64,65]. Subsequent attempts involved fatty-acid esterification into testosterone undecanoate which bypassed first pass portal metabolism by way of intestinal lymphatic absorption [66,67]. Although testosterone undecanoate avoided hepatotoxicity, absorption was highly dependent on fat consumption and led to variable responses [68,69]. For these reasons, oral testosterone has not been widely adopted.

8.1. Jatenzo®

Jatenzo (Clarus Therapeutics, Northbrook, IL, USA) is a novel formulation of oral testosterone undecanoate that attempts to provide a more uniform response, independent of the lipid content in a meal, through a self-emulsifying drug delivery system. Although still dependent on food intake, initial data showed that this formulation allowed for a more even absorption of TU. Administering Jatenzo while fasting or with a very low-fat content meal (<10% fat) resulted in lower absorption; however, all other meals including a normal western diet meal (~30% fat) lead to uniform absorption [70]. Similarly, a phase 3 clinical trial showed no difference in testosterone concentrations after administration, with meals ranging from 15 to 45 g of fat. This study was able to demonstrate that Jatenzo restored testosterone to eugonadal levels in 87.3% of the patients, which is identical to the control arm of topical therapy [71,72]. In addition, it demonstrated a similar side effect profile except for gastrointestinal side effects (nausea, diarrhea, burping) and a mean increase in systolic blood pressure of 3–5 mmHg. Similar to Xyosted, this has led to the addition of the FDA boxed warning for hypertension and increase in risk for major adverse cardiovascular events. Jatenzo demonstrates peak levels roughly 4 hours after the initial administration, necessitating twice daily dosing with food starting at 237 mg. Dose adjustment is based on testosterone measurement 4–6 hours after the morning dose, taken at least 7 days after starting the treatment, with doses ranging from 158 mg BID to 396 mg BID [73]. Jatenzo gained FDA approval in 2019, and currently stands as the only FDA-approved oral testosterone replacement option available in the United States.

9. Conclusion

TD can cause a variety of symptoms that can be treated with the administration of exogenous testosterone. The current landscape for TT includes a plethora of options with different modes of application, each with their own unique advantages and disadvantages. To ensure high-quality care, we recommend that providers and patients use a shared decision-making approach based on patient preference and functionality, dosing interval, treatment burden, cost, and side effect profile in choosing the appropriate form of TT.

10. Expert opinion

The management of TD is very complex because of the wide variety of options (transdermal, IM and subcutaneous injections, subdermal pellets, oral, nasal gel, and buccal tablet). In addition, many of the causes of TD are irreversible which necessitates long-term treatment, rendering patient compliance a critical factor for successful treatment. Many of the drugs require frequent administration or have unique side effects which can be an issue for many users. Although management is focused on maintaining testosterone levels in the normal range (450–600 ng/dL), treatment often leads to sub- and supraphysiological levels of testosterone after drug administration and absorption [10]. For example, males receiving TE and TC injections every 2–4 weeks may have fluctuating levels of serum testosterone, with up to 50% of time below treatment target [74]. These large fluctuations may be responsible for mood swings, decreased libido, and fatigue by the end of the cycle. It has also been demonstrated that supraphysiological levels of serum testosterone, especially those common with intramuscular injections, are the most important cause of many of the side effects (elevated hematocrit, endothelial dysfunction, acne, breast enlargement) [75]. Together, these factors can make TD a difficult disease process to manage. To highlight this, one study demonstrated that up to 25% of the men discontinue TT within 6 months after imitation and 24% switch to another form of TT [76]. As

such, it is imperative to treat men with TD individually through a shared decision-making process to determine the optimal TT regimen.

There are several areas of current research that focus on improving reliability, ease of use, patient compliance, and cost. Many patients seeking TT commonly ask for a 'pill to solve their problems.' However, oral testosterone has long been a nonviable option due to hepatotoxicity and variable absorption. Jatenzo (testosterone undecanoate capsules) appears to be promising as an oral testosterone option in providing resolution of symptoms and normal range serum testosterone levels. Subdermal pellets also represent an excellent option with uniform response; however, Testopel is often expensive with many payers denying coverage. Currently, an ongoing trial is investigating the efficacy of long-term subdermal generic pellets after 4 months versus Testopel. This would provide evidence for an affordable alternative that may allow implantation of pellets to become more ubiquitous [58].

Another area of research involves treatment of TD while preserving fertility. As exogenous testosterone disrupts the HPG axis through a negative feedback loop, males will universally have compromised spermatogenesis. With TD becoming even more common, especially in young males and adolescents, novel methods for TT that preserve male infertility are imperative [9]. The authors believe in two major lines of future research in this arena. First, the use of Leydig stem cells (LSC) appears to be promising in restoring the production of serum testosterone while simultaneously preserving the HPG axis. Previous studies have shown the feasibility and safety of subcutaneous autografting of a combination of Leydig cells, Sertoli cells, and peritubular myoid cells in rats. The ectopic site could not only produce testosterone, but also to respond to hypothalamic-pituitary signaling, corroborating in-vitro findings [77,78]. Future clinical trials should focus on evaluating the efficacy, security, and applicability of LSC autograft in humans with primary testosterone deficiency. Second, very short-acting testosterones have the theoretical potential to preserve the HPG axis by providing short bursts of testosterone which allow for periods of recovery. A single-arm clinical trial evaluating Natesto, a very short-acting testosterone, demonstrated patients had preserved gonadotropin levels and spermatogenesis at 6 months [79]. Further research should focus on short-acting testosterone and its effect on male infertility.

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