Testosterone Replacement Options

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KEYWORDS

• Testosterone • Testosterone injections • Testosterone gels and patches • Testosterone therapies • Nasal testosterone • Buccal testosterone • Oral testosterone

KEY POINTS

- There is a plethora of different testosterone replacement options, each with their own advantages and disadvantages.
- Long-term adherence to testosterone therapy is poor, reflecting unrealistic patient expectations and understanding of the benefits, poor follow-up, provider difficulty with the choice of modality, understanding pharmacologic differences between the modalities.
- Understanding the physiology of hypogonadism and the pharmacokinetics of each preparation is important for the practitioner to understand to make the right choice for each patient.

INTRODUCTION

Testosterone plays a critical role in the regulation of male sexual, somatic and behavioral functions important to lifelong well-being. Testosterone deficiency is a consequence of reduced testosterone production because of hypothalamic-pituitary-gonadal axis pathology or senescence. Hypogonadism, which can be multifactorial, is diagnosed based on a constellation of clinical symptoms and signs and confirmed biochemically by documentation of consistently low serum total testosterone levels.

The treatment of hypogonadism by medical providers can be challenging. Owing to market development and availability of no less than 15 treatment options, both clinicians and patients must decide on the optimal formulation by taking multiple factors into consideration including cost, mode of delivery, ease of use, compliance, and the pharmacokinetics of each preparation. The provider and patient must navigate conflicting scientific evidence about the definition of hypogonadism and indications for treatment, uncertain target clinical and biochemical endpoints, the ambiguity of benefits and risks, regulatory constraints, the overabundance of media hype and internet marketing with its attendant misinformation, the lack of formal education during training in male hypogonadism and the confusing number of options of treatment and schedules of administration. The purpose of this article was to review the physiology of hypogonadism and the differences between the current treatment modalities to equip the reader with the tools to make thoughtful choices among the multitude of modalities available in the treatment of hypogonadism.

PHYSIOLOGY

In order to understand the therapy of hypogonadism, it is important to understand the basic physiology of endogenous testosterone production.

Testosterone Production and Transport

Testosterone is an anabolic steroid that is derived from cholesterol. More than 95% is synthesized in the mitochondria and endoplasmic reticulum of the Leydig cells of the testes, under the regulation of pituitary gonadotropin LH, and the remainder is produced in the adrenal glands. The daily production is between 3 to 11 mg per day.[1] Testosterone

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has a short half-life of 10 to 100 min. LH stimulates testosterone production in a pulsatile fashion, with peaks every one to 3 h. With age, both the frequency and the amplitude of the pulses decrease. In addition, the Leydig cells become less responsive to LH, and their total number decreases with age.[2] Given the short half-life of testosterone, the frequency of natural LH pulses is not surprising.

Testosterone is transported in the serum, tightly bound to sex-hormone-binding globulin (SHBG) (~70%) and loosely bound to albumin (~30%). Approximately 2% is totally free. The SHBG molecule is produced by the liver and binds two testosterone molecules. Typically, SHBG is close to equimolar to testosterone (20 nmoles/L). An abnormally high SHBG, can result in a low free testosterone despite what might seem like a normal total testosterone. In a patient with cirrhosis or hepatitis, the SHBG levels can exceed 100 nmoles/L. For such a patient to have a mid-range calculated free testosterone level, his total testosterone would have to be more than 1000 ng/dL. As men age, their SHBG increases, sometimes resulting in low free testosterone levels with total testosterone levels in the normal range. Other conditions associated with increased SHBG are hyperthyroidism, use of anticonvulsants, use of estrogens or HIV disease.[3]

Testosterone Metabolism

Testosterone is metabolized hepatically and peripherally. It is metabolized into active and inactive metabolites. The two active metabolites produced are dihydrotestosterone (5%–8%) and estradiol (0.3%–5%) by the 5α-reductase and aromatase enzymatic systems, respectively.[4] The 5α-reductase enzymes are found in the prostate and skin and the aromatase enzymes are found in the peripheral fat tissue and testis.

The hepatic cytochrome P450 system is responsible approximately 95% of the metabolism of testosterone through a series of inactivating hydroxylation reactions followed by glucuronidation and to a lesser extent sulfation. The hydrophilic conjugates are excreted in the urine and bile.[5] Less than 5% of testosterone is excreted unchanged in the urine. Medications, medical conditions or inherent individual biodiversity of the cytochrome P450 system can significantly increase or decrease the half-life of testosterone.

The first pass absorption of oral testosterone from the liver and intestine is rapid, as is the clearance. Testosterone injected intravenously has been shown to have a half-life of less than 60 min.[6] The efficient absorption of oral testosterone and its rapid clearance make replacement with oral non-esterified testosterone impractical. To counter the rapid metabolism, esterification of the molecule is necessary.

Testosterone Natural Biologic Activity

The endogenous natural biological activity of testosterone is complex and can be affected by the concentration of testosterone, the differential expression of the androgen receptor in the target tissue types, polymorphism of the androgen receptor, the concentration of androgen binding hormones produced in the liver and testes, tissue-specific levels of 5α-reductase and aromatase enzymes, and tissue-specific levels of androgen receptor (AR) promoters.[7] This may partly explain why different symptoms of hypogonadism (sexual dysfunction vs muscle strength) respond to different levels of testosterone replacement.[8]

Classical and Non-classical Mechanism of Action

Testosterone has both genomic (classical) and non-genomic actions (non-classical). Classical action mediates its effects via a cytoplasmic ligand-dependent nuclear transcription factor AR. The AR is expressed to different degrees in a diverse range of tissues including bone, muscle, prostate, adipose tissue, and the reproductive, cardiovascular, neural, and hematopoietic systems. Testosterone exerts its genomic effect by binding to the AR to regulate target gene transcription. The genomic signaling, also referred to as the DNA binding-dependent action of the AR, occurs when androgens bind to the AR leading to a conformational change in the receptor and translocation of the androgen-AR complex into the nucleus. This complex with promoters then binds to the specific androgen response elements (AREs) within target genes via the DNA binding domain (DBD) of the AR to modulate gene transcription and translation.

Non-genomic effects are rapidly occurring when the androgen-AR complex at the cell membrane level. This complex activates kinase signaling cascades and initiates initiating phosphorylation of a second messenger signaling cascade. In addition, activation of membrane-bound protein receptors such as G-protein coupled receptor and iron-regulated transported like protein 9 (ZIP9) can trigger intracellular signaling pathways.[7,9–11] It is important for the reader to understand that the differential contribution of genomic vs non-genomic effects on clinical presentation is not understood.

General principles

Conditions for treatment Over the last many years, there has been an increase in testosterone

prescriptions with many men using testosterone without a clear indication, criteria, or appropriate follow-up. As per American Urological Association (AUA), the clinical diagnosis of testosterone deficiency is made when patients have both consistently low morning testosterone levels less than 300 ng/dL combined with signs and symptoms of androgen deficiency symptoms including decreased libido, erectile dysfunction, hot flashes, loss of muscle mass, weakness, weight gain, depressed mood, and loss of muscle mass or hair loss. The endocrine society (ES) recommends evaluating hypogonadal men with incomplete or delayed sexual development, eunuchoidism, reduced sexual desire (libido) and activity, decreased spontaneous erections, breast discomfort, gynecomastia, loss of body (axillary and pubic) hair, reduced shaving, very small testes, inability to father children, low or zero sperm count, height loss, low trauma fracture, low bone mineral density, and hot flushes or sweats.[3] Both societies recommend two morning fasting testosterone measurements. **Table 1**.

Are morning testosterones necessary? When to measure testosterone levels? Serum testosterone levels can show a day-to-day and long-term biologic variation, as well as a diurnal variation. In a random sample of 132 asymptomatic men in the Boston Area Community, the majority of whom were eugonadal, the day-to-day and long-term biologic variation ranged from 18% to 54%.[12] The same group of authors reported age-related diurnal variations in 66 asymptomatic healthy men (ages 30–80). In men between 30 and 40, testosterone declined 20% to 25% whereas in men aged 70 the decline was only 10%.[13] Of note is that most studies for testosterone variability are done on healthy volunteers. In a study of the circadian variation in 859 hypogonadal men (T_{mean} 239 ng/dL), a blunted diurnal variation was seen, the mean amplitude was 32.4 ng/dL. Even at the *T* peak level, the hypogonadal men remained hypogonadal.[14] In a retrospective "single draw" study of 2569 men with erectile dysfunction Kohler showed no difference in mean TT at any time between 7 AM and 2 PM in men older than 45.[15]

The regulatory approval of a TRT product is based on achieving a level of testosterone between 300 and 100 ng/dL in at least 75% of men with a diagnosis of hypogonadism ($T < 300$ ng/dL) irrespective of any symptom improvement.[16] All the TRT registry trials were conducted based on two a.m. blood draws showing hypogonadism in order to maximize uniformity. Both AUA and ESA guidelines, therefore, recommend two a.m. blood draws to establish the diagnosis of hypogonadism. Following the guidelines, third-party payers mandate two morning blood draws before approval of insurance coverage. It is important to realize that the choice of a.m. blood draws in clinical trials was arbitrary and one of convenience for the clinical trial staff.

Fasting measurements or not? Testosterone measurements in all the registry trials were done in a fasting state to ensure uniformity. Food intake may suppress serum testosterone concentrations. In a cross-sectional study of 74 eugonadal men aged 37 to 51, glucose ingestion induced a significant reduction in total and free T levels due a direct testicular defect. There was an absence of compensatory response in LH which suggested an alternative central component.[17] Another study done in Sweden compared testosterone levels after overnight fasting to levels measured 60 to 120 min after a standard meal and a decline of testosterone level of 30% was noted.[18] This study also did not find a change in LH or SHBG levels. The effect of food has not been extensively studied in symptomatic hypogonadal men. Fasting should be considered by the practitioner to maximize uniformity of measurements. An early morning draw does not guarantee a fasting state.

Goals for treatment The goal of testosterone therapy is the normalization of total testosterone levels along with improvement in some of the symptoms. Unfortunately, many of these symptoms are vague, difficult to quantitative, multifactorial, and sometimes just associated with aging and the stress of life. The AUA guidelines conditionally recommend using the minimal dosing necessary to bring testosterone levels in the mid tertile of the normal reference range (450–600), whereas the ES suggests a target value to be the mid-range for a normal young man. The exact serum testosterone levels required to achieve optimal efficacy and safety are currently unknown.

When to evaluate therapeutic levels The AUA recommends follow-up lab testing between 2 to 4 weeks after initiation of therapy and then every 6 to 12 months to assess serum testosterone levels, symptomatic improvement, prostate-specific antigen (PSA), and changes in hematocrit (Hct). The ES recommends follow-up 3 months after initiation of TTh and then every 6 to 12 months thereafter. The distinct PK profile of each testosterone formulation accounts for the specific timing when testosterone levels should be measured in reference to the dosage to allow for dose adjustments and monitoring. This is mainly influenced by the way the clinical trials are designed and

Table 1
AUA and Endocrine Society guidelines

Guidelines	AUA[19]	ES[3]
When to measure T	AM fasting total T x 2	AM fasting total T x 2
Normal range total T	450–600 ng/dL	264–916 ng/dL
Biochemical T deficiency	<300 ng/dL	<264 ng/dL
Aim	Middle tertile of normal range and improvement in symptoms/signs	Mid-normal range for young men and improvement in symptoms/signs
First therapeutic evaluation	2–4 wk	3 mo
Long-term follow-up	6–12 mo	6–12 mo

conducted. For most of the gel forms, including Androgel 1% and 1.62%, Testim 1%, and Vogelxo, the levels are measured before the morning dose. Fortesta is an exception, in which the levels are measured 2 h after application based on its specific PK profile. The logic for the recommended testing schedule is not clear (Table 2). If an Hct level increases to greater than 54%, treatment options include discontinuation of TTh, therapeutic phlebotomy, or consideration of switching to another testosterone formulation.[19]

Therapeutic success challenges Although testosterone replacement has the potential to improve symptoms, continuation of therapy is a major problem. Factors contributing to discontinuations are cost, lack of perceived benefit, inconvenience of the administration, inconvenience to the provider. In a British Columbia study, 40% of men discontinued treatment after their first or second treatment and only 27% had 10 or more repeated prescriptions. From a prescriber's perspective, only 36% of patients had post-treatment testosterone levels documented. Primary care and Urologists were responsible for 86% and 5% of prescriptions with gels and injectables accounting for roughly 50% each.[20] In studies of gel therapy adherence to treatment ranged from 15% to 19% at 1 year with no difference between the brands.[20–22] The adherence to short-lasting IM T injections is no better despite arguably higher testosterone levels.[23] Although adherence to office-based therapies such as subcutaneous (SC) pellets, monthly injections, and long-acting TU is high for men who present to the office therapy dropout rates are significant because of the inconvenience of the office visits and associated visit co-payments.

Unrealistic patient expectations The reason men seek testosterone therapy vary and can include well-being, low energy, libido, and erectile dysfunction.[24] Many men are self-diagnosed, getting their information through advertising and the internet where as few as 30% of the websites are deemed to be "high quality," at an appropriate grade level and contain comprehensive information as to the risks and benefits.[25] In older men with organic vasculogenic erectile dysfunction, lack of improvement in erectile function may be perceived by the patient as a treatment failure. Similarly, lack of improvement in energy level, sense of well-being, and obesity despite not addressing lifestyle changes as well can be perceived as treatment failure. It is important for the clinician to have a clear understanding of the symptom being treated and to portray realistic outcomes.

Costs Costs are frequently quoted as a reason for discontinuation Most testosterone therapies can be provided in generic form at great savings to the patients. With proper documentation by the provider (ie, Two a.m. testosterone levels less than 300 ng/dL) most insurance companies will cover treatment. Whereas more expensive non-generic treatments may not be included in a plan or have exorbitant co-payments, generic treatments are generally covered. Many providers are not aware of the inexpensive nature of generic testosterone, frequently falling below co-pay levels for the medication levied by the insurer. Through internet websites, the consumer can frequently find prices that are heavily discounted. The web-based companies partner with the pharmacies to provide competitive pricing and deep discounts helping to make a dent in the problem of medication non-adherence.[26] The price per month if out of pocket can vary from low as $11 to $955 depending on the preparation. Table 3 is a list of the self-pay costs through the web-based company GoodRx. Eleven dollars a month is affordable to most patients.

Provider barriers

A schedule III drug: Testosterone is a schedule III drug subject to the same reporting laws as

Table 2
When to measure serum testosterone levels for monitoring

Testosterone Formulations	Timing of Testosterone Measurement
Gels[a]	Morning preapplication level
Androgel® 1% and 1.62%	Morning preapplication level
Testim® 1%	2 h after application
Fortesta® 2%	Predose
Volgelxo®	
Patches	12 h after application
Androderm®	
Intranasal	2 h after application
Natesto®	
Oral	6 h after morning dose
JATENZO®	
Pellets	End of dosing interval
Testopel®	
Intramuscular injections	Mid-way between the two injections
Testosterone Enanthate and Testosterone Cypionate	
Subcutaneous Injections	Trough concentrations (measured 7 d after most recent dose) obtained following 6 wk of dosing
Xyosted®	
Long-acting subcutaneous injection	Mid-way between the two 10-wk injections
AVEED®®	

[a] Levels are measured at nadir, with the exception of Fortesta.

opiates. All prescriptions get reported to a prescription monitoring program (PMP) in all states. Most states mandate electronic prescribing and limit the number of refills to 6 months. Some states require monthly electronic prescriptions forcing the provider to write 12 prescriptions a year for every patient on testosterone therapy. Depending on the electronic medical record system, 7 mouse clicks may be required with an entry of a multicharacter user identification code for every prescription, not to mention the need to check safety labs before each prescription and adherence to semiannual or annual visits, as per guidelines. These prescriptions cannot be delegated to nonmedically licensed personnel, and the administrative time is non-reimbursable. On the other hand, adherence to therapy is easily monitored through PMP websites.

Prior authorization: Every new prescription submitted to insurance companies is subject to a prior authorization which requires two morning testosterone blood draws to document hypogonadism. This administrative burden can be delegated to a medical assistant but is still time-consuming and incurs a practice cost.

Nonbillable visit and financial liabilities: The SC pellets and long-acting TU IM shots each require 30 min of office time and 3 to 5 visits a year just to deliver a scheduled treatment. As such, Evaluation and Management codes are frequently denied. The federally mandated 6% withhold for Medicare patients results in a financial loss for the pellets or TU if they are purchased by the practice. Nonpayment by insurance or the patient for one treatment of either can easily result in a $1000 loss, by far offsetting the insertion or insertion or injection fee.

Compliance Clinicians should discuss the cessation of testosterone therapy three to 6 months after commencement of treatment in patients who experience normalization of total testosterone levels but fail to achieve symptom or sign improvement.[19] Before discontinuation, though, it is incumbent on the practitioner to ascertain whether the patient is compliant with the therapy. The patient's behavior in sponsor-supported clinical trials is not always reflected in real-life experience. In a clinical trial, compliance is monitored, regular blood draws are rigorously scheduled, the

Table 3
Self pay costs on GoodRx website

Testosterone prep	30 d ($)
Testosterone enanthate 5 mLs (1000 mgs) multiuse vial	11–22
Testosterone cypionate 4 mL (800 mgs) single use vials	27–86
Androgel® Pump 1.62% generic	38–145
Androgel® Pump 1% generic	54–86
Androgel® Packets 50 mgs generic	90–188
Vogelxo® pump 1%	104–361
Vogelxo® packets generic	120–361
Natesto®® (5.5 mg/actuation)	193–305
Xyosted® (50 mg)	456–572
Xyosted® (75 mg)	456–572
Xyosted® (100 mg)	456–572
Testim® packets Brand	590–616
Androgel® pump 1.62% Brand	619–646
Androgel® packets 50 mg Brand	638–666
JATENZO® (237 mg BID)	955

medication is provided by the sponsor and there is frequently a non-coercive financial incentive for continuation. Unrealistic expectations, faulty and sporadic supplication of gels, patches, missed injection or insertion appointments, missed self-injections, delay in prescription refills and renewals and financial pressures can all result in therapeutic failure unrelated to the efficacy of the modality chosen. Patients may not be regularly compliant yet apply their gel the morning of a blood draw, giving the practitioner a false sense of compliance. As testosterone is a schedule III drug, compliance and timing of refills can be checked through the PMP, just as for narcotics. Adding to the confusion as to biochemical efficacy is the variability of when the blood measurements are taken. Although the guidelines specify when testing should be done after treatment is started, the timing of the blood draws varies for each modality. Each formulation has a different PK profile. The timing of labs should be tailored to each individual mode of therapy. Some measurements are recommended at the peak, some mid-cycle, and some at the nadir[27] (see **Table 2**). The pharmacokinetic properties of each modality should be taken into consideration.

TESTOSTERONE PREPARATIONS

Topical/Transdermal

Gels

General principles

- All dermal gels are poorly absorbed. Only 10% to 15% of the gel applied is bioavailable. The rest remains on the body until it is washed off
- Secondary exposure: To prevent inadvertent exposure of women and children to testosterone gels, patients are instructed to wash their hands after using the product. Treated sites are covered with clothing once the gel has dried and to wash treated skin areas if skin-skin contact is anticipated. Currently, all testosterone liquids and gels in the United States contain a US Food and Drug Administration (FDA) warning for the risk of transference.
- Daily application is mandatory as levels return to baseline at 48 h.
- Gonadotropin levels were suppressed in the registry trials. Failure to find suppressed levels despite good T levels in follow-up suggests poor compliance. Failure to find suppressed levels with poor T levels suggests poor application technique, poor absorption, or noncompliance with the application.

Three testosterone gels are available: Androgel, Testim, and Fortesta.

Androgel: Androgel was the first gel and became available in June 2000. Androgel is a hydroalcoholic formulation. It is available in 1% and 1.62% concentrations. The 1% concentration is available in packets and metered-dose pump bottles. The packets contain either 25 mg/2.5 g or 50 mg/5 g of testosterone, whereas the pump delivers 12.5 mg of testosterone per actuation. The starting dose of Androgel 1% is 50 mg. Areas of application include shoulders, upper arms, or abdomen. A patient can swim or shower after 5 h with Androgel 1%. A randomized, parallel study of 227 hypogonadal men evaluated the pharmacokinetics of the Androgel 1% and compared gel 50 mg/d to gel 100 mg/d [28] The C_{max} occurred 18 to 24 h after application and the C_{min} occurred 8 to 12 h later. A steady state is achieved by the second or third day of dosing. The levels return to baseline 48 to 72 h after applying the gel. The levels were measured prior to the morning application.

The Androgel 1.62% preparation is also available packets and metered-dose pump bottles. The unit dose packets contain either 20.25 mg/1.25 g or 50.5 mg/2.5 g of testosterone. The metered-dose pump provides 20.25 mg of testosterone per actuation of 1.25 g of gel. The starting dose of Androgel is 1.62% is 40.5 mg daily. A patient can swim or shower and after 2 h with Androgel 1.62%. Areas of application include shoulders and upper arms. It is not indicated to be applied to the abdomen. A study with 36 male subjects

compared the bioavailability of this preparation at different sites. The study showed 30%–40% lower availability when it was applied to the abdomen than to the arms and shoulders.[29]

Adverse effects specific to Androgel include acne, application site reaction, and increased PSA level.[27]

Testim was approved by FDA in February 2003. Testim is a 1% gel supplied in 5 and 10 g tubes which contain 50 and 100 mg of testosterone, respectively. The starting dose is 50 mg in the morning, but some patients can be titrated to two tubes, or 100 mg of testosterone. Testim is to be applied on the shoulders and upper arms. Testim has been shown to have enhanced absorption and serum testosterone levels due to the presence of the penetration enhancer, pentadectalactone, which is found in many aftershaves and colognes leading to a musk-like odor with its application.[30] Median T_{max} of Testim is 18 h and average serum concentration levels are achieved within 24 h.[31] Levels are measured in the morning after initiation. Patients can swim or shower 2 h after applying Testim. Up to 4% of the patients can experience injection site reaction when using the 100 mg dose of Testim.

Fortesta was approved by the FDA in 2010. Fortesta is a 2% gel that contains oleic acid, a known penetration enhancer. It is supplied in a metered dose pump. Each pump delivers only 0.5 g of gel containing 10 mg testosterone. The starting dose is 4 pump actuations (40 mg) applied topically to the front or inner thighs daily in the morning. The dose can be titrated to 70 mg. The effects of Fortesta 2% gel on serum testosterone levels was evaluated in a multicenter, open-label study of 129 men with hypogonadism.[32] The subjects applied Fortesta 2%, 40 mg/d for 90 days and 77.5% of patients had C_{avg} at 90 days, similar to levels on day 35. Testosterone peaked at 2 to 4 h after application and fell to baseline levels 12 h after application. Also, another study conducted on 34 patients showed normal testosterone levels within 3 h with a steady state being achieved at a median time of 1.1 days. Furthermore, it showed that the gel dries in less than 3 min after application.[33] The levels in these studies were measured 2 h post application. Patients can swim or shower after 2 h. Treatment-related side effects included skin dryness.[27] The clinical trials excluded BMI > 35 and age >75.

Vogelxo TEVA was approved in 1953 and is made in Canada. It is available in unit dose packets, tube, or metered dose pumps. The starting dose is 50 mg of testosterone (one tube or one packet or 4 pump actuations) applied at the same time daily to the shoulders or upper arms. Testosterone concentrations are measured predose to adjust the dosing. The most common side effects are application site reaction, increased blood pressure, and headache.

Axiron: This is a 2% solution. The FDA posted a notice regarding the discontinuation of the manufacture of Axiron in September 2017. The product was not discontinued or withdrawn for safety or efficacy reasons but because of the multiple manufacturers that currently supply the US market.

Patches Androderm

General principles

- Following patch application, T_{max} is at approximately 8 h
- Nadir is achieved within 24 h of patch removal
- The patch is applied at night to mimic normal circadian pattern and the testosterone levels are measured in the morning, 12 h after the application which may not reflect nadir levels
- Skin rash is the most observed adverse effect leading to discontinuation of its use

Transdermal delivery of testosterone first became available in 1994 in the form of a scrotal patch. These were later discontinued because of scrotal irritation and application challenges and are no longer available in the United States.[27]

Androderm: This was FDA approved in 1995. This patch is available in 2 or 4 mg/d formulations. Based on pharmacokinetic analysis of the 5 g patch (which is no longer available), the T_{max} concentration averaged 765 ng/dL and occurred 8.2 h after ⟍ application. The mean T_{min} was 280 ng/dL. The time-average concentration (C_{avg}) over the 24-h dosing interval was 517 ng/dL.[34] Following application, testosterone is continuously absorbed during the 24-h dosing period with a median (range) T_{max} of 8 (4–12) h and hypogonadal concentrations are achieved within 24 h of patch removal.[35] This has an apparent half-life of 1.3 h.[27] A higher rate of testosterone delivery is observed during the first 12 h (~60% of the total) compared with that during the second 12 h. The starting dose is 4 mg patch every 24 h at night at 10 PM to produce physiologic concentrations and mimic normal circadian pattern, the importance of which is questionable in an older man. By applying the patch at night testosterone levels will be lowest at the end of the day, when many men describe their hypogonadal symptoms. The patches can be applied to the back, abdomen, thighs, or upper arms, The patches should be applied daily and sites should be rotated and not re-used within 7 days.[35] Testosterone levels are measured in the morning, 12 h after application of the patch the night prior.[34]

Approximately 30% of men who try this preparation are not able to continue with it because of severe skin rash. Some studies have found that pretreating with 1% triamcinolone acetonide cream applied under the patch can decrease the risk of dermatitis without compromising testosterone absorption. Some men have found benefits in applying hydrocortisone cream on the affected area after removal of the patch. Other adverse reactions include pruritis, skin induration, vesicle formation, allergic contact dermatitis, headaches, and depression. The patient should avoid showering, swimming, or washing the site for at least 3 h after application.[35]

Intranasal gels Natesto

General principles

- Absorption is rapid, with T_{max} occurring at 1 h, requiring multiple daily doses to achieve adequate levels of testosterone
- Levels fluctuate widely in a 24-h period with long periods at hypogonadal levels
- Meant to "mimic" normal circadian variation of testosterone levels throughout the day which is depicted by decreased LH and FSH levels 2 h after dosing with eventual recovery
- TID compliance is problematic and long-term adherence to therapy is questionable
- Replacement strategy with the least effect on sperm count and hematocrit

Natesto was approved by the FDA in 2014 and is the first intranasal testosterone to become available in the United States. It is available as a metered dose pump and each pump actuation gel contains 5.5 mg of testosterone in 122.5 mg of gel. The recommended dose is 11 mg 3 times daily. The nasal mucosa offers high permeability and high bioavailability, as the drug is not subject to first-pass metabolism[36,37].

Over 2 decades ago, an open, randomized, multiple-dose, study of 8 hypogonadal men in Romania tested an intranasal gel containing 7.6, 15.2, and 22.8 g of testosterone which showed that the maximum serum concentration of testosterone was achieved within 1 to 2 h indicating a rapid absorption from the intranasal cavity. It was also noted that the exposure to exogenous testosterone increased approximately linearly between 7.6 and 15.2 mg but leveled off with the higher dose of 22.8 mg likely because of the restricted volume for nasal application reflecting a saturation phenomenon at the site of absorption. Because of the rapid absorption with single dose nasal gel, multiple daily doses are required to achieve appropriate levels of testosterone which is meant to more closely proximate the normal circadian variation of testosterone levels throughout the day in a young man.

Natesto was evaluated in a more recent multicenter, open-label, 90-day clinical study that enrolled 306 men and randomly assigned them to either twice or thrice daily treatments. Intranasal Testosterone gel was self-administered using a multiple dose dispenser consistent with 5.5 mg testosterone per nostril, for a total of 11.0 mg single dose. PK studies were done based on predose samples collected on days 30 and 90. The T_{max} of testosterone appears at about 1 h, followed by a return to endogenous, predose levels 4 to 6 h later.[38] The $C_{average}$ testosterone was 421 ng/dL. The $C_{average}$ reflected the high peak levels, as testosterone levels dropped to baseline within 4 h. LH and FSH levels measured in this study at 2 h after dosing in all instances were decreased compared with baseline however they remained in the normal range. It seems that following this temporal suppression, the levels recovered over time. A study analyzing the preservation of spermatogenesis showed that mean sperm counts were unchanged after 6 months of nasal testosterone treatment in TID dosing. The lack of gonadotropin and sperm count suppression begs the question of the necessity of the maintenance of high levels of testosterone in the treatment of hypogonadism. A placebo randomized controlled trial of nasal testosterone on symptomatic hypogonadal men would be necessary to answer that question. Erythrocytosis was rare as 8 of 306 subjects (2.6%) had Hct values $\geq$ 54%.[39] Adverse reactions include increased PSA, headache, rhinorrhea, epistaxis, nasal discomfort, nasopharyngitis, upper respiratory tract infection (URI), sinusitis, bronchitis, and nasal scab formation[40]

The long-term compliance of TID dosing for short-term medications has been shown to be far inferior to once-a-day dosing.[41] With long-term compliance with once-daily gels being as low as 15%, it is hard to imagine good long-term compliance with TID dosing of Natesto. Long-term prescription data will answer that question.

Oral testosterone JATENZO

General principles

- Low bioavailability due to first-pass hepatic and intestinal metabolism
- Low bioavailability is illustrated in the requirement of large doses of twice daily TU to achieve therapeutic efficacy
- Higher bioavailability is achieved when taken with a fat-containing meal
- Dose adjustments are based on serum levels measured 6 h after the morning dose and do not reflect the nadir levels

- Most expensive therapy with poor insurance coverage
- BID dosing may present a compliance problem

When administered orally, testosterone is subject to significant inactivation in the GI tract and the liver. Adding an alkyl group in the 17-alpha position of testosterone slows its metabolism. In 1975 investigators reported that whereas orally administered free testosterone was not found to increase serum testosterone, esterified testosterone with the 9 carbon undecanoate chain resulted in increases in serum testosterone.[42] It was subsequently shown in four patients in whom their thoracic ducts were cannulated, that orally administered radioactively labeled TU appeared simultaneously in the lymph and serum two to 5 h after the dose was given and subsequently, 2 h after the peak serum levels it appeared in the urine. At 24 h 40% of the administered dose was excreted in the urine, predominantly as testosterone and androsterone-glucuronide. The authors postulated that TU was partially absorbed in the small intestine and absorbed in the lymphatic system and that 100% of the systemically available testosterone ester was lymphatically transported.[43] In March 2019, FDA approved JATENZO, a gelatin oral capsule (158 mg/198 mg/237 mg) containing testosterone undecanoate to be used for patients with hypogonadism. It is lipophilic and is absorbed via the intestinal lymphatic system but is subject to the first pass intestinal and hepatic metabolism. The oral bioavailability is estimated at 7%.[44] The low bioavailability is reflected in the large doses of twice-daily TU to achieve therapeutic efficacy (**Tables 4** and **5**). To promote lymphatic absorption the medication is best taken immediately before breakfast and dinner. The fat content of the meals was found to impact testosterone levels. When JATENZO was dosed with different breakfasts containing various amounts of fat, the bioavailability with the 30 g fat, 45 g fat, and high-calorie high-fat breakfasts was comparable, but there a negative food impact was seen with the 15 g (135 cal) fat breakfast (roughly equivalent to 2 tablespoons of peanut butter) compared with the 30 g (270 cal) fat breakfast. The 15 g fat breakfast had a 25% decrease in testosterone exposure compared with the 30 g fat breakfast. Intake conditions can have a 10-fold impact on T levels and can play a major role in intra- and inter-individual variability of testosterone levels.[45,46]

Efficacy was shown in a 4-month open-label comparator trial involving 166 men on JANENZO and 44 men on the topical gel. Eighty-seven percent of men achieved a daily C_{avg} in the normal range. C_{avg} level achieved was 403 ng/dL. Mean LH and FSH levels decreased 70% from baseline, comparable to the comparator topical T gel group. T_{min} dropped to baseline hypogonadal levels between 9 to 12 and 22 to 24 after dosing. Dose adjustments are therefore recommended based on serum testosterone 6 h after the morning dose and 7 days after starting the therapy. Clinicians outside of a clinical trial setting must make sure that blood draws are mid-to-late afternoon after a healthy breakfast.[44] Seminal parameters were not examined. The 24-h average increase in systolic BP was 4.9 mm Hg and an average HCT increase of 6%. No liver toxicity was detected.

Despite the lack of transference and the convenience of the oral dosing vs injections, the low bioavailability, dependence of testosterone levels on fat ingestion, twice-daily dosing, and expense make this a challenging modality for compliance and adherence to therapy.

Parenteral Testosterone Preparations

Intramuscular injections

General principles

- Oldest testosterone product
- FDA package insert is anachronistic, confusing, and does not reflect the pharmacokinetics of the product
- Least expensive with self-administration
- Most painful administration leading to poor long-term adherence to therapy
- Modality with maximum dosage variability
- Highest rate of erythrocytosis

Currently available long-acting injections include testosterone enanthate and testosterone cypionate. These synthetic compounds of testosterone have been made more lipophilic by the esterification of a fatty acid to the 17-beta hydroxyl group, thereby allowing for a longer duration of action. Owing to the high viscosity of the oils intramuscular (IM) injections are recommended in package insert. Dosing schedule is confusing at 50 mg to 400 mg every one to 4 weeks. Owing to the exponential decay after injection, a 4-week injection results in wide fluctuation of levels with early supratherapeutic levels followed by subtherapeutic testosterone levels toward the end of the treatment period. As testosterone is distributed evenly throughout the whole body an obese man is likely to require more testosterone. With exponential decay during the treatment period, mid-cycle testosterone measurements may overestimate the levels at the end of the treatment period. In general, lower doses more frequently result in

Table 4
Daily dosing

Testosterone Formulation	Dose (mg)	mg/d
Nasal	11	33
Subcutaneous Pellets	150–450	0.83–3.75
Transdermal patch	4	4
Gels	40–50	40–50
IM T Cypionate	50–400/2–4 wk	3.6–14
IM T Enanthate	100–400/1–4 wk	3.6–14
IM T Undecanoate	750/10 wk	27–18.75
SC T Enanthate	50/75/100	7–14
Oral T Undecanoate	158/198/237	316–474

more stable levels but the frequent IM injections are poorly tolerated by patients.

Testosterone cypionate has a half-life of up to 8 days because of its eight-carbon atom ester chain, compared with 4 to 8 days for testosterone enanthate which has a carboxylic acid ester, enanthoic acid composed of seven carbon atoms. All esters are hepatically metabolized by the Cytochrome P450.

Peak serum concentrations are achieved within 72 h, followed by an exponential decay. Many men describe a testosterone crash toward the end of the cycle. Nadir levels are useful to adjust the frequency and dose on an individual basis. Patients taking injectable testosterone are more susceptible to erythrocytosis. One study found an increase in Hct in 24% of patients after injections of testosterone cypionate without any adverse effects. Older patients are much more likely to develop erythrocytosis, and caution should be taken in this population.

Subcutaneous pellets Testopel

General principles

- Testopel provides adequate levels of testosterone for at least 3 months
- Current FDA-approved dosing schedules are based on anachronistic label without pharmacokinetic backup resulting in underdosing (see Table 4)
- Convenience of not having a daily application but the inconvenience of a quarterly office visit for a surgical procedure
- Repeated insertions cause scarring, leading to insertional pain, hematomas and extrusions.
- Levels are tested at the nadir, shortly before re-insertion, to give dosage adjustment
- Package insert restricts flexible dosing

SC 75 mg crystalline testosterone pellets have been available for decades having been FDA approved in 1972 (Bartor Phamacal) and re-introduced into the commercial market in 2008 (Testopel, Slate Pharmaceuticals). Testopel pellets are currently the only long-acting FDA-approved pellet available in the United States. No pharmacokinetic studies were done prior to approval in 1972. Recommended dosing was based on levels achieved with testosterone propionate, an esterified testosterone no longer marketed, with a half-life of 4.5 days. The recommended doing is 4 to 6 pellets (300–450) every 3 to 6 months. That would translate to a maximum and minimum dose of 37.5 mg/wk (6 pellets every 3 months) and 9 mg/wk (4 pellets every 6 months), respectively. Even the testosterone ester with the longest half-life, testosterone undecanoate, is dosed every 10 weeks at a dose of 750 mg (75 mg a week). The current recommended dosing schedule realistically results in subtherapeutic dosing and exposes patients to more frequent pellet insertions.[47] In a multi-institutional retrospective study, Testopel provided sustained levels of testosterone for at least 4 months in men with testosterone deficiency. Implantation of more than 8 pellets achieved optimal results with respect to peak mean testosterone level and duration of effect. Ninety-five percent of men received at least 10 pellets (750 mgs).

Testosterone pellets were generally well tolerated. Retrospective pharmacokinetic studies with Testopel have shown that men with a body mass index (BMI) greater than 25 attained lower total testosterone peaks with slower decay than men with BMI less than 25. No differences were seen in decay rates for men with multiple implant rounds, and no differences in testosterone peaks or decay rates were seen in men with preimplantation testosterone level less than 300 or greater than or equal to 300 ng/dL. They reported that the levels were not impacted by the number of insertions.[48] Anecdotally, as the number of insertions increase, and the SC tissues scar from repeated insertions there is a tendency for more insertional pain, hematomas, and extrusions. There is no guidance provided as to the timing of checking the levels, but it would seem logical to test at the nadir, shortly before re-insertion to adjust the number of pellets and the frequency of insertion.

The pellets typically dissolve more than 4 to 6 months and thus do not need to be removed. Potential benefits of Testopel include a lack of

Table 5
Testosterone therapies

Formulation	Mode of Delivery	Dose	Starting Dose	Application Site
Topical	Packet	25 mg/2.5 g	50 mg of testosterone once daily in the AM	Shoulders/upper arms and/or abdomen
Androgel® 1% (Testosterone Gel)	Pump	50 mg/5 g	2 pumps on each shoulder	Shoulders and/or upper arms
	Packet	12.5 mg/actuation	40.5 mg testosterone daily in the AM	Shoulders and/or upper arms
Androgel® 1.62% (Testosterone Gel)	Pump	20.25 m	1 pump on each shoulder	Inner or front of thighs
	Tube	40.5 mg	50 mg daily in the AM	Shoulders and/or upper arms
Testim® 1% (Testosterone Gel)	Pump	20.25 mg testosterone per actuation.	2 pumps each thigh daily in the AM	Shoulders and/or upper arms
	Tube, Packet	5 and 10 g tubes which contain 50 and 100 mg of testosterone, respectively.	50 mg of testosterone daily at the same time	
Fortesta® 2% (Testosterone Gel)	Pump	10 mg/actuation	4 pumps	
Vogelxo® (Testosterone Gel)		50 mg of testosterone in a unit-dose tube, 50 mg in a unit-dose packet, 12.5 mg per actuation		
Transdermal Androderm®	Patch	2 mg/d, 2.5 mg/d, 4 mg/d and 5 mg/d	One 4 mg/d patches applied at night (10 PM)	Back, abdomen, upper arms, or thighs
Intranasal Gel Natesto®	Pump	5.5 mg of testosterone/pump actuation	11 mg of testosterone (2 pump actuations, one per nostril) three times daily (6–8 h apart)	Intranasal
Oral JATENZO® (Testosterone Undecanoate)	Capsule	158 mg, 198 mg, 237 mg	237 mg once in the morning and once in the evening	Oral
Pellet Testopel®	Pellet	75 mg/pellet	150–450 mg every 3–6 mo	Subcutaneous; Subdermal fat of the buttocks, lower abdominal wall, or thigh
Intramuscular Injection Testosterone Cypionate, Enanthate	Solution	100 mg/mL 10 mL vial; 200 mg/mL 1- or 10-mL vial	75–100 mg once weekly or 150–200 mg every 2 wk [19]	Intramuscular-Gluteal muscle or lateral upper thigh
	Solution	750 mg/3 mL (250 mg/mL)	3 mL (750 mg) at initiation at 4 wk, and every 10 wk thereafter	Gluteal muscle
AVEED®				
Subcutaneous XYOSTED®	Solution in Autoinjector	50 mg/0.5 mL; 75 mg/0.5 mL; 100 mg/0.5 mL	75 mg subcutaneously once weekly	Subcutaneously in the abdominal region

transference and assurance on the part of the provider that the patient has received his treatment. There is the convenience of not having a daily application but the inconvenience of a quarterly office visit at the mercy of the provider's schedule. Potential risks of Testopel are bleeding, infection, expulsion of the pellets, pain, and bruising. The infections and extrusion rates were reported at 1.1% and 0.4%, respectively.[48]

The pellets are placed SC with a 2 mm anesthetized incision through a proprietary trocar in the gluteal fat pad. The procedure usually takes 10 min of the provider's time. Patients are then observed for an additional 10 min thereafter, applying pressure to the insertion site. In all, between the patient registration, the procedure and post insertion observation and follow-up scheduling, approximately 30 min of office time are needed. Medicare will reimburse for no more than six pellets every 3 months at invoice costs minus a mandated withhold of 6% because of the Budget Reconciliation Act. As the procedure is scheduled, only the insertion code (11980) is allowed without an evaluation and management (E/M) office visit code. With an individual pellet cost of approximately $100 each and the Medicare reimbursement for the insertion of $94, an uncomplicated 30-min office visit will result in a $60 payment, be repeated 4 times a year and take the space of four new patient visits or 8 established patients. Though some third-party payers may reimburse the above invoice cost and pay more for the insertion, the time commitment is the same. This is not a sustainable model for practice growth regardless of the payer.

Subcutaneous injections (Xyosted)

General principles

- Generic testosterone enanthate in an expensive proprietary injector
- Convenient, well tolerated, and easily administered
- Poorly reimbursed by insurance companies
- Excellent pharmacokinetics
- Validates the concept of SC testosterone enanthate
- Poor insurance coverage

The parenteral administration of testosterone has historically been intramuscular. The package insert for both generic testosterone cypionate and testosterone enanthate specifically mentions intramuscular injections. Recently SC injections have become increasingly popular. Theoretically, SC deposition of testosterone esters in the relatively hypovascular subdermal space results in a more stable, slower absorption from the lymphatic and vascular spaces and unlike IM injections is less subject to muscular contraction[49] In a study of 64 female-to-male transgender patients normal male levels were achieved in all patient with weekly SC injections of TE or TC and were preferred to IM injections.[49,50] The use of weekly SC testosterone enanthate with a proprietary injector, Xyosted, was approved by the FDA in 2018. TE has a half-life of approximately 4 to 7 days.[51] Xyosted comes in 50, 75, and 100 mg single-dose syringes, assembled in a pressure-assisted autoinjector for SC administration. During a 52-week follow-up period, upward dose titration based on levels only was necessary for up to 30% of the men on 50 mg at week 6,11% on men on 75 mg at week 6 and none on 100 mg at week 6. Downward titration occurred in 11% of men on 75 mg at week 6 and up to 45% on 100 mg at week 6. Blinded dose adjustments if needed were based on nadir levels independent of symptoms at weeks 6 7, 13, 19, 27, and 39. The age range tested was 18 to 75 with BMI <40. The patient reported ease of use was uniformly high and 95% of patients reported no injection-related pain. Therapeutic levels (300–1000 ng/dL) were achieved in 92.7% of patients. Whereas slightly less than 10% of patients achieved a level of greater than 1500 ng/dL, none surpassed 1800 ng/dL.[52] Increases in Hct to $\geq$55% were reported for 12 of the 283 patients in the 2 clinical studies, representing 4.2% of patients who received Xyosted for up to 1 year.

Long-acting testosterone AVEED

General principles

- Long-acting testosterone is dispensed in castor oil with enhances its ability to release over time
- Injected every 10 weeks requiring a 30-min office visit
- Rare cases of spontaneous POME have been reported as adverse event per-injection rate of <1%
- Patients are required to remain in the doctor's office for 30 min after their dose to observe for POME
- Package insert limits the flexibility of dosing schedule and amounts

AVEED is the only long-acting testosterone injection on the US market. AVEED contains 750 mg of TU, which is injected IM in 3 mL of castor oil. TU is injected with a castor oil carrier, which enhances its ability to release slowly over time. The first injection with AVEED requires a 4-week repeat injection. Following this initial repeat injection, AVEED is injected every 10 weeks. There is no

allowance for adjusting the dosing schedule based on levels. As there is only one dose and one dosing schedule on the FDA label, individualization of the regimen is difficult to obtain from third-party payers. The most common adverse events associated with AVEED include acne and pain at the injection site. Rare cases of pulmonary oil micro embolism (POME) have been reported. In a 4.3-year post-marketing review of their Endo Pharmaceuticals Inc safety database, with 90,092 doses, 28 of 633 individual case safety reports were classified as POME, for a yearly spontaneously reported adverse event per-injection rate of less than 1%. Twenty one of the 22 for which the outcome was reported, resolved, and of those with a resolution time reported, most (13 of 17) resolved in 30 min. One fatality was reported 18 months after a documented POME event and appeared unrelated to the reported testosterone undecanoate injection. Despite the POME event, 64% of patients continued the testosterone undecanoate. As part of the AVEED Risk Evaluation and Mitigation Strategy Program[53] patients are required to remain in the doctor's office for 30 min and be observed for POME. Continuation of therapy should be based on achieving symptom resolution for the treatment period. Nadir levels should be checked. If symptomatic improvement is not obtained and eugonadal levels are not maintained throughout the 10-week period, consideration should be given to an alternative replacement modality.

SUMMARY

There is a vast abundance of therapeutic modalities for hypogonadism, each with its own mode of delivery, pharmacokinetic profile, dosing sequence, and side effect profile leading to various advantages and disadvantages. It is important to understand the physiology of hypogonadism and the pharmacokinetics of each testosterone formulation to be able to make the right choice for the patient. Factors contributing to adherence of therapy include patient expectations, follow-up, knowledge about each formulation, access, cost, insurance coverage, and east of use. The practitioner is best using the modality with which he/she is most familiar. Careful consideration of the needs of the patient is important. Continuation of therapy should be predicated on achieving amelioration of hypogonadal symptoms, achieving therapeutic levels in a compliant patient.

DISCLOSURE

No conflict of interests.

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