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Review

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Testosterone replacement therapy for male hypogonadism: Part III. Pharmacologic and clinical profiles, monitoring, safety issues, and potential future agents

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Abstract

Male hypogonadism is associated with potentially distressing adverse effects on diverse organs and tissues. These include sexual dysfunction, particularly diminished libido, as well as mood disturbances, reduced lean body mass, and increased adipose-tissue mass. A wide range of effective and well-tolerated options exists. These include relatively noninvasive therapies, such as testosterone (T) gels and T patches; slightly more invasive treatments, such as the T buccal system; and invasive therapies, such as intramuscular T injections and subcutaneous depot implants (T pellets). Testosterone replacement therapy (TRT) can be individualized to enhance patient health and well-being. Screening and ongoing monitoring are necessary to ensure both the efficacy and safety of TRT, particularly prostate safety. Investigational agents, including selective androgen receptor modulators, may offer new pharmacodynamic and/or pharmacokinetic properties that enhance outcomes of TRT.

Keywords:

efficacy, hypogonadism, pharmacokinetics, safety, testosterone, tolerability

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Introduction

Testosterone replacement therapy (TRT) has been administered to men with hypogonadism for decades.[1] The fundamental aim of TRT is to restore serum T to eugonadal levels and minimize signs and symptoms of hypogonadism. Sexual dysfunction, particularly low libido, is among the most readily reversible symptoms of male hypogonadism. The most recent erectile dysfunction (ED) consensus guidelines recommend evaluation of the hypothalamic–pituitary–gonadal axis, including total T, bioavailable T (BT), and free T (FT), 'in patients with sexual dysfunction and at risk of or suspected of hypogonadism.'[2] These guidelines designate testosterone as a second-line therapy. Recent studies have demonstrated significant short-term improvements in erectile function, as well as longer-term improvements in sexual desire and quality of life, in hypogonadal men receiving adjunctive TRT, including sildenafil nonresponders.[3, 4]

Contraindications to the use of exogenous testosterone formulations, which are Schedule III controlled substances, include prostate cancer (PCa), breast cancer, and/or untreated prolactinoma.[5] TRT with any of the modalities described herein should be instituted according to the screening and monitoring guidelines, which are detailed in this review.

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Topical/transdermal therapies

Testosterone topical gels (T Gels)

Pharmacologic profiles. Two 1% hydroalcoholic T gels have been approved by the US Food and Drug Administration (FDA) for male hypogonadism: AndroGel® from UniMed Pharmaceuticals (Deerfield, IL, USA) and Solvay Pharmaceuticals (Marietta, GA, USA), and Testim® from Auxilium Pharmaceuticals (Malvern, PA, USA).[6, 7] Each 5- to 10-g tube or packet of 1% gel contains 50–100 mg of T. Each gel is formulated with a skin-penetration enhancer and is ≥67.0% ethanol by volume. After daily (preferably morning) application of each agent to clean, dry, intact skin of the upper arms or shoulders (and/or abdomen), 10% of each dose (5–10 mg) is absorbed into the systemic circulation over a 24-h period.

Clinical studies

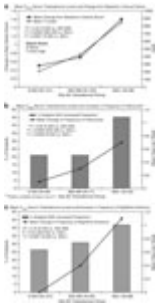
Pharmacokinetics. T gels provide longer-lasting elevations of serum T compared with a transdermal patch (T patch).[8] In a study involving equivalent doses of two T gels,[9] Testim treatment was associated with significantly higher serum T levels and bioavailability than Androgel; the two formulations were not biologically equivalent: both the C_{max} and AUC0-24 for T delivered by Testim were 30% higher than the values for T delivered by Androgel (Table 1). T delivered by gel formulations undergoes no first-pass hepatic metabolism.

Table 1 - T Gels: pharmacokinetics, efficacy, and safety.


Full table

Efficacy. Several multicenter, randomized controlled trials have demonstrated that restoration of serum T levels with T gel was associated with improvements in sexual function,[3, 10, 11, 12] as well as body composition, mood, and/or bone markers[11, 12, 13] (Table 1). In one study, threshold serum T values (C_{avg}) were identified above which significant improvements were noted: 500 ng/dl for the frequency of sexual intercourse and 600 ng/dl for self-rated sexual desire (Figure 1).[10] The frequency of night time erections rose significantly even when serum T levels were low-normal (C_{avg}=400 ng/dl), suggesting that this androgenic effect may be among the earliest to be observed during TRT.

Figure 1.



Changes in sexual desire in relation to serum testosterone levels in hypogonadal patients receiving T gel (a). Proportions of T gel-treated patients reporting increased frequency of intercourse (b) and night time erections (c) in relation to serum testosterone levels. From Seftel *et al.*[10]

Full figure and legend (135K)

The benefits of adjunctive or 'rescue' TRT with a T gel were shown in studies of hypogonadal men with refractory depression[14] or with moderate-severe ED nonresponsive to sildenafil[3] (Table 1). The results from the study of men with ED were particularly noteworthy because 16% of patients also had diabetes mellitus, which frequently renders ED more severe, refractory to treatment, and a greater burden on quality of life.[15, 16]

Three important studies concerning T and both sexual function and depression have been published in 2005. Studying 162 elderly (mean age=64.1 years) men with ED (mean duration=45.6 months), a Korean group reported that hypogonadism (serum T<300 ng/dl) was among the strongest independent predictors of a poor response to sildenafil 25–

100 mg for 8 weeks. Only poor pretreatment erectile function (International Index of Erectile Function (IIEF) erectile function domain score <17) was a stronger independent prognostic factor (OR=2.2; 95% CI=1.45–7.33).[17]

Consistent with this report, an Israeli group demonstrated that short-term treatment with either T gel or adjunctive T gel with sildenafil has potential clinical benefits in hypogonadal men (mean age=60.7 years) with ED.[18] In this study of 49 hypogonadal men (mean serum T=378 ng/dl), 31 reported significant improvements in both sexual desire and erectile function following daily treatment with topical T gel 5 g of a 1% testosterone hydroalcoholic gel daily (AndroGel®; Besins International, Paris, France). Following 3 months of such treatment, the mean serum T was restored to 1013 ng/dl and normalized in all patients. In 31 (63%) of the 49 men, scores on both the sexual desire and erectile function domains of the IIEF were significantly improved compared with baseline, with the sexual desire domain more than doubling (from 4 to 8.9; $P<0.001$) and the erectile function domain nearly doubling (from 15.0 to 26; $P<0.001$); the final value of 26 has been associated with no ED in prior studies.[18]

A total of 17 patients did not have significant improvements in sexual function following 3 months of T-gel therapy as determined by negative responses to the Global Assessment Question (GAQ), 'Has treatment improved your erections?' However, these patients did experience some improvements, with normalization of serum T and BT and an increase in the erectile function domain of the IIEF (from 13.6 to 22 following T-gel monotherapy). Following treatment with an adjunctive sildenafil (100 mg)-T-gel regimen for a further 3 months, the mean erectile function score increased to 27, which is consistent with no ED, and all patients answered the GAQ positively. Two patients discontinued treatment because of urination difficulties. Nine patients reported irritation at the T-gel application site, but no patient discontinued therapy.[18]

Finally, a US group recently reported that treatment of 18 hypogonadal men with depression using T gel (5 g of a 1% gel; AndroGel®; Unimed Pharmaceuticals) for up to 12 weeks significantly improved scores on the Hamilton Rating Scale for Depression compared with baseline but not compared with a placebo phase of equal duration.[19] There were no clinically significant changes in hemoglobin, hematocrit, or prostate-specific antigen (PSA) between the T-gel and placebo phases.[19]

Tolerability and safety. T gels have been well tolerated in trials of up to 6 months. According to the US product labeling for Testim, adverse events (AEs) judged to be possibly, probably, or definitely related to T gel in 0–2% of patients included headache, hot flushes, insomnia, increased blood pressure or increased hematocrit or hemoglobin.[7] AEs considered to be possibly, probably, or definitely related to AndroGel included acne (1–8% of patients); headache (up to 4%); as well as emotional lability, nervousness, gynecomastia, or mastodynia (up to 3%).[6] Application-site reactions represent the most frequent complaints with both T gels, occurring in up to 5% of patients.[6, 7]

With regard to prostate safety, 2.8–18.8% of 106 men receiving T gel (AndroGel) 50–100 mg experienced prostate enlargement or elevation in PSA during a 12-month open-label extension trial, and there was one (0.9%) new diagnosis of PCa.[6] Additional study findings on the effects of T gels on PSA levels[10, 12] are shown in Table 1.

User and prescriber considerations. Skin irritation is approximately 10 times less frequent with T gels (~5–6%) than T patches (~66%).[12] In the smaller US clinical trial, 21% of patients receiving a T patch discontinued because of skin irritation.[12] In clinical trials, treatment continuation rates with T gels typically exceed 90% compared with 65–80% with the T patch.

T gels need to be applied to large skin surface areas. Patients should avoid swimming, bathing, or activities leading to excessive sweating for 5–6 h after T gel administration.[6, 7] Skin contact with others after applying the T gel does not result in significant interpersonal T transfer.[20] Testim has a musky odor that most patients find tolerable.

The average wholesale price for a 30-day supply of T gel 5 g is $199.82 ($6.66 per day) for AndroGel and $186.18 ($6.21 per day) for Testim.[21]

Testosterone transdermal systems (T patches)

Pharmacologic profiles. Across the world, T patches are available for application to the scrotum (Testoderm® TTS; Alza Corp., Palo Alto, CA, USA) or to nonscrotal skin (Androderm®; Watson Laboratories, Corona, CA, USA; Andropatch®, SmithKlineBeecham, UK). However, the Testoderm scrotal patch is no longer marketed in the United States.

Testosterone at a starting dose of 5 mg is delivered via application of a single patch (total skin contact surface area=44 cm^2) containing 24.3 mg of T dissolved in a 15-cm^2 hydroalcoholic drug reservoir that also includes permeation-enhancing agents and gelling agents. An adhesive border is applied to the skin.

After application of a T patch, T is continuously absorbed over 24 h[22] through a non-rate-limiting microporous membrane. Androderm T patches are also available as 2.5 mg T systems containing 12.2 mg of T within a 7.5-cm^2 reservoir. Two 2.5 mg T patches are bioequivalent to a single 5 mg T patch.[23]

Clinical studies

Pharmacokinetics. In a pharmacokinetics study involving hypogonadal men receiving two 2.5 mg T patches, ~4–5 mg was absorbed daily from patches applied to the back, thigh, upper arm, or abdomen compared with 3–4 mg for the chest or shin.[24] Intrasubject variability in serum T levels ranges from 17 to 26%.[22] Testosterone delivered via T patches does not undergo hepatic first-pass metabolism.

Efficacy. A meta-analysis determined that 80.9% of men with ED had positive erectile responses to T patch treatment compared with 51.3% of men receiving intramuscular (i.m.) T and 53.2% of those receiving oral T ($P<0.001$ for each pairwise comparison vs T patch).[25]

In an analysis of the effects of a T patch 5 mg regimen (two Androderm 2.5 mg patches daily) on erectile function in hypogonadal men treated for up to 1 year, patients were observed during (1) a 3-week baseline evaluation during which most (>90%) men received i.m. T injections; (2) an 8-week washout ('androgen-withdrawal') period, during

which hypogonadism recurred (AM serum T<250 ng/dl); (3) a 24-h pharmacokinetics study; and (4) a 12-month assessment.[26] Findings are shown in Table 2.

Table 2 - T patch: efficacy and safety findings.

Full table

The T patch has also been evaluated in other studies for its effects on sexual function, bone markers, and/or body composition (Table 2).[27, 28, 29, 30]

Tolerability and safety. Application-site reactions, particularly skin irritation, constitute the chief AEs with the T patch. Most patients experience transient, mild or moderate erythema at the application site at some time during treatment.[31] AEs include application-site pruritus in 37% of patients, as well as blistering under the T patch (12%), erythema (7%), vesicle formation (6%), or induration (3%).[31] Allergic contact dermatitis has been reported in 4% of T patch recipients.[31] Adhesives, excipients, and active drug all may serve as contact allergens. Headache, depression, rash, and gastrointestinal (GI) bleeding have been observed in ≤4% of patients.[31]

Studies have shown that local skin irritation occurred in 19–66% of T patch users. In clinical trials, 5–10% of patients prematurely discontinued T patch treatment because of skin reactions. Scrotal T patches have been associated with significantly lower frequencies of both skin irritation (5 vs 32%; $P<0.001$) and contact allergy (0 vs 12%) compared with nonscrotal T patches.[32] In addition, T patch treatment for up to 12 months has been associated with significant increases in serum PSA but not to above-normal levels (i.e. >4.0 ng/ml; Table 2).

User and prescriber considerations. Patients are advised to apply T patches to clean, dry, nonirritated, intact skin of the abdomen, back, thigh, or upper arm. Application to the chest results in more variable serum T profiles. Although the shin is not a site of high T absorption compared with other application sites, skin irritation is lowest when the T patch is applied to the shin, followed by the upper arm and back.[24]

T patches should not be applied to body parts subjected to prolonged pressure during sitting (e.g. ischial tuberosity, greater trochanter of the femur) or sleeping (i.e. deltoid). The application site should be rotated weekly to minimize local reactions. Elderly men may be particularly prone to skin irritation with T patches.

In a UK survey of men using a T patch, approximately 66% found the patch unsatisfactory, and 60% discontinued treatment between treatment weeks 4 and 8 because of skin reactions.[33] Patients have reported that T patches sometimes fall off in the shower; leave marks on skin; are visually indiscreet, noisy (with body movement) and/or

otherwise socially unacceptable; and may be unpleasant or difficult to administer or remove, especially for patients with poor manual dexterity who have difficulty opening the package.[33]

However, for men who tolerate T patches and find them well suited to their lifestyles, such treatment is a viable option with a typically favorable reimbursement profile in the United States. Average US wholesale prices for Androderm range from $123.03 to $178.64 per month ($4.10–$5.95 per day).[21]

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Transbuccal (Buccal T) system

Pharmacologic profile

The T buccal system known as Striant® (Columbia Laboratories, Livingston, NJ, USA) delivers a total T dose of 30 mg after administration to the inner cheek or gum surfaces (near the incisors).[34] Testosterone is released from the convex buccal tablets as excipients are slowly hydrated in the mouth. Buccal T is administered twice daily. Food or beverage intake does not affect transbuccal T absorption. Testosterone administered via the transbuccal route is also not subject to first-pass hepatic metabolism.[34]

Clinical studies

Pharmacokinetics. The buccal system releases T in a pulsatile manner, which is similar to endogenous T secretion. Peak T levels are reached rapidly, and steady state is achieved by the second dose. The effects are rapidly reversible upon removal, and there is no drug accumulation over time.[34] Pharmacokinetic findings from various trials using the T buccal system[35, 36, 37] are shown in Table 3.

Table 3 - Transbuccal (Buccal T) system: pharmacokinetics, efficacy, and safety findings.

Full table

Efficacy. Findings from a double-blind, randomized, placebo-controlled pilot trial demonstrated that treatment with buccal T significantly enhanced sexual function compared to placebo across both objective and subjective measures.[35] Objective testing of nocturnal penile tumescence (NPT) demonstrated that maximum penile rigidity, maximum penile circumference, and the duration of NPT in men receiving buccal T 10–20 mg for 8 weeks were restored to levels similar to those observed during i.m. T injections.[35] Both maximum rigidity and duration of full NPT were significantly greater in men receiving the T buccal system compared with placebo at treatment week 8 ($P \leq 0.008$ for each comparison).

Subjective indices of sexual function also improved during buccal T therapy compared with androgen withdrawal (Table 3).

Tolerability and safety

The T buccal system has been well tolerated in trials lasting up to 8 weeks. Typically transient, mild or moderate mouth and gum reactions, as well as a bitter taste or other forms of dysgeusia, are the chief complaints of men treated with the T buccal system. Other AEs possibly related to buccal T therapy include dry mouth, stinging of the lips, toothache, gum erythema, stomatitis, and anxiety. Safety findings from the pilot trials are shown in Table 3.

Frequencies of application-site reactions have been similar in men receiving either the T buccal system (18.2%) or T patch (17.6%). Application-site erythema occurred in 6.1% of men using buccal T compared with 14.7% of those using the T patch.[37] Gum irritation tends to resolve within the first week.[34]

User and prescriber considerations

Some patients find the T buccal treatment unwieldy or are concerned about the system shifting out of place or interpersonal T transfer to sexual partners via the saliva. Others may object to twice-daily dosing. The average wholesale price of a 30-day supply of 30 mg T buccal tablets for twice daily dosing is $190.30, or approximately $6.34 per day.[21]

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Oral therapies

Overview

Clinical trials evaluating oral T therapies for the treatment of low libido and/or ED associated with hypogonadism date back approximately 20 years.[38] However, hepatotoxicity represents a major concern with oral TRT, including the use of 17α-alkylated derivatives such as methyltestosterone (MeT), which was designed to reduce hepatic first-pass metabolism. Owing to the concerns about potential hepatotoxicity, oral MeT treatment is considered obsolete in the United States.

Efficacy

In a study of men with ED, diminished libido, and total T levels <331 ng/dl, 27% experienced a positive response with oral T, but only 9% reported complete restoration of sexual function.[39] In other studies, improvements in sexual function have been reported[40, 41] (Table 4).

Table 4 - Efficacy of oral therapies.


Full table

Tolerability and safety

Stimulatory effects of oral T on hepatic microsomal enzyme systems have been observed *in vitro* for decades, as has the development of peliosis hepatis or hepatocellular carcinoma in patients taking oral androgens (e.g. MeT).[42, 43, 44, 45] Further evidence for direct androgenic effects of oral T (TU; testosterone undecanoate) on the liver include significant, persistent suppression of sex hormone binding globulin (SHBG).[46]

Although the intact ester of TU is absorbed by the lymphatics, most of the oral dose is hydrolyzed in the wall of the gut, and metabolites are absorbed into the portal circulation. During oral TU treatment, about 40% of patients report nausea and/or other GI complaints.

On the other hand, a 10-y safety study found that liver function test results were normal in men receiving oral TU 80–200 mg.[47] Mean values for bilirubin, alkaline phosphatase, lactate dehydrogenase, and aminotransferases were within normal limits during this time frame. Mean PSA levels, measured over the last 2 years of the study, also remained within normal limits.[47]

User and prescriber considerations

Treatment with either oral MeT or TU necessitates multiple daily dosing with meals. Despite a high hepatic load, GI intolerance, frequent dosing, and relatively high cost, oral TRT (e.g. oral TU) represents a potential treatment option, particularly when i.m. T is poorly tolerated or undesirable.[48]

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Intramuscular injections (i.m. T)

Pharmacologic profiles

Formulations of T for i.m. injection include testosterone enanthate (TE; Delatestryl®; BTG Pharmaceuticals, Iselin, NJ, USA) and testosterone cypionate (TC; Depo®-Testosterone; Pfizer, New York, NY, USA).[49] Injectable TU is available in certain non-US markets. Testosterone propionate is used infrequently.

Clinical studies

Pharmacokinetics. Intramuscular T injections are associated with the most variable pharmacokinetics of all forms of TRT. Wide fluctuations in circulating T levels, with supraphysiologic T levels in the first few days after administration and subphysiologic

levels toward the end of the dosing interval, may result in unfavorable variations in the patient's mood, energy level, sense of well-being, or sexual function. Termed 'roller-coaster' effects, these changes are potentially distressing to both hypogonadal patients and their loved-ones.[50]

In a 24-week, multicenter, randomized active-comparator trial, the percent of time during the dosing interval that T was within the normal range (PTNR) was significantly lower in men receiving i.m. TE injections (72%) compared with a nonscrotal T patch (82%; *P*=0.05).[51] In a different trial, the PTNR was >50% for up to 60 days after a single injection of TU (500–1000 mg) in men with primary hypogonadism.[52] Mean serum T reached supraphysiologic levels of 1378–1562 ng/dl on postinjection days 5–7.

Efficacy. Intramuscular T injections have been associated with favorable clinical effects on libido and other barometers of sexual function, as well as body composition and/or mood[53, 54, 55, 56, 57, 58, 59] (Table 5).

Table 5 - Intramuscular T injections: efficacy and safety findings.

Full table

Tolerability and safety

Injection–site reactions are common with i.m. T injections. In the 24-week pharmacokinetics trial, 33% of men reported one or more local reactions following i.m. TE, although no patient discontinued treatment because of such effects.[51] Other AEs included headache (9.1%) and pruritus (3.0%).[51] Safety/tolerability results from studies of oral T are shown in Table 5.

Gynecomastia occurs in one-quarter to one-third of patients within the first few days of i.m. T therapy, when T levels are highest (often supraphysiologic) and subject to substantial aromatization to estradiol. Gynecomastia may be less readily reversible in men receiving i.m. T injections compared with T patches.[51] Increased appetite has also been reported by men receiving i.m. TU injections.[52]

US prescribing information for Delatestryl recommends discontinuing TRT in the event of cholestatic hepatitis with jaundice or abnormal liver function tests.[60] Biochemical tests of liver function are often normal in cases of androgen-dependent hepatoma associated with i.m. T therapy. Other signs potentially suggestive of hepatic tumor include hepatomegaly, abdominal mass, jaundice, and/or abdominal discomfort.[61]

User and prescriber considerations

Intermittent i.m. T injections represent the most cost-effective and often the most readily reimbursed form of TRT. These considerations are important to many elderly hypogonadal men with limited incomes. Given recommended doses of 50–400 mg of TE or TC every 2 to 4 weeks and average wholesale pricing in the US,[21] the price of a daily i.m. dose of TE or TC ranges from about $0.21 to $3.34. As recently as 2000, consensus guidelines have recommended i.m. injection of T esters as first-line forms of TRT.[48]

On the other hand, pricing disparities between parenteral therapies and other, at-home treatments lessen when taking into account fees for office visits to receive the i.m. injections. Commercially available prefilled syringes often have long (1.5-in) 20-gauge needles, and some patients experience discomfort or concerns about this.

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Subcutaneous testosterone implants (T Pellets/Depot T)

Pharmacologic profile

Testosterone has also been formulated as fused cylindrical crystalline implants for TRT (**Testopel**®, **Bartor** Pharmaceuticals, Rye, New York).

T pellets serve as a nearly ideal depot, maintaining normal serum levels of T for months. Once implanted, T pellets form a slowly dissolving subdermal depot with zero-order release kinetics, such that T absorption is complete or nearly complete by treatment day 189.[62, 63] T pellets have among the longest durations of biologic activity among all forms of TRT, with a mean residence time of 87 days and a half-life of 70.8 days.[63] Approximately 1.18 mg of T is released from each 200 mg pellet daily.

Clinical studies

In a study involving 50 hypogonadal men (ages 18–61 years) with serum T<104 ng/dl (mean T=33.7 ng/dl), a European group implanted six 200 mg T pellets in each patient.[63] After implantation, serum T peaked at ~1326 ng/dl within 30 min.[63] The mean serum T exceeded 288 ng/dl up to treatment days 147–246. Treatment effects of T pellets waned after about 6 months, with patients reporting declining libido and erectile function.[63]

Similar pharmacokinetic profiles were reported in an Australian study of hypogonadal men receiving T pellets 600–1200 mg,[64] which showed that absorption rate was not influenced by the sizes or number of pellets implanted.

In a review of 13 years of experience with T pellets, Handelsman reported favorable clinical outcomes, with few AEs and a treatment continuation rate of approximately 93%[62] (Table 6). Other study findings are shown in Table 6.[63, 64, 65] In a number of studies, patients were so satisfied with T pellet treatment that they elected to continue receiving this form of therapy rather than return to their prior form of TRT.

Table 6 - T Pellets: pharmacokinetics, efficacy, and safety.


Full table

The chief AEs with T pellets include pellet extrusion; minor bleeding, which is typically insignificant and controlled by applying pressure to the surgical wound; and infection, which is infrequent and may also result in pellet extrusion. Some patients develop fibrosis (scarring, nodules) around implantation sites, but this typically does not prevent further implantations.

Prospective randomized clinical trials have demonstrated that neither washing T pellets in filtered sterile alcohol nor soaking them with an antibiotic (gentamicin) prior to implantation significantly reduces the likelihood of pellet extrusion.[65, 66] However, the use of povidone-iodine skin disinfectant prior to the procedure does appear to lower pellet extrusion rates. The likelihood of pellet extrusion may decline with increasing operator experience.

User and prescriber considerations

In an office procedure lasting approximately 15 min, T pellets are implanted into the subdermal fat of the lower abdominal wall using a stainless-steel wide-bore trocar under sterile conditions and a local anesthetic. Through a small (0.5–1.0 cm) incision ≥ 5 cm from the midline at the umbilical level, a 7.5 F gauge 7-cm long trocar with an inner diameter of 5 mm is introduced and the implants discharged into fan-like tracks 5–10 cm from the puncture site using an obturator. In addition to the lower abdomen, implantation sites include the deltoid, proximal thigh, or buttocks. Most patients return to work the day of, or the day after, implantation but are advised to avoid bending or vigorous physical activity.

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Screening/monitoring

Baseline screening and on-treatment monitoring are required to evaluate both the efficacy (Table 7) and safety (Table 8) of TRT.

Table 7 - Suggested monitoring for testosterone replacement therapy (*I. Efficacy*).


Full table

Table 8 - Suggested monitoring for testosterone replacement therapy (*II. Safety*).


Full table

Screening

In a recent review in the *New England Journal of Medicine*,[67] Rhoden recommended the following baseline assessments: (1) voiding function or history, including use of standardized questionnaires such as the International Prostate Symptom Score (IPSS); (2) digital rectal examination (DRE); (3) serum T assay; (4) PSA testing with prostate biopsy if PSA exceeds 4.0 ng/ml or substantially increases over a short period of time, or DRE is abnormal; (5) history of sleep apnea; and (6) hematocrit (normal=42–52% for males) or hemoglobin (normal=13–18 g/dl for males) because TRT may increase the risk of erythrocytosis (polycythemia).

TRT should not be administered to men with high or significantly increasing PSA levels.[5] Other baseline safety tests include serum chemistries; liver function tests; and a lipoprotein profile, although most clinical studies indicate neutral or possibly beneficial effects of TRT on lipids and lipoproteins.[67]

Monitoring

Serum T levels are typically measured within 2–4 weeks after the first treatment or at the midpoint between i.m. T doses (Table 7).[5, 68] With most TRT formulations, doses can be adjusted upward or downward depending on clinical responses. In general, safety evaluations are performed every 6 months for the first 18 months of therapy, then annually thereafter if results are stable and normal (Table 8).[5, 67, 68]

Digital rectal examination should be performed and prostate-related symptoms assessed every 6–12 months. Patients with symptomatic prostatism should undergo further assessment before continuing TRT. PSA may be measured at baseline and quarterly during the first year, then annually thereafter. An increase in PSA to $\geq$ 4.0 ng/ml or rapidly increasing PSA levels are widely accepted standards for urologic referral and/or prostate biopsy. Annual PSA increases $\geq$ 1 ng/ml should prompt prostate biopsy, whereas annual increases of 0.7–0.9 ng/ml should trigger repeat measurements in 3–6 months, with biopsy if there are further increases.[67] Other potential criteria for prostate biopsy include a PSA increase >1.0 ng/ml during the first 6 months of TRT or an annual increase >0.4 ng/ml thereafter.[69]

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On the horizon: issues and agents

Prostate and other safety issues

Most of the potential risks associated with TRT are infrequent or of marginal clinical significance (Table 9).[67] However, elderly men are prone to certain disorders considered to be androgen dependent, including benign prostatic hyperplasia (BPH), PCa, erythrocytosis, and sleep apnea.

Table 9 - Potential risks associated with testosterone replacement therapy.


Full table

A major clinical controversy is whether the efficacy of long-term TRT offsets its potential risks in elderly hypogonadal men. Certain critics contend that the benefits of TRT (T gel, i.m. T, T patch) on erectile function and overall treatment satisfaction may not persist beyond treatment month 1.[4] On the other hand, studies suggest that the clinical benefits of TRT extend up to 1 year. In addition, TRT that restores serum T levels even to low-normal values (>400 ng/dl) significantly enhances nocturnal erections.[10]

By one estimate,[70] however, 50% of men >50 years old harbor occult PCa, which might, in theory, be 'unmasked' via TRT. The debate regarding the therapeutic index of TRT may be partly colored by findings from the Women's Health Initiative and other epidemiologic and clinical studies.[71, 72, 73]

Also of potential influence on the debate is the recent decision by an FDA advisory panel that any clinical benefits of treatment with a combined T-estrogen patch for women with hypoactive sexual disorder associated with surgical menopause (Intrinsa®, Procter & Gamble, Cincinnati, OH, USA) do not necessarily offset potential long-term safety concerns.

A study assessing the effect of TRT (T patch or i.m. T) on serum PSA levels found that changes in neither PSA nor prostate-specific membrane antigen (PSMA) levels were testosterone dependent.[74] A two-tailed *t*-test did not show a significant relation between serum T levels and either serum PSA or PSMA concentrations, suggesting that neither parameter is androgen dependent.[74] Although TRT may be associated with growth of the seminal vesicles and prostate gland, these changes typically do not exceed age-related trends.[75]

In clinical studies considered in Part III of this review, men with abnormal PSA and other evidence of prostate pathology were generally excluded. In these trials, changes in PSA and prostate volume on TRT were in general modest and considered clinically insignificant; TRT did not significantly augment or otherwise alter age-related trends in these parameters. Findings from the recent *New England Journal of Medicine* review[67]

are consistent with these data (Table 10).[12, 28, 29, 51, 76, 77, 78] In clinical trials of up to 3 years, PCa occurred in 1.0% of TRT recipients compared with 0 placebo controls. Increases in PSA to >4 ng/ml occurred in 7.2% of TRT recipients compared with 9.8% of placebo controls.

Table 10 - Prostate cancer and prostate-specific antigen elevations in clinical trials of testosterone replacement therapy (TRT).


Full table

On the other hand, the number of patients included in the above analysis was relatively small (*N*<600). By one estimate, 6000 elderly hypogonadal men would need to be randomized to TRT or placebo and followed for 6 years to discern a 30% increase in PCa risk on active treatment.[70]

Given these data, Snyder recommended that diagnostic criteria for hypogonadism should be more stringent in men >65 years of age, with TRT being initiated only in men with signs or symptoms and serum T<200 ng/dl rather than <300 ng/dl. In addition, it may be appropriate to utilize age-specific T targets for TRT, the mid-normal range of which is 300–450 ng/dl in elderly men.[70]

Testosterone and its metabolites have diverse tissue effects. Through interactions with the androgen receptor (AR), T affects muscle, bone, bone marrow, and the brain. Via AR transcription effects and signaling pathways,[79, 80, 81, 82] exogenous T may enhance muscle and bone strength, promote erythropoiesis, and bolster patients' energy levels but may also increase the risk of erythrocytosis and/or sleep apnea.[70]

5α-Reductase converts T to dihydrotestosterone (DHT), which has higher AR binding affinity than T. Through 5α-reductase activity in the skin, a certain amount of T from T gels and T patches is converted to DHT. The prostate gland, external genitalia, and skin may be affected by DHT.

Potential future agents

As exogenous DHT is not a substrate for aromatase, it is not a source of estradiol and may have clinical utility in hypogonadal men with gynecomastia or microphallus.[83] Estrogens may also have pharmacodynamic benefits in men, conferring enhanced bone strength and increased libido. Animal studies have been undertaken to evaluate the effects of AR modulators on osteoporosis.[84]

The effects of DHT, a growth factor, on the prostate are debated. DHT gel was evaluated in elderly men as a potential form of androgen replacement in the late 1990s.[85] Recent findings regarding AR signaling pathways have spawned the development of dutasteride,

a dual 5α-reductase inhibitor, for the treatment of BPH.[86] *In vitro* and other preclinical studies have investigated factors underlying or regulating phenotypic expression of PCa and BPH, including DHT.[87, 88, 89]

Selective androgen receptor modulators (SARMs). Of investigational agents under development to enhance the tissue selectivity and other pharmacodynamic properties of TRT, none is more prominent than SARMs.[82] This term is analogous to *selective estrogen receptor modulators* (SERMs; e.g. raloxifene, tamoxifen).

The ideal SARM for primary and secondary male hypogonadism would be (Table 11):

Table 11 - Desired profile of activity of new selective androgen receptor modulators.


Full table

orally active, ideally with a pharmacokinetic profile consistent with once a day administration, capable of stimulating prostate, seminal vesicles, and other sex accessory tissues at doses equipotent to those needed to provide increases in muscle mass and strength and fat-free mass, support bone growth, and maintain/restore libido, virilization, and male habitus.[82]

Nonsteroidal SARMs are under preclinical investigation for the treatment of male hypogonadism and/or its manifestations.[90, 91, 92] Treatment of orchidectomized rats with the nonsteroidal AR ligand S-40503 promoted osteoblastic activity. The investigators reported marked increases in femur bone mineral density, with reduced virilizing activity and minimal prostate growth compared with DHT.[93]

Injectable/implantable agents. A number of other AR ligands, including novel derivatives and formulations of T, are under investigation. Implantable agents include 7α-methyl-19-nortestosterone (MENT), a synthetic androgen with a favorable tissue selectivity profile, as well as biodegradable T microspheres (T micro) and T buciclate (TB).

7α-methyl-19-nortestosterone (MENT). This compound is about 10 times more potent than T in terms of anabolic activities and gonadotropin suppression, is not bound by SHBG in circulation, is not a substrate for 5α-reductase, and has a relatively low potency for stimulation of prostate growth: approximately four times less than that of T.[94, 95] MENT is aromatizable to 7α-methyl estradiol, which may confer beneficial tissue effects via the estrogen receptor.

In a randomized crossover trial involving hypogonadal men from two disparate societies (Edinburgh and Hong Kong), patients were allocated to treatment with two MENT acetate 115 mg upper-arm implants for 6 weeks and two i.m. injections of TE 200 mg at

3-week intervals. Compared with a 6-week androgen washout period, both MENT and i.m. TE significantly enhanced sexual function, with no between-group differences.[94]

Although the physiologic benefits of TRT on erectile function as assessed objectively by RigiScan® (Timm Medical Systems, Eden Prairie, MN, USA) were significant across treatment centers,[94] other sexual effects were less robust. Both MENT and i.m. TE significantly enhanced self-rated interest in sex, masturbation, sexual intercourse, and overall sexual activity in Scottish, but not Chinese, men. These findings reflect the cultural context and specificity of certain sexual outcome measures.

Similar trends were observed with regard to TRT effects on mood: significant increases in self-reported cheerfulness and energy level, coupled with significant decreases in lethargy, depression, and irritability in Scottish, but not Chinese, patients. Improvements in mood represent among the least robust outcomes of TRT and may reflect other, more stable physiologic improvements. Some clinical trials have demonstrated clinical benefits on mood with TRT,[40, 54, 96, 97] whereas others have not.[53, 56]

T Microspheres (T Micro). Injectable microcapsules consist of 267 mg of T, which is encapsulated in a biodegradable matrix. Release follows zero-order kinetics, and the duration of activity is up to 12 weeks.[98, 99]

In a US study of hypogonadal men, the effects of T micro 267 mg were evaluated for up to 8 weeks and 534 mg for up to 12 weeks.[100] T micro resulted in rapid and prolonged restoration of T to eugonadal levels, with C_{avg} values of 413–522 ng/dl and a half-life of 20.4–22.3 days[100] over the dose range. Serum T peaked at 731 ng/dl on day 2 after the lower dose and at 995 ng/dl on day 1 after the higher dose.[100]

T micro significantly enhanced the quality and duration of erections, as well as relieving feelings of irritability from baseline. Treatment was well tolerated. Two patients reported transient injection–site pain with erythema. There were palpable nodules near injection sites, but induration resolved by week 12. There were no significant changes in hematocrit, PSA, or lipids up to 12 weeks. Chemical stability problems have impeded the development of T micro.

T Buciclate (TB). Characterized by an advantageous pharmacokinetic profile compared with other long-acting T esters for i.m. injection, i.m. TB maintained serum T within the low-normal range for up to 12 weeks in a phase I study of hypogonadal men. The half-life of TB was 29.5 days, and the mean residence time 65.0 days in men receiving i.m. TB 600 mg.[101]

Unlike other forms of i.m. T, there was no serum T 'burst' to supraphysiologic levels within the first few days after administration, and serum androgen levels were more stable. Mean DHT and estradiol levels remained below upper normal limits, and SHBG within normal limits, through week 16.[101] Subjective improvements in sexual interest and satisfaction were observed, with the number of morning erections increasing significantly compared with a pretreatment control phase. There were no clinically significant on-treatment changes in PSA or prostate volume by transrectal ultrasound or uroflow parameters.[101]

Other. Alternative forms of treatment for male hypogonadism are under various stages of development. These include clomiphene, which increases pituitary gonadotropin output. Clomiphene treatment enhanced sexual function in 75% of 178 ED patients, particularly younger patients and men with anxiety-related disorders, and also significantly increased gonadotropin levels during 4 months of treatment.[102] In addition, T buccal mucoadhesive film is also under investigation.

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Conclusions

In summary, male hypogonadism is associated with a wide range of potentially distressing symptoms and signs, many of which are reversible through TRT. Such treatment confers at least short-term clinical benefits on sexual function, particularly libido, as well as erectile function, body composition, and possibly mood and/or a sense of vitality. In addition, some patients need only to achieve a relatively low threshold of serum T levels (300–600 ng/dl) to experience reduced symptoms of hypogonadism. Adjunctive T may play a role as a rescue therapy for treatment-refractory depression or ED in men with hypogonadism. Effective noninvasive therapies are available, including T gels, buccal T, and T patches, which are formulated for daily or twice-daily administration. More invasive options, including long-acting i.m. T and T pellets, enable less frequent dosing and potentially more cost-effective treatment. Randomized controlled trials involving larger numbers of patients treated over longer periods of time may help to further evaluate the efficacy, tolerability, and safety profiles of these treatments and other prospective agents with potentially enhanced pharmacokinetic and pharmacodynamic properties.

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