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Long vs short acting testosterone treatments: A look at the risks

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Abstract

Prescriptions for testosterone therapy (TT) to treat testosterone deficiency have increased in recent years. The purpose of this review was to evaluate the risks of several treatment modalities to better counsel patients. Both short-acting and long-acting TT has been shown to restore normal serum testosterone levels and improve symptoms of testosterone deficiency. Short-acting pharmacology mimics normal physiology more closely than long-acting TT but requires multiple doses per day, while long-acting TT has a higher rate of patient adherence but is more likely to create supraphysiologic serum testosterone and pathologic sequelae.

Keywords

Testosterone deficiency; Intramuscular injections; Intranasal gels; Oral testosterone; Subcutaneous pellets; Testosterone therapy

Introduction

Testosterone therapy (TT) can be used for physiological reasons or be abused. In the former case, testosterone (T) replacement is prescribed for pathologic androgen deficiency, including disorders affecting the hypothalamic-pituitary-testicular (HPT) axis where luteinizing hormone or testosterone secretion is reduced. The objective is to restore the physiologic pattern of circulating T levels[1,2]. In the latter case, the supraphysiologic dosing of testosterone exploits the androgenic effects on muscle, bone, and other tissues in men, especially in eugonadal patients[1].

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However, the misuse of androgens without a valid clinical indication has become prevalent over the previous decades due to the combination of marketing drive, single-issue clinics, and poor regulatory standards in responding to off-label usage[1–3]. For instance, Canada had a four-fold increase in per capita testosterone prescribing due to internet pharmacies physically based in the country which are not subjected to national prohibitions of import/export controls of androgens[4]. Androgen misuse has taken the form of prescriptions for male infertility, anti-aging, and body sculpting, which has led to a 100-fold increase in expenditure on prescription T products over the three decades leading to 2010[2]. However, coinciding with an FDA communication about potential cardiovascular events following testosterone therapy, there was a decrease of 3.2% use of testosterone in men in 2013 to 1.67% in 2016, with new users decreasing from 1.26% to 0.48%[5]. Nonetheless, we are now seeing the rise of online direct-to-consumer clinics that provide questionnaires to patients who self-report symptoms of erectile dysfunction or premature ejaculation. These questionnaires are reviewed by physicians but do not require a physical exam, a laboratory workup, or counseling about the risks. This may be a future route for testosterone delivery and may potentially contribute to androgen misuse[6].

Due to challenges in the diagnosis and treatment of male testosterone deficiency, different societies have established guidelines for diagnosing T deficiency[7]. The American Urologic Association (AUA) states that a patient must have two total morning T measurements on separate occasions that are below 300 ng/dL and present with symptoms of testosterone deficiency (e.g., erectile dysfunction, low sex drive, lack of energy, and decreased strength)[7]. Meanwhile, the European Association of Urology (EAU), British Society for Sexual Medicine (BSSM), Endocrine Society (ES), International Society for Sexual Medicine (ISSM), and International Society for the Study of the Aging Male (ISSAM) have different cutoffs; the ISSAM and EAU use an early morning measurement of <350 ng/dL to diagnose a patient with T deficiency[8–10], the ES uses a measurement of <264 ng/dL[11], and both the ISSM and BSSM use values <8 nmol/L (230 ng/dL) for definite treatment and values between 8 nmol/L and 12 nmol/L (346 ng/dL) for potential treatment[12]. Additionally, these societies suggest that free testosterone can be used if there is a low-normal total T measurement and/or sex hormone binding globulin (SHBG) levels are abnormal[13].

The purpose of TT is to restore and maintain hormone levels at the physiologic serum concentration in order to alleviate symptoms of testosterone deficiency without causing significant side effects or safety concerns[7]. The benefits of TT have been well demonstrated by the Testosterone Trials by Snyder et al., which highlight its benefits in sexual desire and erectile function, distance walked, improved mood and depressive symptoms and increased volumetric bone mineral density[14]. Available in multiple delivery methods, several different types of T therapies exist including intranasal gels, oral pills, intramuscular (IM) injections, transdermal gels and patches, and subcutaneous (SQ) pellets[7,15]. These treatments can be classified into short-acting and long-acting modalities. Short-acting therapies consist of intranasal gels, oral testosterone capsules, and transdermal gels and patches, while long-acting therapies include IM injections and SQ pellets. These modalities have distinct influences on male reproductive function and patient medication adherence.

While both short-acting and long-acting T have been shown to restore normal T levels, there are significant differences between the two modalities. Patients have the option of using transdermal gels or patches that can be applied directly to the axilla or thigh, but these delivery methods increase the risk of transference[7]. Overall, short-acting T has less impact on the male hypothalamus-pituitary-gonadal (HPG) and has the potential to better preserve fertility[7,15]. Meanwhile, long-acting injectables, specifically testosterone undecanoate, require decreased frequency of administration, with some manufacturers recommending dosing only at weeks 0 and 4 and then every 10 weeks thereafter[16]. In addition, there are potential risks associated with the use of any exogenous T with patients who have a history of prostate cancer or who have a susceptibility to CVD and stroke[17,18]. Currently, the AUA states that there is insufficient evidence linking testosterone therapy to the development of prostate cancer or showing an increased risk of recurrence of prostate cancer in treated men[7]. Thus, the benefits and risks of these modalities influence the shared decision-making between physicians and patients when selecting an appropriate TT.

Given the recent surge of TT usage due to increased consumer advertising, relaxation of the indications for T prescriptions, and the establishment of clinical care centers devoted to men's health, an evidence-based method to selecting the appropriate type of TT is critical[7,19]. The purpose of this review was to document the risks of short-acting and long-acting TT [Table 1].

The findings shown here will better enable clinicians to make appropriate decisions for men with testosterone deficiency interested in receiving TT.

Short-acting TT

Short-acting T therapy consists of administering one or more doses a day of T with a shorter half-life throughout the day. This allows patients to maintain homeostasis that closely reflects the body's normal levels, with minimal impairment of spermatogenesis[20]

The currently available modalities for short-acting exogenous TT are intranasal testosterone: Natesto®, 2% transdermal testosterone gels: Fortesta®, AndroGel®, and Testim®, transdermal testosterone patches: Androderm® and oral testosterone capsules: Jatenzo® and Tlando®[21,22].

Short-acting TT Risks

Generally, the use of short-acting TT causes several side effects including polycythemia, gynecomastia, suppression of spermatogenesis, and impaired fertility, though these are also side effects of long-acting TT[21,22]. However, it is difficult to interpret the impact of short-acting TT on sperm parameters, as the misuse of TT for male infertility, anti-aging, and body sculpting purposes confounds study results. Most of the other side effects noted in clinical trials of short-acting TT have been minor and directly related to the area of treatment application (i.e., site irritation, nasal discomfort). Importantly, TT is absolutely contraindicated in older men with a history of heart failure, patients with a hematocrit > 50%, men with metastatic prostate cancer, and men desiring fatherhood[23].

Relative contraindications include severe lower urinary tract symptoms and severe untreated obstructive sleep apnea[23]. Formulation-specific risks are outlined below.

Intranasal Testosterone

There are few studies that extensively discuss the risks of using short-acting intranasal T. In an open-label phase III trial of Natesto®, adverse events included headache, rhinorrhea, nosebleed, upper respiratory tract infection, sinusitis, and bronchitis[24,25]. In a 2017 open label, single arm trial, researchers documented the following adverse events: nasal irritation (8.3%), oligospermia (5%), epistaxis (1.7%), sinusitis (1.7%), and azoospermia (1.7%). However, the participant with azoospermia recovered to normal levels within 3 months after treatment cessation[26]. Given these side effects, Natesto® is not recommended for patients with a history of nasal disorders[24].

Transdermal Testosterone Gels

Adverse events reported from a study of 155 subjects who received 2% topical T solution were application site irritation to the axillae (7.1%), application site erythema (5.2%), headache (5.2%), increased hematocrit (3.9%), nasopharyngitis (3.9%), diarrhea (2.6%), and vomiting (2.6%)[27,28]. A meta-analysis by Nackeeran et al. found an increase in hematocrit by 3% for men using transdermal testosterone gels[29]. There is also the risk of transference with the use of topical gels, which may cause alterations in hormonal levels and subsequent side effects in women or children who come in physical contact male users. This risk can be mitigated via hand washing and wearing barrier clothing prior to anticipated contact with others[30]. Studies have also shown that transdermal testosterone gels do not preserve sperm counts, but more head-to-head studies are needed when comparing modalities[31].

Transdermal Testosterone Patches

In terms of adverse events from the T patches, one study found that administration site reactions occurred in 35 patients (18.8%)[32]. The patch was well tolerated in most patients with no negative impact either on lipid profile. Other adverse effects include pruritus, application site vesicles, and back pain[33]. One meta-analysis reports an increase in hematocrit by 1.4%[29].

Oral Testosterone Pills—Consistent with other TT modalities, Jatenzo® adverse events included elevated hematocrit, though this side effect is lower than the rates reported with injectable TT, and a small number of cases of increased systolic blood pressure by an average of 3–5 mmHg[34,35]. The former issue can be resolved by temporarily stoppi1ng the treatment. The latter issue has led to the boxed warning stating that Jatenzo® can cause blood pressure to rise, increasing the risk of heart attack, stroke, and cardiovascular death. As such, blood pressure should be regularly monitored in those using Jatenzo® and adequately controlled by the patient's primary health care provider. These findings are likely related to the high-density lipoprotein decline seen with use of oral testosterone use[34]. Additionally, patients experienced minor gastrointestinal adverse events, including nausea, diarrhea, and burping, which is specific to this TT product. Unlike the previous side effects observed with older oral TT, hepatotoxicity was not found in the short-term or long-term study[34]. This is due to the drug design that allows for absorption to occur primarily through

the intestinal lymphatic system, which bypasses first-pass metabolism by the liver[34]. Thus, this medication must be taken with meals to be absorbed by the lymphatic system through the thoracic duct. Other studies have reported an increase in hematocrit by 4.3%, the highest amongst all TT examined in the study[29]. More studies are needed to quantify the long-term impact that Jatenzo® has on sperm parameters. The adverse events related to Tlando® included blood prolactin increase (6.3%), weight increase (2.1%), headache (2.1%), and musculoskeletal pain (2.1%), with an average increase in hematocrit of 0.9%[36]. However, there were no significant changes in blood pressure or reported hepatotoxicity[36].

Long-acting TT

The currently available modalities for long-acting exogenous TT are intramuscular (IM) or subcutaneous (SQ) injections of testosterone cypionate (TC) – marketed under the brand name Depo-Tesosterone®, testosterone enanthate (TE) – marketed under the brand name Delatestryl® or Xyosted®, testosterone undecanoate (TU) – marketed under the brand names Aveed® (750 mg/3 mL vial) and Nebido® (1000 mg/4 mL vial), and subcutaneous T pellets, marketed under the brand name Testopel®. The major difference between these medications and other T formulations is that patients are typically injected with TC or TE every one to two weeks, TU approximately four times per year, while Testopel® pellets are typically replaced every three to four months[7].

Injectable T, particularly TC and TE, is available in both IM and SQ forms. However, based on previous studies, IM formulations tend to be favored as IM T achieves higher peak T, faster time-to-peak levels, and a shorter half-life (i.e., 173 hours) when compared to SQ T[37] In general, smaller IM doses at more frequent intervals (e.g., 100mg weekly) are preferred over higher-dose, less frequent administrations (e.g., 200mg biweekly) subcutaneously[38]. The best time to obtain monitoring blood tests for IM testosterone has not been defined. Given the half-life of approximately seven days, it is reasonable to obtain testosterone levels four weeks after starting therapy. Other reports have found value in assessing peak level (18–36 hours after injection) as the adverse events may be related to the peak level.[7]

Patients rarely reported pain while using the SQ TE auto-injector. In one study, 9 out of 1519 injections were reported as painful, rated at a scale of 1 or 2 out of 10[39], while another demonstrated 1 patient with mild pain out of a total of 954 injections[40]. However, formulations such as TC can be taught to patients to be self-administered subcutaneously, which is thought to result in a lower risk of erythrocytosis and less variability in T levels[35,41,42].

Long-acting TT Risks

Commonly reported side effects of long-acting TT—of which all patients should be aware—are similar to those of short-acting TT and include nausea, vomiting, headache, skin color changes, changes in libido, oily skin, hair loss, and acne[43,44]. Many of these effects are considered mild and typically do not necessitate discontinuation of therapy. The potential adverse events or risks associated with long-acting TT that may require interruption of treatment or other intervention are also like those associated with short-acting TT.

Polycythemia, defined as a hematocrit of >52%, is a known side effect of T supplementation for which patients should be monitored and, if severe, may require therapeutic phlebotomy if T dose reduction is ineffective[7,45,46]. Increased risk of CVD and prostate cancer related to TT is somewhat controversial. Newer research shows that physiologic T in testosterone-deficient men may actually provide CVD benefit and may provide important symptomatic relief in patients with treated prostate cancer or low-risk prostate cancer on active surveillance without increasing cancer risk[47,48]. The official stance of the AUA is that there is insufficient evidence linking T supplementation to increased risk of cardiovascular mortality or to increased risk of prostate cancer[7]. All patients should be counseled regarding these points prior to initiation of T supplementation of any kind.

Patients should be counseled that normalization of semen parameters can take six to 12 months following discontinuation of T therapy[49]. In the case of long-acting T formulations, this could mean 9 to 15 months following the last dose. In a 2009 study by Gu et al. of approximately 1000 fertile Chinese men, over 90% achieved azoospermia within 6 months of initiation of TU[50]. In long-term follow up, spermatogenesis returned to the normal fertile reference range in all but two participants at an average of 16 months[50]. Similarly, in a multicenter study of 271 men receiving 200 mg TE weekly by IM injection to assess the contraceptive efficacy of hormonally-induced azoospermia, 65% of men became azoospermic at 6 months[51]. The mean time to become azoospermic was 120 days (SD 40 days), while the estimated median time from azoospermia to recovery (sperm concentration > 20 million/ml) was 3.7 months (range: 3.6–3.9) after stopping the T injections[51].

Testosterone Cypionate and Testosterone Enanthate

In addition to the previously mentioned risks of long-acting TT, there are risks associated with the actual injection of the medication – either IM or SQ, such as injection site wounds or hematoma, which are rare[7,40]. Additional risks of which patients and providers should be aware are return of symptoms of testosterone deficiency related to subtherapeutic testosterone and hypertension[7]. TE comes with a black box warning of increased blood pressure and injections are known to cause discomfort due to fluctuating serum T levels and frequent injections[21,52,53].

Testosterone Undecanoate

Specific to IM injections of TU, risks include immediate post-injection cough or syncope due to pulmonary oil microembolism (POME) and post-injection hematoma. In 2015, Middleton et al. published the results of a prospective observational study assessing the incidence of these adverse events[54]. They found that across 3022 injections of TU given to 347 patients over 3.5 years, POME incidence was 19 per 1000 injections, no post injection hematomas occurred — including four men on antiplatelet therapy[54]. Due to these potential risks, IM injections are performed slowly with a small gauge needle and patients are generally observed for 30 minutes after injection for signs of hypersensitivity. In the event of the development of a POME, oxygen therapy, corticosteroids, and supportive therapy have been used, though continued research is needed to determine an effective treatment strategy[55].

Testosterone Pellets

Risks specific to subcutaneous pellet implantation center around the procedure associated with in-office implantation[56]. These include pellet extrusion, minor bleeding, and infection. Some patients develop fibrosis (scarring, nodules) around implantation sites, but this typically does not prevent further implantations[57]. Kelleher et al. published their experience in a prospective, randomized, controlled trial investigating whether washing pellets prior to implantation reduced extrusion rate. The extrusion rates were not significantly different between the intervention and control groups, with each around 10%[58]. This 10% extrusion rate figure is consistent with other published large volume experiences[59,60].

An additional risk associated with T pellets is related to the pharmacokinetics of the drug. Several studies have observed that men with BMI > 25 kg/m2 tend to have large volume of distribution and therefore lower serum T compared to men with BMI < 25 kg/m2 at the same dose[61]. This presents the risk of under-dosing by clinicians, creating a longer time to appropriate dose titration.

Limitations & Future Directions

Limitations of this review include the heterogeneity of study designs and subject populations across studies, which made it challenging to compare T formulations directly and so indirect comparisons were necessary. Additionally, there is still a research need for more long-term data examining the risks and benefits of TT and its alternative treatment options in males[61]. Controversy still exists surrounding the use of testosterone in functional testosterone deficiency in middle-aged men due to the thought that optimization of PDE-5 inhibitors and lifestyle modifications may improve sexual function and reduce the need for TT[62]. For example, comorbidities such as untreated obstructive sleep apnea may negatively influence testosterone levels and be a risk factor for secondary polycythemia in this patient population[63]. Thus, physicians must weigh these benefits against the risks of worsening symptoms of hyperviscosity and erythrocytosis that accompany the use of TT[29,64].

There are three major T research domains that need to be further explored. First, as mentioned above, more studies focused on the long-term risks and benefits of TT are necessary[61]. Second, a deeper examination of which patients are most susceptible to risks of TT. There is significant alarm over the use of exogenous T in patients with a history of prostate cancer and in those who are more susceptible to CVD and stroke[17,18]. Further research is necessary to determine the significance of these risks, and how to mitigate them in patients who are testosterone deficient with comorbidities. Finally, a better understanding of the effects of supraphysiologic T in males is needed. As T use in males without testosterone deficiency becomes more prominent, there needs to be better understanding of the risks of elevated exogenous T[4].

Conclusion

There is a growing need for exogenous T treatment, and prescriptions have increased[1]. There are, however, a variety of T formulations and the differences between these formulations must be understood before prescribing medication. Short-acting T has less

impact on fertility but requires more frequent dosing. Long-acting T results in improved patient compliance, but sperm parameters are often impaired in patients while taking the medication. Additionally, there are a variety of treatment modalities to treat testosterone deficiency without exogenous T. Continued research is necessary to fully understand the long-term impacts of these medications.

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Table 1:

Pharmacokinetics, Efficacy, and Potential Risks of Short-acting and Long-Acing Testosterone Therapy

Testosterone Therapy	Pharmacokinetics	Efficacy	Potential Risks
Short-acting Testosterone Therapy			
Intranasal Gel [24–26]	• Reaches maximum concentrations in around 40 minutes • Serum half-life: 10–100 minutes	• 90-day open trial reported 69 (90%) of 73 men had an average testosterone concentration within the specified normal range (300–1,050 ng/dL) after using 2 actuations (11 mg) three times daily	• Not recommended for patients with a history of nasal disorders • Nasopharyngitis • Rhinorrhea • Epistaxis • Headache • Sinusitis • Upper Respiratory Tract Infections • Bronchitis
Transdermal Testosterone Gels [27–31]	• Variable pharmacokinetic profiles and solubilities • Varied absorption profiles may make dose adjustments necessary	• 74–87% of men achieve testosterone levels in the normal range	• Application site reactions (erythema) • Transference risk • Irritation to the axillae • Headache • Increased hematocrit • Nasopharyngitis • Diarrhea • Vomiting • Increase in hematocrit by 3 %
Transdermal Testosterone Patches [32–33]	• Dependent on dosing, location, and scheduling of administration • Topical patches: levels achieved directly relate to the amount of surface area exposed to drug.	• Achieve testosterone levels within normal physiologic ranges (2 patches every 24–48 hours) in 77–100% of individuals with >85% achieving values >300 ng/dL.	• Application site reactions (reported in up to 60% of patients) • Pruritus • Application site vesicles • Back pain • Increase in hematocrit by 1.4%
Oral Testosterone Pills [34–35]	• Oral mucosa absorption avoids liver deactivation	• Serum testosterone levels rise rapidly after absorption • Peak levels reached by the second 12-hour daily dose. • Restores circulating testosterone level to physiological range	• Gum/mouth irritation • gum tenderness • gum pain • gum edema • elevated hematocrit
Long-acting Testosterone Therapy			
Testosterone Cypionate (TC) & Testosterone Enanthate (TE) [42,53–54]	• IM T achieves higher peak T, faster time-to-peak levels, and a shorter half-life (i.e., 173 hours)	• IM TE achieved trough levels of 239 ng/dL	• Injection site wounds • Hematomas • Return of symptoms of testosterone deficiency (subtherapeutic testosterone and hypertension) • TE – increased BP and discomfort
Testosterone Undecanoate [55–56]	• Peak concentrations achieved at a mean 7 days after injection (range 4–42 days).	• 94 % of men in study maintained normal testosterone levels after administration at weeks 0,4, and every 10 weeks after	• Injection site pain • Acne • Fatigue • Coughing secondary to pulmonary microemboli • Patients should be monitored 30 minutes after administration
Testosterone Pellets [57–61]	• Dissolves slow in SQ spaces	• Mean peak testosterone levels is dose-dependent • Therapeutic levels in 100% of men at 4 weeks and maintained levels >300 ng/dL at 4 months.	• polycythemia • ecchymosis • tenderness • pain • swelling • risk of under-dosing due to dose-dependency by BMI • pellet extrusion • fibrosis around implantation sites

Data Source: AUA Guidelines Appendix B (Therapeutic Agents for Treatment of Testosterone Deficiency)[7] and sources cited within the short-acting and long-acting sections