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REVIEW

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The Evolving Role of Novel Oral Agents for Testosterone Replacement Therapy; A Historical Perspective

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Abstract

There have been multiple attempts at an oral testosterone option for men with testosterone deficiency (TD), however many have been unsuccessful due to severe adverse reactions and lack of efficacy compared with other options. Due to a recent development in the pharmacology of delivery of oral testosterone through a self emulsifying drug delivery system, there has been the advent of new oral options for men suffering from TD. This review covers the history and challenges of oral testosterone, the development of a novel drug delivery system to allow men to absorb oral testosterone safely, and the efficacy of three oral testosterone options.— Jatenzo, Tlando and Kyzatrex. Clinicaltrials.gov identifier: NCT04467697.

Keywords: testosterone; hypogonadism; Jatenzo

Introduction

Testosterone (T), a steroid hormone, is the primary androgen in males and is necessary for a variety of physiologic processes, including sexual and reproductive function, cognition, metabolism, and body composition.^{1–3} Testosterone deficiency (TD), synonymous with male hypogonadism, is defined by two morning serum total testosterone levels <300 ng/dL and having one or more symptoms attributable to low circulating levels of testosterone.^{4,5} Symptoms of TD include decreased energy, decreased libido, erectile dysfunction, decrease in muscle mass and strength, decrease in bone

mass, increase in central body fat, anemia, and impaired memory, mood, concentration, and sleep.^{6,7}

Testosterone decreases with age with ~1% annual decrease in free testosterone levels after the age of 30, or about a decrease 100 ng/dL every 10 years.^{6,7} Approximately 20% of men over the age of 45 and 40% of men over the age of 80 are hypogonadal. Aging males are more likely to have an acquired cause or idiopathic etiology of hypogonadism. The decline in testosterone levels can be due to several factors, including decline of Leydig cell function, decline in pituitary-hypothalamic axis function with loss of circadian variation, increase

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in the levels of sex hormone binding globulin, changes in testosterone receptor sensitivity, and the effects of altered inflammatory and metabolic states.

Moreover, a reason for the prevalence of hypogonadism can be ascribed to the acquisition of co-morbid conditions, such as obesity, diabetes, and metabolic syndrome, as men age.^{7–10} Previous studies have shown that hypogonadism is associated with abdominal adiposity, insulin resistance, and metabolic syndrome. A few studies have shown that treatment of diabetes and improvement in obesity lead to a modest increase in testosterone, without the restoration of testosterone concentrations to normal.^{11,12} Studies have even shown that over 50% of renal transplant patients had TD, and these patients were found to have lower levels of hemoglobin (Hb), glomerular filtration rate, and serum albumin.¹³

The high prevalence among the general population, burdensome symptoms, and the utilization in improvement of comorbidities render TD a commonly encountered problem for physicians. There has been a significant rise in the number of prescriptions of testosterone in the United States over the past few years, which has accelerated the need to develop a superior tolerated formulation that is easier to use.¹⁴ The treatment options to increase testosterone levels and ameliorate TD symptoms include intramuscular injections, transdermal gels, implanted pellets, nasal sprays, and buccal tablets (Table 1).

Each of these formulations has certain drawbacks that most health care providers and patients are aware of, such as pain with injection, dermal irritation, testosterone transference, and others.¹⁵ The difficulties with the formulations can often lead to difficulty with adherence to daily treatments. What has been missing from the health care providers armamentarium of testosterone therapy (TTh) is an oral testosterone formulation that can both comply with federal regulation stipulations for safety and meet the need for standards of efficacy.

Table 1. Comparison of Clinical Advantages of Oral Versus Topical Testosterone Replacement Therapy Formulations

Oral	Topical
No transference	Possible transference to others
No dermal irritation	Dermal irritation
GI symptoms—diarrhea, belching	No GI symptoms
Risk of increased SBP	Risk of increased SBP
Improved medication adherence	Lower medication adherence

GI, gastrointestinal; SBP, systolic blood pressure.

Early oral testosterone was associated with serious hepatotoxicity and the later version of oral testosterone undecanoate (TU) was highly influenced in terms of absorption and clinical bioavailability from fat content in the patient's diet, which led to inpatient variability and questionable utility. A recent oral TU formulated in a distinctive self-emulsifying drug delivery system (SEDSS), Jatenzo, was recently developed to treat male hypogonadism. Another oral testosterone formulation, Tlando, was released in 2022 and a third formulation, Kyzatrex, was Food and Drug Administration (FDA) approved in 2022. The purpose of this review is to address the safety, efficacy, and durability of oral testosterone.

History of Oral Testosterone

Prior oral testosterone formulations have relied on two different mechanisms of action that avoid metabolism by the liver.^{1,16,17} The first is alkylation of testosterone at the C-17 position to create isomers such as methyltestosterone, which are able to circumvent the presystemic hepatic metabolism (before it reaches the body).¹⁸ The second is by combining the fatty acid of testosterone with an alcohol fatty acid to create a testosterone ester. TU is an example of a testosterone ester and it is able to be absorbed via the intestinal lymphatic system, thereby bypassing the portal circulation and absorption by the liver.

Oral methyltestosterone, which was first discovered in 1935 and prescribed to patients at that time, is the only oral TTh ever approved for use in the United States. However, by preventing its degradation by the liver, there were serious complications due to hepatotoxicity such as cholestasis, peliosis hepatis, and hepatic adenocarcinoma.^{19,20} Nevertheless, it is no longer clinically utilized for the management of male hypogonadism. In addition, oral methyltestosterone significantly decreased high-density lipoprotein (HDL) cholesterol and increased low-density lipoprotein cholesterol (LDLc) concentrations, increasing the risk of cardiac side effects.¹ For these reasons, methyltestosterone is no longer present in the formulations of oral testosterone.

An early formulation of oral TU, Andriol, was used in many countries starting in the 1970s but was never approved in the United States. Andriol concentration was highly dependent on dietary fat intake and patients would be able to achieve a high concentration with a higher fat consumption. Therefore, there was significant patient variability in testosterone response and ability to achieve adequate testosterone levels. This



drug was then reformulated as Andriol Testocaps to improve the consistency in drug concentration and reduce the effect of dietary fat.

Multiple pharmacokinetic studies showed that when Andriol Testocaps was consumed with food, regardless of fat content, it increased serum testosterone levels in a dose-dependent fashion to that within normal physiologic range. However, Andriol Testocaps did require men with TD to take multiple capsules throughout the day to maintain adequate drug levels, which was a significant issue for patient compliance. In addition to the need for frequent dosing, patients were not able to obtain testosterone levels in eugonadal range and men were not able to attain clinically meaningful improvement of somatic and psychological symptoms.²¹

Therefore, these formulations of oral testosterone have not been extensively utilized to treat T deficiency.²² It was not until 2019 when the first oral TU, Jatenzo, was released in the United States. In 2022, Tlando became the second oral TU to be released in the United States. Later in 2022, Kyzatrex was FDA approved as the third oral TU in the United States.

Pharmacologic Mechanism of Oral Testosterone

TU is a testosterone prodrug formulation that is lipophilic due to the long carbon sidechain and favors absorption via the lymphatic system, which is the opposite of other testosterone esters, which are more likely to be taken up by the portal system. TU has been integrated into a new proprietary SEDDS formulation. SEDDS stimulates a level of saponification of the lipophilic T esters, which leads to more preferential absorption by the intestinal lymphatic system. This leads to a decrease in first-pass hepatic metabolism.²³ SEDDS formulations syndicate lipophilic and hydrophilic components, which promote the solubilization of molecules such as TU, which are normally lipophilic. Thus, they can be absorbed in the intestines without the necessity of maintaining a diet high in fat content.³²⁴

SEDDS is defined as uniform amalgam of lipophilic oils (synthetic or natural) plus solid or liquid surfactants or hydrophilic solvents. On activation followed by reduction in aqueous solution, which is what happens in the human gastrointestinal tract, these systems produce a fine oil in water emulsion, which is physically stable (unlikely to be degraded or absorbed through the portal system) and readily absorbed by the intestines to the bloodstream.²⁵

The SEDDS specific mechanism in the bloodstream has been well studied in the literature. In the blood-

stream and fatty tissue, TU undergoes a swift enzymatic de-esterification, which results in a release of testosterone. The free undecanoic acid component is metabolized via beta-oxidation to produce multiple acetyl-coenzyme-A compounds and a singular propionyl-coenzyme-A molecule, which assist with absorption. Next, the gut produces dihydrotestosterone (DHT) undecanoate and DHT through enzymatic activation with 5-alpha reductase.²³

A phase II pharmacokinetics study²³ showed that hypogonadal men who took TU with an SEDDS formulation had a dose-proportional response that was well tolerated. The specific formulation that was assessed comprised TU dissolved in lipid formulations with other compounds such as borage seed oil (a rich source of C-20 fatty acids) and peppermint oil along with a hydrophilic surfactant [hydrogenated castor oil (Cremophor® RH 40)] to promote solubilization. These were encapsulated in soft gelatin capsules of various strengths, which would enable highly lipophilic molecules such as TU to be dissolved, and thus can be absorbed after a normal meal (without requiring a fat high content)

When an experimental oral testosterone, which included 200 mg of TU in the proprietary prodrug SEDDS formulation, was administered twice a day, average serum T levels were able to attain an eugonadal testosterone level in more than 75% of patients. Within a month, 87% of men had mean blood T levels within the adult male range, and none of the patients were found to exhibit a hypergonadotropic response and have an average serum T level greater than 1500 ng/dL. Patients did have a better response with the intake of a meal compared with fasting, as patients given 200 mg of oral TU twice daily incorporated in an SEDDS formulation had over a twofold higher average T concentration with food intake.²³

Further studies incorporating various levels of fat content in the diet are necessary to better elucidate the effect of food on TU with SEDDS formulation absorption. After these data are obtained, specific recommendations for dietary intake and the necessity of food intake with medication can be developed.

One consideration is the 5-alpha reductase enzymatic transition of T to DHT and the affect on various aspects such as lipid levels, muscle mass, sexual function, prostate size, hematocrit levels, etc. The most common mechanism that has been proposed is that the conversion of testosterone to DHT is not the sole



pathway, but it does emphasize the level of testosterone in tissues with high 5 α -reductase activity, including skin and prostate, compared with tissues with low 5 α -reductase activity including bone and muscle.

One clinical trial showed that the increase in body mass composition (while decrease in fat) with graded testosterone levels did not change in men who took dutasteride (suppressing DHT) from those treated with placebo. This showed that the DHT from conversion of testosterone is not necessary to mediate the anabolic building of skeletal muscle.²⁶

Safety Profile of Oral Testosterone

Due to previous issues with severe side effects with oral testosterone such as hepatotoxicity and hypercholesterolemia, the safety of the new oral testosterone formulation has been investigated thoroughly.

A randomized controlled trial investigating Andriol versus placebo demonstrated no safety concerns, and it was well tolerated with no difference in safety parameters compared with placebo. The one exception was lower back pain, which was reported more often in the treatment arms compared with placebo. The reason for the back pain was not elucidated and was not found to lead to patient noncompliance. Importantly, there was no concern for increase in liver toxicity compared with placebo.

As with all other testosterone preparations, there were higher rates of polycythemia, and the increase in hematocrit levels were seen with higher doses of testosterone. Further, patients who were treated with oral testosterone did not have a higher rate of prostate cancer diagnosis or benign prostatic hyperplasia symptoms. In addition, treatment with oral testosterone did not result in an increase in prostate symptoms as demonstrated by the lack of an increase in mean prostate specific antigen (PSA) or international prostate symptom score (IPSS), respectively.²⁷ It is important to note, however that even through this study did not express concern over liver damage, there has been a case report illustrating a patient who developed severe cholestasis and jaundice.²⁸

In the first Jatenzo trial^{29,30} comparing oral testosterone with testosterone gel, the authors investigated the rate of adverse events from initial exposure of Jatenzo and treatment over the course of 1 year. First, patients taking oral TU had an increased incidence of gastrointestinal side effects such as diarrhea and frequent eructation compared with patients on the topical T-gel. These gastrointestinal side effects, however, were

reported to be mild, and were not a reason for any patient to discontinue oral TU.

Hematocrit levels increased at 4 and 12 months by $+2.1 \pm 3.4\%$ and $+2.9 \pm 3.9\%$, respectively, in patients taking oral TU, which was a statistically significant change compared with the small hematocrit increase seen from T-gel. There were no clinically significant changes in liver function defined by measurement of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin, and alkaline phosphatase between the oral TU and T-gel patients over the year.

But one patient in the oral TU cohort developed two momentary episodes of elevated AST and ALT, which were a two- to three-fold increase from the upper range of normal; however, these returned back to normal with no clinical implications. At the 3-month time-point, patients on oral TU had a median decrease in HDL of 23.5%, compared with patients on T-gel with a median decrease of 12.5%, which was found to be statistically significant. A similar trend was seen between the two groups at 365 days.

Yet, the change in LDLc or triglycerides between the two groups was $<5\%$, which was not found to be clinically significant. The average absolute change in LDLc from baseline for oral TU agents was only $5.95 \pm 26.04\%$, demonstrating an overall small increase while taking the oral formulation. However, more patients in the oral TU group saw elevations from normal baseline total cholesterol to elevated cholesterol levels in the oral versus topical formulations (7.8% vs. 3.7%).

In terms of prostate health, there was a mean growth from baseline in prostate volume at 365 days, which was comparable between oral TU and T-gel (2.97 ± 9.83 cc and 1.81 ± 26.40 cc, respectively). In 1 year, patients with oral TU had an increase in median PSA of 0.15 ng/dL compared with patients on T-gel who had a rise of 0.1 ng/dL, which was not statistically different. None of the patients had a PSA that increased out of the normal range. Generally, a clinically significant change is defined as an increase of 1.4 ng/dL over a year, and these small increases do not come close to that value. However, it is interesting to note the trend of an increased PSA. The prostate saturation model can best explain the increase in PSA, without an increase in prostate cancer diagnoses.

At a low androgen concentration state, the prostate is more sensitive to an increase in serum testosterone, but this sensitivity decreases or plateaus, meaning that further increases in androgens in the bloodstream



elicit a minimal response from the prostate. Thus, this increase in PSA is most likely a normalization of low levels associated with the hypogonadal state over the first 6 months. Longer-term studies investigating PSA response to oral testosterone are definitely warranted. Patients on oral TU also did not have an overall increase in American Urologic Association Symptom Score (AUASS), and there was no change in the average AUASS category classification, indicating that even with a small increase in prostate volume, there was no change in symptom score of the patient.

Further, in the first Jatenzo trial, there was no significant effect on cardiovascular biomarkers, specifically high-sensitivity C-reactive protein, which is prognostic of cardiovascular disease risk. Average systolic blood pressure (SBP) increased by 5 and 3 mm Hg from baseline in patients who received oral TU versus T-gel respectively during the 365 days of the study. In both oral and topical groups, 31% and 32% of men with normal or elevated baseline blood pressure (BP) respectively saw an increase in BP to stage 1 or 2 hypertension (HTN) based on American Heart Association classifications. These results have an important implication, which is that in these patients receiving testosterone, there should be regular monitoring of BP, especially in those who have a previous diagnosis of HTN.

In the second Jatenzo trial^{29,30} comparing oral TU with T-gel (Axiron), 18.7% of patients in the oral TU group and 14.5% in the T-gel group had treatment-related adverse events. These adverse outcomes resulted in a discontinuation rate of 1.8% in both groups. The adverse events that happened the most often were increase in SBP, higher hematocrit values, and lower HDL values. The SBP increased at the end of the study compared with baseline in both treatment groups (oral TU, 2.8 ± 11.8 mm Hg; topical T, 1.8 ± 10.8 mm Hg).

Moreover, 28.9% of patients taking oral TU had a decrease in HDL from normal at first visit to below normal range at 1 year of follow-up, compared with 14.8% of patients taking T-gel. Of note, no patients had substantial changes in liver function tests in either group. Although two patients taking oral TU had a transient rise in liver function tests to values over two times the normal upper limit, these changes were not found to be attributable to any cause. There was a small and clinically insignificant decrease LDLc between both groups.^{29,30}

An open-label, multicenter study of Tlando indicated that after 24 days of administration, the drug was well tolerated with no treatment related side effects, no changes in liver parameters, and zero mortal-

ity.³¹ Another study demonstrated that the incidence of treatment-related adverse events from Tlando intake was 21%. The most common reported treatment-related events were weight increase (2.1%), headache (2.1%), and musculoskeletal pain (2.1%).

No patients died during the study. There was an average increase in hematocrit of $\sim 1\%$ and PSA increase of $0.2 \mu\text{g/L}$. There was also an increase in serum prolactin of 6.3%, which had no clinical implication. There was a pan reduction in lipid values with decreases of 6.9 mg/dL of HDL, 1.5 mg/dL of LDL, 8.9 mg/dL of triglycerides, and 10.6 mg/dL for total cholesterol.³² In addition, in a Phase 3 clinical study known as the Study of Oral Androgen Replacement (SOAR), 210 patients were randomized to Tlando and 105 patients were randomized to the active control, AndroGel for a total of 52 weeks.

The treatment-related side effects, which were all defined as mild or moderate, included upper tract respiratory infections (5.2% Tlando, 5.8% control), headache (0.5% for Tlando, 3.9% control), fatigue (2.4% for Tlando, 6.2% for control), and acne (2.9% for both groups). Cardiac adverse event profiles were consistent between treatment groups and included $<1\%$ of patients. Of note however, there was a 38% discontinuation rate of Tlando compared with 32% discontinuation rate from the control group.^{31,32}

The latest oral testosterone product Kyzatrex, recently approved by the FDA, was evaluated in an open-label 6-month phase 3 study. The safety and efficacy of the drug was evaluated in 155 men with TD starting at a dose of 200 mg twice a day. In the study, 4 (2.6%) patients experienced an adverse reaction of HTN with an average increase in SBP (measured in clinic) of 2.4 mm Hg at 6 months. Of note, 5 (3.2%) of the patients began taking antihypertensives; however, no patients with existing HTN had to add a medication. Although the BP increase is less than that compared with Jatenzo or Tlando, the drug still has a black box warning of increased BP. Other side effects include increased Hb in 7 (4.5%) of patients, headaches in 3 (1.9%) of patients, and mean PSA increase of 0.15 ng/dL at 6 months of follow-up. No patient had to discontinue the drug for these side effects.

Pharmacokinetics and Dose Response of Oral Testosterone

In the first and second Jatenzo trials,^{29,30} the starting dose of oral TU was 316 and 237 mg, respectively. Patients were able to have their dose adjusted based on their average serum testosterone concentrations



measured at regular intervals. The optimal time to obtain blood levels was determined through extensive simulation and modeling to define a specific time 4 to 6 h after oral TU of administration and sample amount that would consistently produce a T value with constant agreement with the true T C_{avg} and a concordance analysis that compared the consistency between the choice to increase or decrease the oral TU dose and the outcomes in achieving circulating levels in the eugonadal range.

While creating and adjusting the new oral TU medication, researchers realized the T can be enzymatically cleaved from TU, and it would happen during the regular processing of blood specimens drawn from hypogonadal men treated with oral TU. Therefore, there was an artificially higher increase in T values measured in the blood because of the constant production of T from the enzymatic cleavage. In the first Jatenzo trial, the values of T were overestimated by 20% due to the post-collection conversion of T from the TU during the processing of the blood sample.

Therefore, in the second Jatenzo trial, the blood that was collected was placed into Ferric Sodium Ethylene Diamine Tetraacetic Acid (NaF-EDTA) tubes placed on ice before centrifugation. This decreased the conversion of TU to T in blood samples in men treated with TU. Since this type of processing of blood would be difficult in clinical practice, an algorithm based on testosterone measurements in the NaF-EDTA plasma was created to help dose titrate for blood collected into a regular collection tube without the addition of any other chemicals.

The conversion factor for T concentration measured in NaF-EDTA plasma to an approximate equivalent T concentration measured 6 h after oral TU in serum required multiplying the NaF-EDTA plasma T concentration by 1.214. The reason that 6 h is utilized is the serum T concentration at this sample time after oral TU dosing is a reasonable approximation of C_{avg} .²³

The Jatenzo trials did reveal that after taking oral TU, the testosterone levels peaked at 4 h after AM and PM dosing. These peak levels were eugonadal in the second Jatenzo trial. In addition, the concordance between peak measurements on two different occasions was over 95%, meaning that oral TU dosing can be adjusted based on one blood test if not achieving adequate testosterone levels. It is important to note that ~72% of men taking oral TU who completed the study required an increased dose (32% to 316 mg and 40% to 396 mg TU, two times a day [BID]) to maintain eugonadal symptoms; 26% continued at their initial oral dose of 237 mg TU, BID. Only 3% were down-titrated (237 to 198 mg TU, BID).

Although Jatenzo starting dose is 237 mg BID, it can be titrated to lower or higher levels based on serum testosterone values. Jatenzo can be titrated down to a minimum of 158 mg BID and titrated up to a maximum of 396 mg BID. Kyzatrex's starting dose is 200 mg BID and can be titrated to a minimum dose of 100 mg BID and a maximum dose of 400 mg BID based on serum testosterone values. In contrast, Tlando is not titrated and the starting dose is 225 mg BID.

Primary and Secondary Efficacy of Oral Testosterone

In the first Jatenzo trial, after allowing for two dose adjustments, 83.6% of patients achieved 24-h average circulating concentrations of T in the mid-eugonadal range (300–1000 ng/dL) at 90 days and were sustained at 365 days with 85% of patients still maintaining normal testosterone values. The effectiveness was similar to topical testosterone, with 79.0% achieving eugonadal range of testosterone. The C_{avg} serum T on days 90 and 365 in trial I were 628 ± 343 and 524 ± 215 ng/dL, respectively.

In this trial however, 13% of patients had C_{max} levels ranging from 1800 to 2500 ng/dL and 13.7% had C_{max} levels greater than 2500 ng/dL, which was over the expected for a good clinical result. The definition for desired outcomes for testosterone maximal levels (C_{max}) was established by the FDA for the proportion of patients who are in the categories during any time of the trial. The cutoff values for T were that over 85% of patients had a $C_{max} < 1500$ ng/dL and less than 5% of patients had a C_{max} from 1800 to 2500 ng/dL. Lastly, a strict cutoff of no patients with C_{max} greater than 2500 ng/dL was established.

It is known that the T levels obtained during this first Jatenzo trial overshot the true circulating level of T during the time of the blood drawn by about 20% on average. After correction described by Ceponis et al³³ and Lachance et al,³⁴ as discussed earlier, the C_{max} levels in the second Jatenzo trial were found to be more closely aligned with desired targets. In the second Jatenzo trial, blood samples were placed in NaF-EDTA tubes to curtail *ex vivo* cleavage of TU to T. Currently, per the first Jatenzo trial, clinicians can utilize a conversion factor to determine the T levels measured in blood collected in plain tubes from men receiving oral TU. This accounts for the post-collection conversion of T from TU and capitulates as if the blood would be collected in an NaF-EDTA tube.

In the second Jatenzo trial, within 120 days, 87.3% of oral TU patients were able to attain normal



testosterone values and achieve improvement in hypogonadal symptoms. Like the previous trial, this was similar to the patients who received topical testosterone with 87.3% achieving eugonadal range of testosterone. The average NaF-EDTA plasma T_{Cavg} observed was 403 ± 128 ng/dL. In addition, 90.7% of patients had a maximum concentration less than 1500 ng/dL and only 2% of patients had a maximal concentration greater than 2500 ng/dL, which were all determined to be due to a contamination.

The issue with the contamination was deemed to be isolated, and thought to happen during specimen handling. However, moving forward, there may need to be further investigation on reasons for contamination when assessing testosterone levels.

In the SOAR study, the percentage of subjects who received 450 mg were split into two doses with C_{max} less than 1500 ng/dL and between 1800 and 2500 ng/dL were 85% and 7%, respectively. Moreover, the patients who received the same 450 mg were split into three doses and met all C_{max} thresholds as determined by dose values and determined by days administered.

In the preliminary study evaluating Kyzatrex (clinicaltrials.gov identifier: NCT04467697), 88% of patients (95% confidence interval [CI]: 82–93%) achieved an average NaF-EDTA plasma testosterone level of 222–800 ng/dL on day 90 (primary endpoint). Further, the percentage of patients who had a maximum total testosterone concentration threshold less than or equal to 1200 ng/dL, between 1400–200 ng/dL and greater than 2000 ng/dL, was 88%, 4%, and 0% respectively.

With regard to secondary efficacy, Legros et al,³⁵ in their randomized trial, followed patients for 12 months who took placebo or oral TU at three dose values of 80, 160, or 240 mg/day while evaluating for hypogonadal symptom improvement. The Aging Males Symptom score, which is a health care quality-of-life questionnaire encompassing psychological, somatic, and sexual symptoms, improved with all four groups. However, there was no statistically significant difference between placebo and oral TU. Sexual function score on the Derogatis Interview for Sexual Function–Self-Report scale improved in all the four groups, but there again was no statistical difference between the groups. Thus, although oral testosterone was well tolerated, it did not result in a clear improvement in sexual, somatic, or psychological symptoms.

In the two Jatenzo trials,^{29,30} the three secondary parameters that were assessed in the trials were psychosexual function measured using a Psychosexual Daily

Questionnaire (PDQ) score, body composition (lean and fat mass), and bone mineral density of the hip and spine. Oral TU was associated with a statistically significant improvement from baseline ($p < 0.0001$) in all PDQ responses at 4 months, including ability to achieve full erection, satisfaction with erection, weekly sexual activity with and without a partner, sexual energy, sexual desire, positive mood, and decrease of negative mood.

Oral testosterone was also associated with a greater increase in hip bone density compared with topical testosterone. Oral testosterone was also associated with an increase in lean body mass (of 3.16 ± 2.70 kg) and a decrease in fat mass (2.40 ± 3.64 kg) compared with topical testosterone after 1 year.

In the SOAR study, which was a comparison of Tlando and control,³⁶ mental and sexual function patient reported outcomes were compared from the end of the study to the baseline at the beginning of the study by using the PDQ and Short Form-36 surveys. The study demonstrated first that the dosing did not require a titration, which is in strict contrast from Jatenzo, in which the majority of patients required up titration. The patient reported outcomes that were improved included the sexual domain, less negative mood, more positive mood, increased sexual activity, and ability to have and maintain an erection. Most other sexual and mental patient-reported outcomes were comparable to T-gel.

In these three studies, the primary endpoints varied from 90 to 365 days, and they raised an important question in patients starting oral testosterone in clinical practice about time to response. In all the studies, patients required up to two dose adjustments to achieve a safe eugonadal state and secondary endpoints were taken at 1 year of follow-up. Thus, a 6-month trial of oral testosterone may be necessary to understand if it will benefit a patient. Further studies are needed to investigate the best way to follow-up these patients.

Summary and Conclusions

Although efficacy and demand of TTh through intramuscular injections, transdermal gels, and other formulations have been positive, the development of oral testosterone to add to the urologist's armamentarium has been a focus of much pharmacologic research over the past 20 years. As previous oral testosterone treatments, such as methyltestosterone, have been associated with significant hepatotoxicity and cardiac risk, focus has shifted to the utilization of TU as a potential oral regimen despite its previously documented issue with dietary influence.



Two new drugs, Jatenzo and Tlando, have been used in advanced drug delivery, such as SEDDS, to deliver a more stable and predictable dose-response curve regardless of diet. Although these drugs still exhibit adverse effects of polycythemia, changes in lipid composition, and mild increases in SBP, their magnitudes are comparable to the effects seen in approved topical TTh. Importantly, they also do not appear to pose any clinically significant increase in PSA, IPSS, or AUASS as compared with topical testosterone.

These new oral testosterone treatments appear able to deliver a sustainable increase in serum testosterone to the eugonadal range with a low risk for hypergonadal levels. Specifically, Jatenzo has shown that 87.3% of patients reach eugonadal testosterone ranges at 120 days, and 85% of Tlando patients reach a safe eugonadal range below 1500 ng/dL as well. They also exhibit promising improvements in psychosexual outcomes, with both demonstrating improvements in PDQ scores. In addition, Jatenzo appears to improve bone density and lean body mass as well.

However, oral T was associated with a small but statistically significant increase in SBP *versus* the topical T. This observation indicates the need for regular monitoring of BP in men receiving testosterone replacement therapy, particularly in those with existing HTN. Another limitation is these drugs are the first in their class and still need adequate insurance coverage in order for uptake to be enthusiastic for patients and providers.

In addition, given their relative novelty, no established recommendations exist for follow-up intervals and dosing adjustments for patients who do experience an alteration in their BP or cholesterol. According to both Jatenzo trials, 74% of patients required some dosing adjustment over the study period, but only with regard to their serum testosterone level. More study is necessary to determine a safety follow-up regimen and dose adjustment protocol for patients exhibiting unsafe rises in BP or total cholesterol level.

Finally, although an oral agent is likely a welcome alternative option to other formulations for many patients, medication adherence to a twice-daily dosing regimen (BID) may, nonetheless, present problems. Medication adherence in other chronic diseases has been studied frequently and shown an inverse relationship between medication adherence and dosing frequency. In a meta-analysis on cardiovascular oral medications, Weeda et al demonstrated only a 50.4% adherence rate for BID regimens versus 74.2% for once daily regimens.³⁷

Another meta-analysis on oral anti-retroviral therapy for HIV showed similar findings, with patients being approximately three times more likely to be adherent to once-daily regimens than more frequent regimens (3.07, 95% CI 1.80–5.23; $p < 0.001$).³⁸ Existing medication adherence rates for topical TTh have also been demonstrated to be as low as 15.4% at 1 year, however³⁹ In short, oral formulations may increase compliance, whereas twice-daily dosing requirements may somewhat limit this advantage.

In conclusion, through many advances in pharmacologic delivery systems and testosterone formulation, oral testosterone has become a promising new avenue for TTh. Oral T administration is convenient, and twice-daily dosing with food (i.e., with breakfast and dinner and without the need for a high fat content) is a simple regimen that should promote better patient adherence over transdermal and injectable T products that dominate use among hypogonadal men.

Both Jatenzo and Tlando provide a unique combination of convenience and ease of use with stable efficacious testosterone levels without the previous adverse effects of hepatotoxicity and increase cardiac risks. These drugs now represent an FDA-approved safe and effective oral testosterone agent for use in the United States.

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Abbreviations Used

ALT	= alanine aminotransferase
AST	= aspartate aminotransferase
AUASS	= American Urologic Association Symptom Score
BID	= two times a day
BP	= blood pressure
CI	= confidence interval
DHT	= dihydrotestosterone
FDA	= Food and Drug Administration
Hb	= hemoglobin
HDL	= high-density lipoprotein
HTN	= hypertension
IPSS	= international prostate symptom score
LDLc	= low-density lipoprotein cholesterol
NaF-EDTA	= Ferric Sodium Ethylene Diamine Tetraacetic Acid
PDQ	= Psychosexual Daily Questionnaire
PSA	= prostate specific antigen
SBP	= systolic blood pressure
SEDDS	= self-emulsifying drug delivery system
SOAR	= Study of Oral Androgen Replacement
T	= testosterone
TD	= testosterone deficiency
TTh	= testosterone therapy
TU	= testosterone undecanoate

