

REVIEW ARTICLE



JATENZO®: Challenges in the development of oral testosterone

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Testosterone therapy (TT) for the treatment of testosterone deficiency (TD) can be administered via several routes of administration. Due to a variety of concerns such as hepatotoxicity, an oral formulation has long been absent in the United States. Recently, JATENZO® (testosterone undecanoate) oral capsules was approved by the US FDA as an oral option for men suffering from TD. In this article, we will discuss the history and challenges in the development of a viable oral formulation of exogenous TT and examine how JATENZO® addresses these concerns.

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INTRODUCTION

Testosterone deficiency (TD) is defined as having low serum testosterone in addition to clinical signs and symptoms of low testosterone. As the primary male sex hormone, testosterone plays an integral role in homeostasis with low serum levels often manifesting as fatigue, low libido, poor muscle mass, and osteoporosis [1–5]. Testosterone therapy (TT) attempts to treat TD with the goals of improving symptoms and increasing serum testosterone to physiologic levels in the range of 450–600 ng/dL [6]. Multiple population-based studies have demonstrated an overall prevalence of TD of 6%, an estimate that significantly increases as men age [7–9]. A recent study also demonstrated that rates among young males and adolescents is rising over time, possibly indicating that this disease process may become even more common [10]. The burdensome symptoms and high prevalence among the general population render TD a commonly encountered problem for physicians.

The number of TT prescriptions has dramatically increased in the United States over time [11], which has sparked interest in developing easier to use, better-tolerated formulations. Physicians now have a plethora of options to offer patients with various routes of administration including intranasal, buccal, intramuscular and subcutaneous injections, transdermal gels and patches, and pellet implants, each of which has unique advantages and disadvantages (Table 1). Until recently, however, physicians lacked FDA-approved oral options to offer patients. Oral formulations of testosterone are convenient, easy to use, and avoid common problems of other TT such as painful injections, rashes, nasal symptoms, and transference to women and children. In other disease processes such as rheumatoid arthritis and multiple sclerosis, studies have suggested patients prefer oral medications over other formulations with improved adherence, quality of life, and patient satisfaction [12, 13].

Oral testosterone has long been sought after as a viable option for patients, yet has been difficult to obtain. Recently approved in 2019, JATENZO® (Clarus Therapeutics, Northbrook, IL, USA) is one of the only FDA-approved oral testosterone agents. Here, we review the history of the development of oral testosterone, the

current landscape of oral testosterone, and how JATENZO® addresses the concerns of prior oral options.

PHARMACOLOGY OF ORAL TESTOSTERONE THERAPY

Oral administration of exogenous TT historically has proven to be unsuccessful. Despite adequate absorption in the gastrointestinal system, this form of testosterone undergoes extensive first-pass metabolism through the liver, and thus requires ingestion of supra-physiological doses to attain therapeutic serum levels [14]. As a way to circumvent the liver metabolism pathway, research efforts to administer oral testosterone have taken two primary paths: alkylation of testosterone at the carbon-17 position and fatty-acid esterification of testosterone to create a testosterone ester (Fig. 1).

Alkylation of testosterone at carbon 17 α results in 17 α -methyltestosterone which allows for the ability to bypass the first metabolism in the liver. However, this modification has been linked to significant liver toxicity including cholestasis, hepatitis, and hepatic adenocarcinoma [15–17] and lowering of HDL cholesterol [18, 19]. The effects of methyltestosterone on liver function were first described in the 1940s, with studies of liver function demonstrating elevations in both serum direct and indirect bilirubin levels [19]. Foss and Simpson also described a case series of 42 patients who developed jaundice during methyltestosterone therapy [20]. They noted that the duration of therapy to the onset of jaundice ranged from 8 days to 10 months and withdrawal of methyltestosterone therapy resulted in remission of hepatocellular dysfunction within a few days to weeks. Recent work has focused on testing the effects of synthetic androgens on liver function utilizing animal models [21] and has corroborated prior work demonstrating direct increases in alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, and sorbitol dehydrogenase. Therefore, methyltestosterone is largely not recommended for the management of male hypogonadism [6, 22].

Esterification of testosterone at carbon 17 β yields testosterone esters such as testosterone cypionate, testosterone propionate,

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Table 1. Advantages and disadvantages of the various formulations of testosterone preparations.

Formulation	Advantages	Disadvantages
T enanthate/cypionate	Flexible, infrequent dosing	Injection discomfort Extreme peaks/valleys can cause fluctuating symptoms Higher risk of erythrocytosis
T undecanoate (injectable)	Long-acting (very infrequent dosing)	Injection discomfort Pulmonary oil microembolism
Transdermal patch	Easy application	Skin reaction Less efficacious than other therapies
Transdermal gels	Easy application Flexible dosing	Transference to partners/children Skin irritation
Transdermal axillary solution	Easy application	Transference to partners/children Skin irritation
Buccal	Easy application Discreet and convenient Quick reversal	Gingivitis/gum irritation
Subcutaneous pellets	Least frequent dosing	Requires office procedure under local anesthesia Risk of extrusion, infection, and hematoma
Nasal gel	Rapid absorption Avoids first-pass metabolism Quick reversal	Nasal irritation Requires multiple daily doses
Oral (testosterone undecanoate)	Convenient and easy to use Quick reversal	Hepatotoxicity and other GI side effects May require a fatty meal for absorption

and testosterone undecanoate (TU). Specifically for TU, this modification allows testosterone to be absorbed via the lymphatic system and therefore bypass liver degradation. An early oral TU formulation (ANDRIOL®) was approved for use in many countries but never in the United States. This formulation is heavily reliant on dietary fat intake as a means of increasing absorption and therefore leads to significant intra- and inter-patient variability in testosterone response [23, 24]. This results in the need to dose hypogonadal men with several capsules three or more times daily affecting compliance. Several studies have also demonstrated both gastrointestinal and liver adverse effects including severe cholestasis and jaundice [25, 26]. Consequently, these oral TU formulations have never been widely utilized to treat TD in the United States although they remain available in many countries.

SELF-EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS)

TU has been formulated in a unique self-emulsifying drug delivery system (SEDDS) that was initially evaluated in multi-institutional placebo-controlled studies in Europe [27]. SEDDS formulations combine hydrophilic and lipophilic components that enable the solubilization of lipophilic molecules such as TU in the gut (Fig. 2). This promotes intestinal lymphatic absorption of lipophilic testosterone esters, thereby reducing first-pass hepatic metabolism. Furthermore, this formulation allows absorption after oral ingestion with a typical meal as opposed to high-fat content meals required for prior formulations. Yin et al. showed that this TU with SEDDS resulted in adequate serum testosterone levels within the physiologic range after dosing with just TU 200 mg twice per day in most hypogonadal men [28].

JATENZO®

JATENZO®, an oral TU in SEDDS formulation, became the first oral testosterone ester pro-drug approved by US regulatory authorities in 2019, and only the second oral androgen approved for TT use in the United States, the last being methyltestosterone over 60 years ago.

This novel formulation of TU was recently studied in a long-term and short-term phase III trial to evaluate safety and efficacy [29, 30]. In this study, hypogonadal men (serum testosterone <300 ng/dl) aged 18–65 were recruited into a 365 day (trial I) or 105 days (trial II) randomized multicenter trial. Patients were randomized 1:1 to oral TU ($n = 161$) or T-gel ($n = 160$) in trial I, and 3:1 to oral TU, twice daily JATENZO® ($n = 166$) or a topical testosterone product [Axiron® ($n = 56$)] in trial II. Oral TU efficacy, defined as % of patients with eugonadal average testosterone concentrations, was 84 and 87% in trials I and II, respectively. Furthermore, oral TU significantly ($p < 0.0001$) improved all Psychosexual Daily Questionnaire parameters in trials I and II. In trial I, oral TU led to significant increases in lean mass and bone density as well as a significant decrease in fat after 365 days ($p < 0.0001$). In addition, testosterone levels were not significantly altered by the meal fat composition (between 15–45 g), indicating that JATENZO® absorption was not dependent on consumption with fatty meals as has been the case with other oral testosterone formulations [30].

Oral TU-associated adverse effects were consistent with other TT including elevated hematocrit (6.8%). Importantly, oral TU use in this study was not associated with liver toxicity in either the long-term or short-term study, in contrast to methyltestosterone which has been historically associated with potentially serious hepatotoxicity. However, oral TU patients experienced a greater number of mild gastrointestinal adverse effects (e.g., nausea, diarrhea, burping) relative to topical testosterone gel therapy. The authors of this clinical trial note that these gastrointestinal-related side effects were transient, minor in severity, and did not result in patients discontinuing oral TU. Oral TU was also associated with a small but statistically significant increase in systolic blood pressure versus topical testosterone (mean increase of 3–5 mmHg). Therefore, this finding indicates the need for routine monitoring of blood pressure in men receiving this form of oral TU, particularly in those with existing hypertension. JATENZO® contains a boxed warning on its labeling stating that the drug can cause blood pressure to rise, increasing the risk of heart attack, stroke, and cardiovascular death. Although a significant departure from

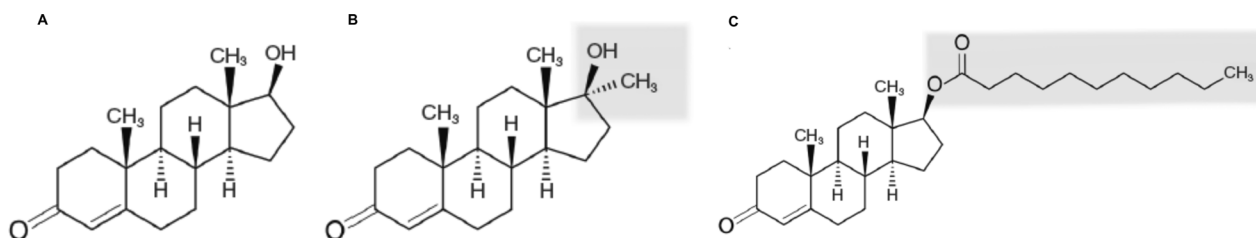


Fig. 1 Molecular structure of testosterone with modifications to improve tolerability of oral formulations. **A** Testosterone **B** 17 α -methyltestosterone **C** Testosterone undecanoate.

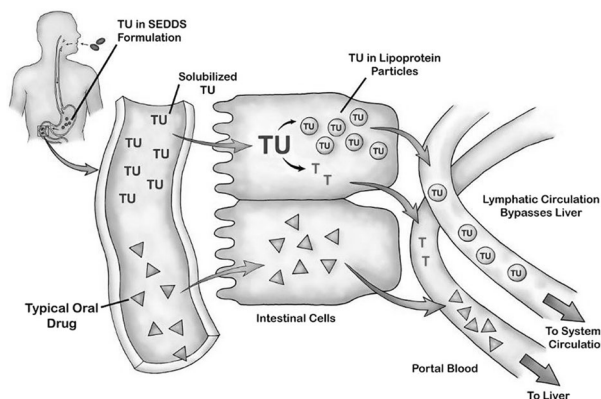


Fig. 2 Pictorial representation of TU lymphatic absorption after oral delivery in SEDDS formulation. Reprinted from Swerdloff et al., 2020 [29] with permission from SAGE Publishing.

other TT FDA labels, this may be a result of stricter FDA requirements. After an FDA Advisory Committee meeting in 2014 discussing the cardiovascular effects of TT, the FDA has required all commercial TT manufacturers to conduct ambulatory blood pressure studies during clinical studies. Notably, both TT options that were FDA approved after 2015 carry this boxed warning (JATENZO® and XYOSTED®).

JATENZO® provides a unique combination of convenience and ease of use with stable efficacious testosterone levels. Because it is the first in its class, we believe, with adequate insurance coverage, uptake will be enthusiastic for both patients and providers in the United States.

CONCLUSIONS

Until the recent approval of JATENZO®, oral testosterone has been absent from the landscape of TT in the United States. The development of a viable oral testosterone agent has been plagued by hepatotoxicity and poor, variable absorption but now has been overcome with a unique SEDDS. JATENZO® bypasses first-pass liver metabolism and provides consistent testosterone levels, and now represents a FDA-approved safe and effective oral testosterone agent for use in the United States.

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CONFLICT OF INTEREST

The authors declare no competing interests.

ADDITIONAL INFORMATION

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