

# Oral testosterone therapy: past, present, and future

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## Abstract

**Introduction:** Testosterone replacement therapy (TRT) remains a commonly utilized treatment for men with testosterone deficiency (TD). Despite the recent FDA approval of new oral TRT medications, concerns remain regarding their efficacy and safety, and prescription rates for these medications have decreased compared to those for TD medications with other routes of administration.

**Objective:** In this study we sought to investigate the efficacy and safety of oral testosterone undecanoate (oTU), a new oral TRT medication.

**Methods:** A comprehensive review of the literature was performed using the Medline, EMBASE, and Cochrane Library databases; 1269 articles were identified, with 44 articles included in the final review and 12 used to perform meta-analyses to investigate the change in serum total testosterone (TT) and risk of adverse effects following oral testosterone undecanoate (oTU) use. Articles were also reviewed to investigate the reported effects of oTU on body composition, liver function, hematologic assays, lipid profiles, hormone assays, prostate growth, hypertension, and symptoms of TD.

**Results:** Across placebo-controlled randomized trials, there was no significant increase in TT for those receiving oTU vs placebo (mean difference,  $-0.26$  [95% CI,  $-1.26$  to  $0.73$ ]). On subanalysis, when eugonadal participants received oTU, a significant decrease in TT was demonstrated (mean difference  $-0.86$  [95% CI,  $-1.28$  to  $0.43$ ]). When participants who were hypogonadal at baseline received oTU, a significant increase in TT compared to placebo was seen (mean difference  $1.25$  [95% CI,  $0.22$ - $2.29$ ]). There was no significant risk of adverse effects (RR,  $-0.03$  [95% CI,  $-0.08$  to  $0.03$ ]) or serious adverse effects (RR,  $0.15$  [95% CI,  $-0.66$  to  $0.96$ ]) in the oTU groups compared to placebo.

**Conclusion:** oTU was found to be well tolerated in hypogonadal patients, resulting in improved testosterone levels, height velocity, and sexual symptoms, without significant hepatotoxicity, prostatic enlargement, or worsening hypertension. There was no consensus regarding the effect of oTU on lean and fat mass percentages, hematologic assays, lipid profiles, mood, and general well-being.

**Keywords:** hypogonadism; testosterone; hormone replacement therapy; testosterone undecanoate.

## Introduction

Testosterone replacement therapy (TRT) remains a commonly used treatment option for men with testosterone deficiency (TD), with additional trials investigating the use of TRT in boys with congenital delay of growth and puberty (CDGP). Treatment with TRT has been associated with improvements in libido, erectile function, body composition, and mood, with possible improvements described for insulin sensitivity, cognition, and overall quality of life.<sup>1-7</sup> The popularity of TRT has grown, with rapidly increasing prescription rates noted within recent decades<sup>8,9</sup> and ongoing clinical trials featuring varying formulations of TRT. Recent literature suggests that injectable and topical formulations have become more commonplace within the United States, United Kingdom, and Canada, while prescription rates for oral formulations have steadily declined.<sup>8-10</sup> However, given recent trends in the fields of oncology, endocrinology, and rheumatology demonstrating that patients prefer oral therapies over other regimens,<sup>11-13</sup> the decreasing prescription rate of oral TRT raises questions. To further investigate the safety and efficacy of oral TRT, a literature review was performed to examine the history of oral TRT, its current place within urology and endocrinology guidelines, and recent trials featuring oral TRT.

## History of oral testosterone

The first recorded use of exogenous testosterone is attributed to Brown-Séquard, who in 1889 experimented by self-

injecting a mixture of testes, testicular vein blood, and semen. In his later report, he described improved energy, strength, and urinary function.<sup>14</sup> While some investigators would go on to experiment with testis transplantation afterward, the next major advance in TRT was not made until 1935. At this time, Ruzica and Butenandt reported the first cases of testosterone synthesis in the form of  $17\alpha$ -methyl-testosterone (MT).<sup>15</sup> Soon after the isolation and synthesis of MT, various groups sought to determine the effectiveness of MT as a treatment for TD, including Miescher and Tschopp, who performed trials in hypogonadal animal models,<sup>16</sup> and later Foss and Spence, who performed trials in hypogonadal men and children.<sup>16,17</sup>

Shortly thereafter, reports of cases of hepatotoxicity associated with MT use were published, initially with descriptions by Werner and Werner et al of 3 patients who developed jaundice and hepatitis following oral administration of MT.<sup>18,19</sup> As hepatotoxicity was repeatedly described in larger patient trials,<sup>20,21</sup> the use of oral TRT as a treatment for TD progressively fell out of favor until the development and application of oral testosterone undecanoate (oTU).

Beginning in the 1970s, trials featuring oTU as a treatment for TD were reported in the literature. Initial trials in animal models<sup>22</sup> and men with hypogonadism<sup>23</sup> demonstrated increasing serum testosterone levels following administration, without levels of hepatotoxicity similar to those seen with MT. As described by Horst et al., the improved absorption and reduced hepatotoxicity of oTU were attributed to its

absorption through the intestinal lymphatic system, thereby allowing the medication to avoid first-pass metabolism.<sup>24</sup> Following these discoveries, the prescription of oTU as a treatment for TD gained in popularity, with oral formulations comprising more than 70% of TRT prescribed in the 1990s.<sup>25</sup>

Despite the relative benefits of oTU over prior formulations of oral TRT, concerns regarding its bioavailability became apparent. In multiple trials, the absorption of oTU to consistently therapeutic levels was found to be partially dependent on the intake of multiple daily doses, often taken alongside meals with up to 19 g of fat.<sup>26-28</sup> In part due to these absorption concerns, as well as the development of newer transdermal patch, topical gel, and subcutaneous pellet formulations, the popularity of oral TRT once again decreased.<sup>8-10</sup>

### Oral testosterone within current guidelines

Current urological and endocrinological guidelines reveal the current place of oral TRT within the management of TD, the most common indication for TRT. Guidelines from the European Academy of Andrology (2020),<sup>29</sup> Society for Endocrinology (2021),<sup>30</sup> and British Society for Sexual Medicine (2017)<sup>31</sup> include explicit recommendations against the use of oral TRT. These societies have noted that their recommendations stem from the variability in absorption of oral agents and the need for simultaneous food intake to ensure adequate absorption. While the American Urological Association 2018 guidelines<sup>32</sup> similarly recommend against the use of oral TRT, this recommendation is specifically aimed at the use of MT in relation to its hepatotoxicity; no mention of oTU is made throughout these latter guidelines.

Alternatively, guidelines including those from the International Society for Sexual Medicine (2015),<sup>33</sup> European Association of Urology (2019),<sup>34</sup> Endocrine Society (2018),<sup>35</sup> and the fourth International Consultation on Sexual Medicine (2015)<sup>36</sup> do not include recommendations for or against the use of oTU. These guidelines instead note the relative benefits, including the convenience of administration and low side-effect profile, and disadvantages, including variability in absorption and dependency on fat intake, of oral TRT. Similarly, the guidelines of the Canadian Men's Health Foundation (2015)<sup>37</sup> recommend neither for nor against the use of oral TRT, but note that the decision to initiate TRT, including the decision of which agent to use, should be made following a conversation with the practitioner and patient regarding the risks and benefits of each available option.

While the above guidelines reference individual trials relating to the use of oTU, reported systematic reviews and meta-analyses have rarely specifically pertained to the use of oTU. Furthermore, while multiple reviews and meta-analyses exist within the current literature, the majority do not include a sufficient number of trials examining the effects of oTU, such that meaningful conclusions regarding its effects can be made. As such, we performed a systematic review regarding the use of oTU and its various impacts.

### Methods

A systematic review was performed using the Medline (PubMed), EMBASE, and Cochrane Library databases. Articles published through April 2022 were searched using

the keywords, “Oral Testosterone” and “Testosterone Replacement Therapy”, “Testosterone Deficiency”, or “Hypogonadism”. Articles were included if they featured a randomized controlled trial (RCT), single-arm trial, or cohort study that evaluated the use of oTU in male patients. The main outcomes of interest were changes in total testosterone (TT), free testosterone (fT), lipid profile, liver enzymes, hematologic assays, prostate-specific antigen (PSA), blood pressure, body composition, and symptomatic response. The titles and abstracts of the retrieved citations were reviewed by 3 investigators (JAM, TTN, CL) and kept when confirmed to meet the inclusion criteria. Articles were then reviewed in full to assess for the risk of bias and for data extraction.

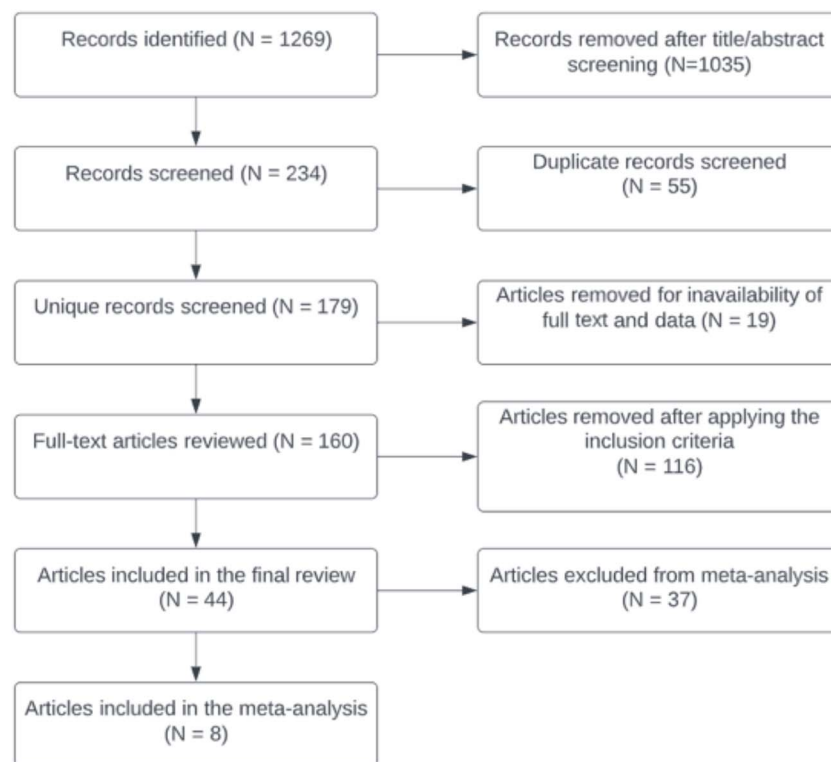
To assess the risk of adverse effects with oTU, a separate search was performed using the same keywords and databases listed above. For this search, the inclusion criteria were as follows: (1) inclusion of an oTU treatment group, (2) inclusion of a placebo group, (3) data on the number of adverse effects experienced by each group, (4) inclusion of male patients, and (5) an RCT design. Adverse effects were defined as recorded negative medical outcomes, including symptoms or changes in laboratory values, which were not necessarily related to the treatment but were recorded during the study period. Serious adverse effects were those resulting in death, life-threatening illness, hospitalization, incapacity, or disability. Articles included for this analysis were reviewed for risk of bias using the Cochrane Collaboration's risk of bias tool and excluded if the risk of bias was high.<sup>38</sup>

Pairwise meta-analyses of RCTs were performed to address the questions of whether oTU compared to placebo led to increased total serum testosterone and adverse effects. Studies were included from the searches detailed above if they were placebo controlled and included data related to adverse effects, serious adverse effects, or change in total serum testosterone. A subanalysis was performed to investigate if oTU increased total serum testosterone in all participants versus those with hypogonadism alone compared to placebo. The outcomes of the analyses investigating adverse effects were reported as the log of the risk ratio with 95% CIs by use of the random-effects model and Hunter-Schmidt method, with the analysis related to the change in total serum testosterone reporting the mean difference. Results were considered statistically significant when the 2-sided *P* value was <.05. Heterogeneity was calculated using *I*<sup>2</sup> statistics, with *I*<sup>2</sup> > 50% considered to represent substantial heterogeneity. Statistics were performed using the Stata 16 software.<sup>39</sup>

### Results

#### Search results

The results of the search strategy are summarized in Figure 1. After the inclusion criteria were applied, the search yielded 44 articles, consisting of 28 RCT's, 14 single-arm studies, and 2 retrospective cohort studies. Of the 28 RCTs, 22 included a placebo-controlled group, while the remaining 8 studies relied on alternative androgen replacement regimens as comparisons. While the majority of studies included men who had been diagnosed with hypogonadism (*n* = 24), other notable populations included men with symptoms of hypogonadism and low-normal or normal testosterone levels (*n* = 10), boys with CDGP (*n* = 5), men with other comorbidities (*n* = 3), elderly men without comorbidities (*n* = 1), and



**Figure 1.** Flow diagram showing study selection.

boys with other comorbidities ( $n=1$ ). The characteristics of the included studies are further described in Table 1. Twelve placebo-controlled randomized trials were included for one or both meta-analyses; their risk of bias is described below (Figure 2).

### Changes in testosterone

The results of the meta-analysis performed on placebo-controlled trials to investigate changes in total serum testosterone for those taking oTU are summarized in Figure 3. Overall, there was no significant increase in total serum testosterone for those receiving oTU vs placebo (mean difference  $-0.26$  [95% CI,  $-1.26$  to  $0.73$ ]). On subanalysis, when eugonadal participants received oTU, a significant decrease in total serum testosterone was demonstrated (mean difference  $-0.86$  [95% CI,  $-1.28$  to  $0.43$ ]). However, when participants who were hypogonadal at baseline received oTU compared to placebo, a significant increase in total serum testosterone was seen (mean difference  $1.25$  [95% CI,  $0.22$ – $2.29$ ]).

Fifteen additional studies examined changes in total serum testosterone following oTU administration, but either were not placebo controlled, or did not provide sufficient raw data to be included within the meta-analysis. In a study by Franchimont et al., hypogonadal men treated with oTU experienced a significant and sustained elevation in mean TT (from  $1.20$  to  $4.34$  ng/mL,  $P < .0004$ ).<sup>48</sup> In a study by Franchi et al., patients receiving oTU for a period of 243 days experienced significantly increased levels of TT as early as 3 weeks after beginning treatment ( $3.92 \pm 1.69$  to  $11.65 \pm 2.46$  nmol/L,  $P < .05$ ).<sup>49</sup> In their 2021 single-arm trial, DelConte et al. found that up to 80% of patients receiving oTU had average TT concentrations within the eugonadal range. For this cohort, the mean TT concentration was  $476$

$\pm 174$  ng/dL.<sup>44</sup> Similar data were presented by Yin et al., who noted that 86% of hypogonadal men treated with oTU had average TT concentrations within the eugonadal range, with an average serum TT level of  $17.9 \pm 2.0$  nmol/L following treatment. Of this cohort, 53.3% of patients had peak testosterone concentrations under the upper limit of normal.<sup>46</sup> In the final single-arm trial, Hong et al. recorded significantly increased TT levels for participants receiving oTU ( $2.13 \pm 1.20$  to  $6.04 \pm 3.08$  ng/mL,  $P < .005$ ).<sup>51</sup>

Five additional RCT studies were performed to examine hypogonadal men. In the first of these studies, Schubert et al. randomly assigned hypogonadal men to receive mesterolone, oTU, or injectable testosterone formulations for a period of 6 months. In patients receiving oTU, a significant increase in average TT levels was seen ( $2.9 \pm 0.4$  to  $5.7 \pm 0.3$  nmol/L,  $P < .01$ ). Notably however, although testosterone levels were found to be significantly elevated, Schubert et al. found that on average the patients did not reach eugonadal levels of TT.<sup>76</sup> The trials conducted by Swerdloff et al. and Swerdloff and Dudley had similar results, with between 84% and 94.8% of men who received oTU found to have average concentrations of TT within the eugonadal range. Within these 2 studies, between 4.0% and 27% of participants were noted to have transient peak TT concentrations greater than 1800 ng/dL, which was established in these studies to represent a supratherapeutic level of testosterone replacement.<sup>74,75</sup> While all trials in which the use of oTU in hypogonadal men was examined noted statistically significant increases in TT levels following treatment, results were mixed in those trials with alternative populations. In the 1993 cross-over trial conducted by Wu et al. in men with coronary heart disease, treatment with oTU compared with placebo was associated with significantly increased TT ( $16.79 \pm 6.63$  nmol/L to  $26.68 \pm 15.62$  nmol/L,  $P < .001$ ).<sup>60</sup>

**Table 1.** Study characteristics of trials involving the treatment of male patients with oral testosterone undecanoate.

Study	Subjects	Design	Treatment groups	Participants included, <i>n</i>	Duration	Variables assessed
Yang et al. (2012) <sup>40</sup>	Men with hypogonadotropic hypogonadism; repeated TT <2.49 ng/mL and low or normal FSH and LH	Retrospective cohort study	oTU (40-120 mg/d) intramuscular hCG (2000 IU every 3 days) combination hCG/hMG (2000 IU/75 IU every 3 days)	84	6 mos	Virilization, testicular volume, semen analysis
Conway et al. (1988) <sup>41</sup>	Men with hypogonadism	Randomized cross-over trial	oTU (120 mg BID) intramuscular testosterone esters (250 mg every 2 weeks) subcutaneous testosterone pellets (6 × 100 mg, once)	15	1 mo	Hormone assays, hematologic assays, biochemical assays, subjective clinical response, adverse effects
Luisi et al. (1980) <sup>42</sup>	Men with hypogonadism; TT <2.00 ng/mL	Randomized, double-blind trial	oTU (120 mg/d) oral mesterolone (150 mg/d)	12	1 mo	Benkert's Sexual Question Form, Koch's Mood Questionnaire
White et al. (2021) <sup>43</sup>	Men with hypogonadism documented prior to age 65 years; repeated TT <300 ng/dL	Multicenter, single-arm study	oTU (22.5 mg BID)	138	4 mos	Blood pressure, heart rate, hematologic assays, adverse effects
DelConte et al. (2021) <sup>44</sup>	Men with hypogonadism; repeated TT <300 ng/dL	Multicenter, single-arm study	oTU (22.5 mg BID)	95	1 mo	Hormone assays, hematologic assays, biochemical assays, PSA, adverse effects
Morales et al. (1997) <sup>45</sup>	Men with hypogonadism; repeated TT <11.5 nmol/L	Single-arm study	oTU (40 mg TID)	23	2 mos	Hormone assays, subjective clinical response, adverse effects
Yin et al. (2013) <sup>46</sup>	Men with hypogonadism; repeated TT <300 ng/dL	Single-arm study	oTU (SEDDS formulation) (200 mg/d)	15	1 mo	Hormone, biochemical, hematologic assays, adverse effects
Abdelmassih et al. (1992) <sup>47</sup>	Men with infertility	Single-arm study	oTU (40 mg TID)	11	3 mos	Fertility, semen analysis
Franchimont et al. (1978) <sup>48</sup>	Men with hypogonadism	Single-arm study	oTU (40-80 mg TID)	10	9 wk.	Hormone assays, subjective clinical response
Franchi et al. (1978) <sup>49</sup>	Men with hypogonadism	Single-arm study	oTU (40-160 mg/d)	34	243 d	Hormone assays, subjective clinical response, biochemical assays
Li et al. (2002) <sup>50</sup>	Men with partial androgen deficiency in the aging male	Single-arm study	oTU (40 mg TID × 2 weeks, 40 mg BID × 6 weeks)	86	2 mos	Hormone assays, body composition, blood pressure, biochemical assays, PSA
Hong et al. (2002) <sup>51</sup>	Men with PADAM; repeated TT <2.8 ng/mL or fT <13 pg/mL	Single-arm study	oTU (80 mg BID × 3 weeks, 80 mg qD × 9 weeks)	28	3 mos	Hormone assays, Korean Andropause Questionnaire, IIEF, PSA
Boyanov et al. (2003) <sup>52</sup>	Men with type 2 diabetes and symptoms of andropause or erectile dysfunction; TT <15.1 nmol/L	Randomized, no-treatment controlled study	oTU (80 mg qAM, 40 mg qPM) no treatment	24	3 mos	Hormone assays, biochemical assays, body composition, blood pressure, PADAM questionnaire, IIEF
Maisey et al. (1981) <sup>53</sup>	Men with testicular insufficiency	Single-arm study	oTU (80-160 mg/d)	76	9 wks.	Hormone assays, biochemical assays, subjective clinical response
Gooren et al. (1994) <sup>54</sup>	Men with hypogonadism	Single-arm study	oTU (80-200 mg/d)	33	10 years	Hormone assays, biochemical assays, PSA, urinary function
White et al. (2021) <sup>55</sup>	Men with hypogonadism; repeated TT ≤ 281 ng/dL	Multicenter, single-arm study	oTU (200 mg BID)	125	180 d	Hematologic assays, blood pressure, body composition, adverse effects
Zhang et al. (2012) <sup>56</sup>	Men with symptoms of testosterone deficiency; TT <230 ng/dL or fT <22.5 pmol/L	Single-blinded, randomized, placebo-controlled trial	oTU (120-160 mg/d) Placebo	80	6 mos	Hormone assays, ADAM questionnaire, AMS scale, HADS, PSS, SF-12, adverse effects
Pusch (1989) <sup>57</sup>	Men with sperm density >40 mil/mL; normal or low normal TT concentrations; FSH, LH within normal ranges	Double-blinded, randomized, placebo-controlled trial	oTU (40 mg TID) placebo	30	3 mos	Hormone assays, biochemical assays, fertility, semen analysis

(Continued)

Table 1. Continued

Study	Subjects	Design	Treatment groups	Participants included, <i>n</i>	Duration	Variables assessed
Benkert et al. (1979) <sup>58</sup>	Men with erectile dysfunction	Double-blinded, randomized, placebo-controlled trial	oTU (80 mg qAM, 40 mg qPM) placebo	13	2 mos	Hormone assays, HDRS
Høst et al. (2019) <sup>59</sup>	Men with Klinefelter syndrome	Double-blinded, randomized, placebo-controlled, cross-over study	oTU (80 mg BID) Placebo	13	6 mos	Hormone assays, hematologic assays, biochemical assays, blood pressure, body composition
Wu et al. (1993) <sup>60</sup>	Men with coronary heart disease	Randomized, placebo-controlled, cross-over study	oTU (120 mg/d × 2 weeks, 40 mg/d × 2 weeks) placebo	62	1 mo	Hormone assays, Cardiac function, Subjective clinical response, Adverse effects
Uyanik et al. (1996) <sup>61</sup>	Elderly men	Randomized, placebo-controlled, cross-over study	oTU (120 mg/d) placebo	17	2 mos	Hormone assays, biochemical assays, body composition, blood pressure, side effects
Haren et al. (2004) <sup>62</sup>	Men with symptoms of hypogonadism; free testosterone index between 0.3- 0.5 and TT > 8 nmol/L	Double-blinded, randomized, placebo-controlled trial	oTU (80 mg BID) placebo	32	12 mos	Hormone assays, ADAM questionnaire
Wittert et al. (2003) <sup>63</sup>	Men with symptoms of hypogonadism; free testosterone index between 0.3- 0.5 and TT > 8 nmol/L	Double-blinded, randomized, placebo-controlled trial	oTU (80 mg BID) placebo	39	12 mos	Hormone assays, biochemical assays, ADAM questionnaire, adverse events
Meuleman et al. (2015) <sup>64</sup>	Men with hypogonadism; FT < 0.26 nmol/L	Multicenter, double-blinded, randomized placebo-controlled trial	oTU (80 mg/d) oTU (160 mg/d) oTU (240 mg/d) placebo	237	12 mos	Body composition, PSA, IPSS
Skakkebaek et al. (1981) <sup>65</sup>	Men with hypogonadism	Double-blinded, randomized, placebo-controlled, cross-over trial	oTU (160 mg/d) placebo	10	2 mos	Hormone assays, Subjective clinical improvement
Holmång et al. (1993) <sup>66</sup>	Men with slight or moderate obesity	Double-blinded, randomized, placebo-controlled, cross-over trial	oTU (80 mg BID) placebo	11	8 mos	Hormone assays, PSA, Subjective clinical improvement
Bancroft et al. (1983) <sup>67</sup>	Men with hypogonadism; TT < 300 ng/dL	Randomized, placebo-controlled, cross-over trial	oTU (160-240 mg/d) placebo	8	2 mos	Hormonal assays, subjective clinical response, erectile response
Cavallini et al. (2004) <sup>68</sup>	Men with symptoms of partial androgen deficiency in the aging male	Double-blinded, randomized, placebo-controlled trial	oTU (160 mg/d) propionyl-L-carnitine with acetyl-L-carnitine (2-2 g/d) placebo	40	6 mos	Hormonal assays, PSA, erectile response, IIEF, HDRS, adverse effects
Park et al. (2003) <sup>69</sup>	Men with symptoms of hypogonadism; TT < 400 ng/mL	Single-blind, randomized, placebo-controlled trial	oTU (80 mg BID) placebo	33	3 mos	Hormone assays, biochemical assays, PSA, ADAM questionnaire, PNUH QoL scale
Emmett-Vonk et al. (2008) <sup>70</sup>	Men with TT < 13.7 nmol/L (50th percentile)	Double-blinded, randomized, placebo-controlled trial	oTU (80 mg BID) placebo	113	6 mos	Hormone assays, hematologic assays, biochemical assays, body composition, blood pressure, SF-36, SHAQ, cognitive testing, adverse effects

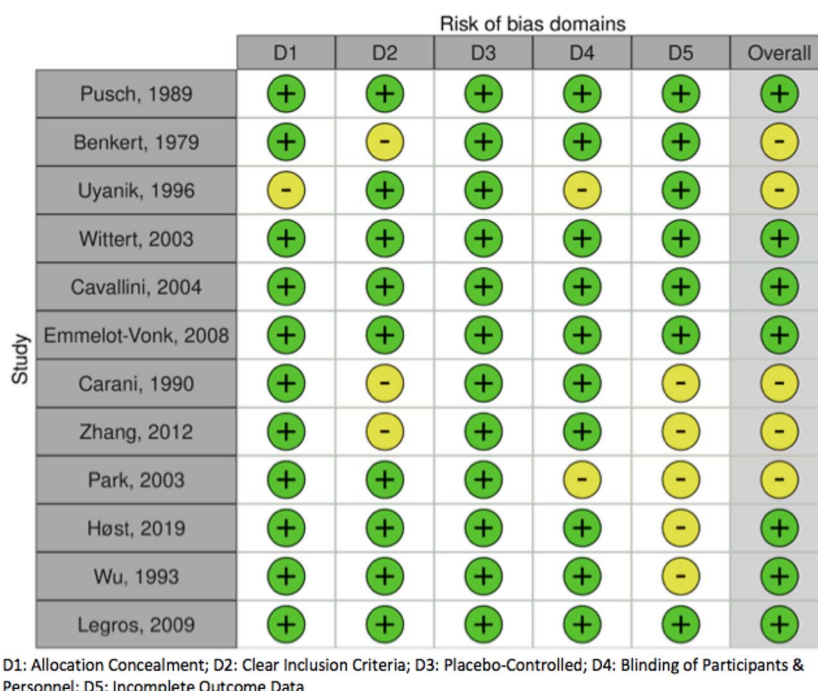
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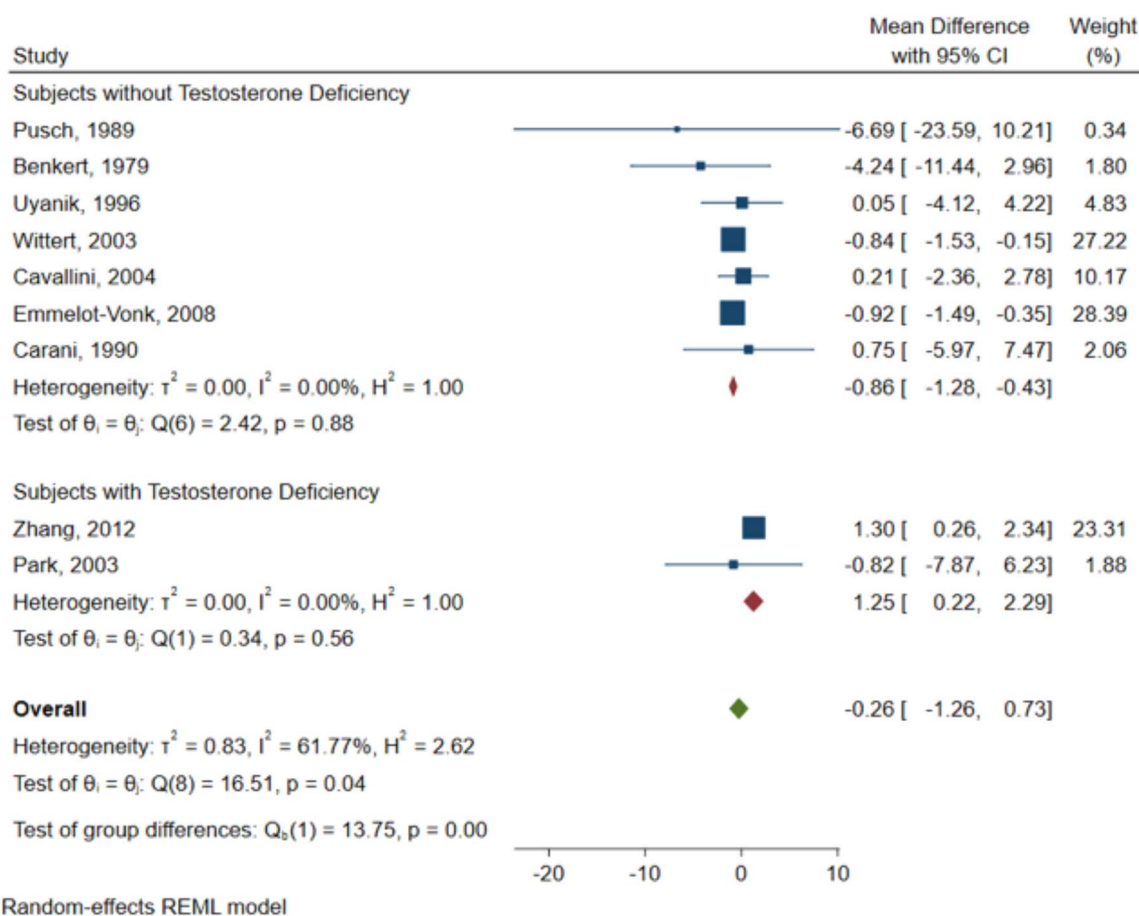
Table 1. Continued

Study	Subjects	Design	Treatment groups	Participants included, <i>n</i>	Duration	Variables assessed
Aversa et al. (2010) <sup>71</sup>	Men with metabolic syndrome or type 2 diabetes mellitus; repeated TT <3.20 ng/mL or FT <10 pg/mL	Double-blinded, randomized, placebo-controlled trial	oTU (80 mg BID) placebo intramuscular testosterone undecanoate (1000 mg every 12 weeks)	10	6 mos	Hormone assays, Hematologic assays, biochemical assays, PSA, IIEF, IPSS, AMS scale, adverse effects
Legros et al. (2009) <sup>72</sup>	Men with symptoms of partial androgen deficiency in aging males; repeated FT <0.26 nmol/L	Multicenter, double-blinded, randomized placebo-controlled trial	oTU (80 mg qD) oTU (80 mg BID) oTU (80 mg TID) placebo	237	12 mos	DISF-SR scale, AMS scale, SF-36, adverse effects
Carani et al. (1990) <sup>73</sup>	Men with TT at the lower range of normal and a low TT/LH ratio	Double-blinded, randomized, placebo-controlled, cross-over trial	oTU (80 mg BID) placebo	14	6 wk.	Hormone assays, subjective clinical response
Swerdlow et al. (2020) <sup>74</sup>	Men with hypogonadism; repeated TT <300 ng/dL	Randomized controlled trial	oTU (158-396 mg BID) Topical Testosterone Solution (30 mg-120 mg/d)	166	3 mos	Hormone assays, hematologic assays, biochemical assays, PSA, blood pressure, subjective clinical response, adverse effects
Swerdlow and Dudley (2020) <sup>75</sup>	Men with hypogonadism; repeated TT <300 ng/dL	Randomized controlled trial	oTU (316 mg BID, titrated) topical testosterone solution (30-120 mg/d)	161	12 mos	Hormone assays, hematologic assays, biochemical assays, adverse effects, PSA, IPSS, PDQ
Schubert et al. (2003) <sup>76</sup>	Men with hypogonadism; repeated TT <3.6 nmol/L	Randomized control trial	oTU (160 mg/d) intramuscular testosterone enanthate (250 mg every 3 weeks) subcutaneous testosterone pellet (1200 mg × 1) mesterolone (100 mg/d)	13	6 mos	Hormone assays, body composition
Chapman et al. (2009) <sup>77</sup>	Men and women diagnosed as being malnourished	Randomized, placebo-controlled trial	oTU (80 mg BID) with and without nutritional supplement placebo with and without nutritional supplement	11	12 mos	Hospitalizations, hormone assays, hematologic assays, Bbiochemical assays, SF-36, IPSS, body composition, muscular strength
Albanese et al. (1994) <sup>78</sup>	Male children with constitutional delay in growth and puberty	Randomized controlled trial	oTU (40 mg qD) oxandrolone (2.5 mg qD)	17	3 mos	Body composition, adverse effects
Butler et al. (1992) <sup>79</sup>	Male children with constitutional delay in growth and puberty	Single-arm study	oTU (40 mg qD)	4	6 mos	Hormone assays, induction of puberty, body composition
Liu et al. (2021) <sup>80</sup>	Male children with 5-alpha-reductase deficiency and micropenis with concurrent hypospadias	Single-arm study	oTU (2-3 mg/(kg*d))	90	3-6 mos	Penile length, hormone assays, biochemical assays, body composition, adverse effects
Lawaetz et al. (2015) <sup>81</sup>	Male children with constitutional delay in growth and puberty	Retrospective cohort study	oTU (40 mg qD, 80 mg BID) no treatment	96	0.8 yrs	Hormone assays, body composition, induction of puberty
Gregory et al. (1992) <sup>82</sup>	Male children with constitutional delay in growth and puberty	Double-blinded, randomized, placebo-controlled trial	oTU (40 mg/d) placebo	10	3 mos	Body composition, muscular strength
Brown et al. (1995) <sup>83</sup>	Male children with constitutional delay in growth and puberty	Double-blinded, randomized, placebo-controlled trial	oTU (20 mg/d) placebo	11	6 mos	Hormone assays, biochemical assays, body composition

AMS, Aging Males' Symptoms scale; BID, twice daily; DISF-SR, Derogatis Interview for Sexual Functioning-Self Report; FSH, follicle-stimulating hormone; FT, free testosterone; ; HADS, Hospital Anxiety and Depression Scale; HDRS, Hamilton Depression Rating Scale; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; LH, luteinizing hormone; oTU, oral testosterone undecanoate; PADAM, partial androgen deficiency in the aging male; PDQ, Psychosexual Daily Questionnaire; PNUH QoL, Pusan National University Hospital Quality of Life Scale; PSA, prostate-specific antigen; PSS, Perceived Stress Scale; qAM, administered each morning; qD, once daily; qPM, administered each night; SEDDS, self-emulsifying drug delivery system; SF-12, 12-Item Short Form Survey; SF-36, 36-Item Short Form Survey; SHAQ, Stanford Health Assessment Questionnaire; TID, 3 times daily; TT, total testosterone.



**Figure 2.** Assessment for the risk of bias in studies included for meta-analysis. D1: Allocation concealment; D2: Clear inclusion criteria; D3: Placebo controlled; D4: Blinding of participants & personnel; D5: Incomplete outcome data.



**Figure 3.** Forest plot comparing change in total serum testosterone between patients receiving oral testosterone undecanoate vs placebo.

Contrary to these findings, when eugonadal men received oTU in the single-arm study by Li et al., patients with partial androgen deficiency receiving 2 months of oTU were found to have a decrease in TT levels from  $21.1 \pm 8.11$  nmol/L to  $19.2 \pm 7.22$  nmol/L ( $P < .05$ ).<sup>50</sup> Similarly, in a study by Butler et al., boys with suspected CDGP who were treated for 6 months with oTU, showed a significant decrease in mean TT levels ( $13.0 \pm 2.5$  nmol/L to  $8.3 \pm 1.8$  nmol/L).<sup>79</sup> In the studies by Boyanov et al., Holmång et al., Brown et al., and Chapman et al. there were no significant changes in TT or fT.<sup>52,66,77,83</sup>

### Changes in hematologic tests

In all studies for which a significant change was demonstrated, hemoglobin and/or hematocrit levels were found to increase following treatment with oTU. In the single-arm trial conducted by White et al., hematocrit significantly increased, with a mean change of  $3.2\% \pm 3.6\%$  ( $P < .001$ ). An additional increase in hemoglobin was seen, with a mean change of  $0.87 \pm 1.05$  g/dL ( $P < .001$ ).<sup>43</sup> This effect was matched in the study by Yin et al., in which participants receiving oTU were found to have significant increases in hematocrit (mean change  $0.04\% \pm 0.02\%$ ) and hemoglobin (mean change  $0.75 \pm 0.70$  mg/dL).<sup>46</sup>

Similar effects were seen in 5 RCTs. In the placebo-controlled trial conducted by Wittert et al., patients in the active treatment group were noted to have a significant increase of 2% in hematocrit ( $P = .026$ ). In addition, in the placebo-controlled trial conducted by Høst et al., those receiving oTU were described as having a statistically significant increase in hemoglobin at the end of the study.<sup>59</sup> Similar increases were seen in hematocrit following treatment with oTU in the trials by Swerdloff and Dudley (mean change,  $2.1 \pm 3.4\%$ ,  $P < .0001$ )<sup>75</sup> and Emmelot-Vonk et al. (mean change,  $0.01 \pm 0.01\%$ ,  $P < .009$ ).<sup>70</sup> This effect was examined further in the placebo-controlled trial conducted by Legros et al. In this trial, not only did the patients receiving oTU experience increases in hematocrit, but these changes were also found to be dose dependent, with mean changes from baseline of  $-0.5\%$ ,  $1.0\%$ ,  $2.1\%$ , and  $5.2\%$  being recorded for those receiving placebo, 80 mg/d, 160 mg/d, and 240 mg/d of oTU, respectively.<sup>72</sup> Contrasting the findings above, no significant hematologic changes were noted following oTU use in Hong et al., Boyanov et al., White et al., Brown et al., Chapman et al., Swerdloff et al., Aversa et al., or DelConte et al.<sup>43,44,51,52,71,74,77,83</sup>

### Changes in lipid profile

In all trials for which statistically significant changes were seen, decreases were noted in either overall cholesterol or HDL. In the study by Yin et al., participants receiving oTU were found to have a significant decrease in HDL, with a noted 19.1% decrease from baseline ( $36.1 \pm 7.1$  to  $29.2 \pm 6.5$  mg/dL).<sup>46</sup> A similar decrease in HDL was also observed in the study by Swerdloff and Dudley, in which a more significant percentage decrease in HDL was seen for those receiving oTU than those receiving topical testosterone ( $-23.5\%$  vs  $-12.5\%$ ,  $P < .0001$ ).<sup>75</sup> Likewise, in the RCT conducted by Conway et al., those patients who received oTU were noted to have a significant decrease in total cholesterol ( $5.61 \pm 0.38$  mmol/L vs  $5.27 \pm 0.37$  mmol/L,  $P < .005$ ).<sup>41</sup> Last, in the Swerdloff et al. trial, a larger percentage decrease in HDL from baseline was noted in the group of patients receiving oTU ( $-13.91\% \pm$

$15.67\%$ ) than in those receiving topical testosterone ( $-3.39 \pm 16.06\%$ ). Swerdloff et al. noted that the percentage decreases in HDL were larger in those patients who received higher doses of oTU (twice daily doses of 316 and 396 mg).<sup>74</sup>

The effects reported for the studies mentioned above were mirrored by those seen in a number of placebo-controlled trials. In a study by Uyanik et al., significant declines in both total cholesterol ( $198 \pm 30.7$  to  $174 \pm 41.9$  mg/dL,  $P < .05$ ) and LDL ( $111 \pm 18.1$  to  $87.9 \pm 29.4$  mg/dL,  $P < .01$ ) were described for those randomized to the active treatment group. Within this group there were no significant changes to HDL or triglyceride levels, nor were there any significant changes to lipid profiles within the placebo group.<sup>61</sup> Furthermore, in a study by Emmelot-Vonk et al., compared to study participants who received a placebo, those participants who received oTU were found to have significant decreases in both total cholesterol (mean change,  $-0.2 \pm 0.2$  mmol/L,  $P < .03$ ) and HDL (mean change,  $-0.1 \pm 0.1$  mmol/L,  $P < .001$ ).<sup>70</sup>

Contrary to the above findings, no significant change to lipid profiles were seen in the studies by Hong et al., Boyanov et al., Høst et al., Wittert et al., Park et al., Chapman et al., Aversa et al., DelConte et al., Franchi et al., and Li et al.<sup>44,49,50,51,52,59,63,69,71,77</sup>

### Changes in liver enzymes

Reports of 15 studies included comments on changes to liver enzymes following administration of oTU. In the study by Conway et al., the use of oTU was associated with decreases in AST from a baseline of  $33.1 \pm 3.2$  to  $29.7 \pm 2.5$  U/L.<sup>41</sup> Boyanov et al. reported a similar decrease in alkaline phosphatase in those treated with oTU in ( $P < .05$ ).<sup>52</sup> Otherwise, in these trials there were no significant changes in liver enzymes from baseline or compared to the control groups. Likewise, no significant changes to liver enzymes were noted in the studies by Hong et al., Maisey et al., Gooren, Pusch, Høst et al., Uyanik et al., Gregory et al., Park et al., Emmelot-Vonk et al., Legros et al., Liu et al., Swerdloff et al., Swerdloff and Dudley, and Franchi et al.<sup>49,51,53,54,57,59,61,69,70,72,74,75,80,82</sup>

### Prostatic changes

In the study by Cavallini et al., participants who received 6 months of oTU were found to have a significant increase in prostate volume ( $15.3 \pm 2.8$  to  $18.4 \pm 2.8$  cm<sup>3</sup>,  $P < .001$ ). Despite this change, there were no statistically significant changes to PSA.<sup>68</sup> Similarly, Holmång et al. reported that participants receiving oTU were found to have a similarly significant increase in prostate volume ( $24.6 \pm 1.8$  to  $27.6 \pm 2.1$  mL,  $P < .012$ ) without significant changes in PSA.<sup>66</sup> In concordance with these findings, there were no significant changes to prostate volume, PSA, or IPSS scores in the studies by Hong et al., Gooren, Wittert et al., Meuleman et al., Emmelot-Vonk et al., Chapman et al., Legros et al., Swerdloff et al., Swerdloff and Dudley, Aversa et al., DelConte et al., and Li et al.<sup>44,50,51,53,54,63,64,70-72,74,75,77</sup>

### Changes in body composition

While studies including those conducted by White et al., DelConte et al., Li et al., Boyanov et al., Høst et al., Emmelot-Vonk et al., and Aversa et al.,<sup>44,50,52,55,59,70</sup> found that there was no significant effect from oTU on weight or BMI, reports of numerous studies included comments on significant changes following oTU use in relation to fat and lean body mass. Following treatment with oTU, patients in the



study by Høst et al. were noted to have significantly reduced abdominal fat compared to patients who received placebo ( $28.1\% \pm 16.8\%$  vs  $29.9\% \pm 14.9\%$ ,  $P = .03$ ).<sup>59</sup> Similarly, in the Wittert et al. study, participants receiving oTU were noted to have significantly increased lean body mass ( $1.04 \pm .07$  kg,  $P < .00001$ ) and decreased fat mass ( $0.2 \pm 0.1$  kg,  $P < .0001$ ), changes that were found to be significant when compared those in patients who received a placebo.<sup>63</sup> In the 1992 trial performed by Gregory et al. to study the effect of oTU in boys with CDGP, significant increases in lean mass were seen in patients randomized to receive oTU ( $2.6 \pm 0.3$  kg) compared with those who received placebo ( $1.7 \pm 0.4$  kg) ( $P < .05$ ).<sup>82</sup> Likewise, despite noting no significant change in BMI, In Emmelot-Vonk et al., patients randomized to receive oTU demonstrated a significant increase in lean mass and decrease in fat mass when compared to those changes seen in participants receiving placebo. The use of the phrase placebo-controlled increase is meant to demonstrate that these participants not only had an increase in lean mass following the study, but also an increase that was significantly larger in effect than that seen in participants receiving a placebo in lean mass ( $+1.2$  kg [95% CI, 0.7-1.7];  $P < .001$ ) and decrease in fat mass ( $-1.3$  kg [95% CI,  $-1.8$  to  $-0.8$ ];  $P < .001$ ).<sup>70</sup> Last, when comparing the effects of oTU to topical testosterone, Swerdloff and Dudley demonstrated that those receiving oral treatment were more likely to experience an increase in lean mass ( $P < .0001$ ) and decrease in fat mass ( $P = .006$ ).<sup>75</sup> Despite these findings, no significant changes to lean or fat mass were noted in Boyanov et al., Chapman et al., and Aversa et al.<sup>52,71,77</sup>

Additional studies, specifically those featuring boys with CDGP, investigated the effect of oTU on height. In the study by Butler et al., boys receiving oTU were noted to have a significant increase in the velocity of height gain following 6 months of treatment ( $3.2 \pm 0.3$  cm/year to  $8.9 \pm 0.2$  cm/year).<sup>79</sup> In a similar trial conducted by Albanese et al., boys with CDGP who received oTU were noted to have a significant increase in height velocity ( $4.4 \pm 1.8$  cm/year to  $10.1 \pm 2.3$  cm/year,  $P < .0001$ ).<sup>78</sup> Likewise, in the placebo-controlled trial conducted by Gregory et al., boys randomized to receive oTU saw improved increases in height velocity compared to placebo ( $4.4 \pm 0.9$  cm/year to  $4.8 \pm 0.8$  cm/year) ( $P < .05$ ).<sup>82</sup> Furthermore, in their 2015 trial comparing boys with CDGP receiving oTU or no treatment, Lawaetz et al. described significant improvements in height for boys receiving oTU, with a change from a baseline height of 1.9 SDs below the mean to 1.5 SDs below the mean following treatment ( $P < .001$ ).<sup>81</sup> Last, in the 1995 placebo-controlled study, Brown et al. noted that boys randomized to receive oTU saw significant increases in height velocity ( $3.18 \pm 0.29$  cm/year to  $5.84 \pm 0.53$  cm/year) when compared to the placebo group ( $3.31 \pm 0.41$  cm/year to  $3.38 \pm 0.22$  cm/year) ( $P = .001$ ).<sup>83</sup>

### Changes in blood pressure

Within the study by Li et al., participants receiving oTU were noted to have small, but statistically significant, decreases in both mean systolic ( $129.0 \pm 12.9$  mmHg to  $125.0 \pm 15.3$  mmHg,  $P < .001$ ) and diastolic ( $82.4 \pm 7.3$  mmHg to  $80.1 \pm 8.4$  mmHg,  $P < .01$ ) blood pressure.<sup>50</sup> Contrary to this finding, in the study by White et al., men treated with oTU were found to have significant increases in 24-hour systolic blood pressure (mean change 1.8 mmHg,  $P = .016$ ). However, in this trial a significant change in diastolic blood pressure

was not also demonstrated.<sup>55</sup> In a second trial by White, a more in-depth analysis of the effect of oTU on blood pressure was performed in which men received 225 mg of oTU twice daily, 10.2% of patients were noted to have an increase in 24-hour average systolic blood pressure  $\geq 20$  mmHg. In this same trial, 0.8% of patients noted an increase in 24-hour average diastolic blood pressure  $\geq 15$  mmHg. However, when patients were grouped by baseline systolic and diastolic pressures, 32% of those with baseline systolic blood pressures  $>140$  mmHg and 33% of those with baseline diastolic blood pressures  $>90$  mmHg saw posttreatment reductions in blood pressures to normal ranges.<sup>43</sup> Alternatively, no significant changes to blood pressure recordings were noted in the studies by Høst et al., Wittert et al., Brown et al., Aversa et al., Swerdloff et al., and Boyanov et al.<sup>52,59,63,71,74,83</sup>

### Symptomatic response to testosterone

Numerous studies included investigations of the effects of oTU on sexual arousal and erectile function. While no significant change in IIEF results was recorded in Aversa et al.,<sup>71</sup> significant improvements were recorded in Hong et al. ( $37.2 \pm 19.6$  to  $40.2 \pm 22.0$ ,  $P = .033$ )<sup>51</sup> and Cavallini et al. (oTU:  $22 \pm 3.9$  to  $36 \pm 6.0$  vs placebo:  $21 \pm 4.4$  to  $22 \pm 6.3$ ).<sup>68</sup> Using alternative measures, Legros et al. recorded significant improvements in Derogatis Interview for Sexual Functioning–Self Report scores for participants receiving oTU ( $P = .044$ ). Likewise, Swerdloff and Dudley noted significant improvements following oTU use in participant scores on the Psychosexual Daily Questionnaire-Q4 ( $P < .0001$ ).<sup>75</sup>

While the majority of studies using validated scales to measure changes in libido and sexual function showed improvements, additional studies addressed subjective improvements in sexual functioning. In their randomized, placebo-controlled trial, Haren et al. found that patients in the oTU group described themselves as having less frequent occurrences of poor libido (77% to 59%,  $P = .034$ ) compared with patients receiving placebo (97% to 83%).<sup>62</sup> Likewise, study participants treated with oTU in the studies by Franchimont et al. and Maisey et al. demonstrated high rates of subjective improvement in sexual symptoms of TD, with 90% and 79% of participants noting improved symptoms, respectively.<sup>48,53</sup>

Additional studies, including those reported by Skakkebaek et al., Boyanov et al., Bancroft et al., Swerdloff et al., and Carani et al., demonstrated statistically significant improvements in subjective ratings of libido, erectile function, and/or ejaculatory function ( $P < .05$ ).<sup>52,65,67,73,74</sup> Similarly, Luisi et al. demonstrated statistically significant improvements favoring oTU over mesterolone for libido and erectile function ( $P < .001$ ).

Despite these findings, poor clinical responses with oTU were noted in 4 trials. In the trial by Conway et al., treatment with oTU was associated with worse rates of improved libido compared to treatment with intramuscular injection and subcutaneous pellets. In this trial, only 3 of 14 subjects receiving oTU noted a subjective clinical response, defined as increased libido, muscular strength, and general sense of well-being.<sup>41</sup> Similarly, in the trials conducted by Morales et al., Wu et al., and Holmäng et al., only 22%, 47%, and 46% of participants noted improved subjective sexual functioning following treatment with oTU, respectively.<sup>45,60,66</sup> Notably, of the trials revealing a poor subjective response to oTU, only Conway et al. examined hypogonadal men.

Regarding changes in mood, Benkert et al., Haren et al., and Cavallini et al. found no significant impact of oTU on ratings of depression or anxiety.<sup>58,62,68</sup> Countering this finding were the findings of Zhang et al., in whose study patients receiving oTU demonstrated statistically significant improvements on the Hospital Anxiety and Depression Scale for depression ( $4.91 \pm 0.6$  to  $2.39 \pm 0.30$ ,  $P < .05$ ) and anxiety ( $3.47 \pm 0.40$  to  $1.72 \pm 0.20$ ,  $P < .05$ ) subscale scores compared to both baseline and placebo. Similarly, when assessed for levels of stress using the PSS, men in the active treatment group experienced similar improvement ( $12.88 \pm 2.10$  to  $9.83 \pm 1.70$ ,  $P < .05$ ), a result that was significant compared to both baseline and placebo.<sup>56</sup> Additionally, in Skakkebaek et al., when assessed for changes in mood, those treated with oTU noted significantly improved anxiety ( $P < .01$ ) when compared to placebo. However, in this trial, no significant differences were noted for subjective ratings of depression.<sup>65</sup>

Last, regarding the effects of oTU on general well-being and somatic symptoms, no significant changes in the SF-36 questionnaire were described in Emmelot-Vonk et al., Chapman et al., or Legros et al.<sup>70,72,77</sup> Similarly, no significant changes in Aging Males' Symptoms scale scores following oTU use were seen in Aversa et al., Zhang et al., or Legros et al.<sup>56,71,72</sup> Despite these findings, other studies demonstrated the beneficial effects of oTU use. In one such study, Hong et al. noted significant improvement in the symptoms of TD following oTU use as measured by the Korean Andropause Questionnaire ( $56.2 \pm 21.7$  to  $46.5 \pm 25.6$ ,  $P = .028$ ). In the same study, when assessed for quality of life using the SF-12, men in the active treatment group experienced statistically significant improvement in the physical ( $46.11 \pm 6.2$  to  $52.93 \pm 6.9$ ,  $P < .05$ ) and mental ( $51.19 \pm 7.1$  to  $56.13 \pm 7.3$ ,  $P < .05$ ) subscales.<sup>51</sup> Similarly, Park et al. reported that treatment with oral TU appeared to confer improved scores for the Pusan National University Hospital Quality of Life Scale compared to placebo in the domains of sexual (percentage change: 43.9% vs 30.8%), cardiopulmonary (41% vs 10%), metabolic (38.3% vs 0%), musculoskeletal (34.2% vs 0%), neurologic (30.3% vs 11.1%), and gastrointestinal functioning (28.2% vs 0%). Within this assessment, only in the mental functioning domain did those receiving oral TU show lesser improvement than those receiving placebo (24.4% vs 46.3%).<sup>69</sup> Finally, Wu et al. noted that during treatment with oTU, 83.9% of men with coronary heart disease reported subjective improvements in general somatic symptoms.<sup>60</sup>

### Adverse effects of testosterone

The results of the meta-analyses performed in placebo-controlled trials describing rates of adverse effects for those taking oTU are summarized in Figures 4 and 5, which show there was no significant risk of adverse effects (RR  $-0.03$  [95% CI,  $-0.08$  to  $0.03$ ]) or serious adverse effects (RR  $0.15$  [95% CI,  $-0.66$  to  $0.96$ ]) in the oTU groups compared to placebo. While single-arm trials or RCTs without a placebo-controlled group, including the studies by White et al., DelConte et al., Morales et al., and Swerdloff et al., reported rates of adverse effects associated with oTU use to be between 10.1% and 21.1%, other trials, notably those by Conway et al. (42.8%) and Swerdloff and Dudley (31.1%), reported higher rates. Despite this variance, all

agreed that the vast majority of adverse effects following oTU use were mild. The most commonly noted adverse effects included gastrointestinal distress and nausea, while rates of skin reactions were noted to be low.<sup>41,43-45,74,75</sup> Hong et al., Boyanov et al., Albanese et al., and Aversa et al., simply noted that no adverse effects were recorded following oTU use or that the rates of adverse effects were nonsignificant.<sup>51,52,71,78</sup>

### Discussion

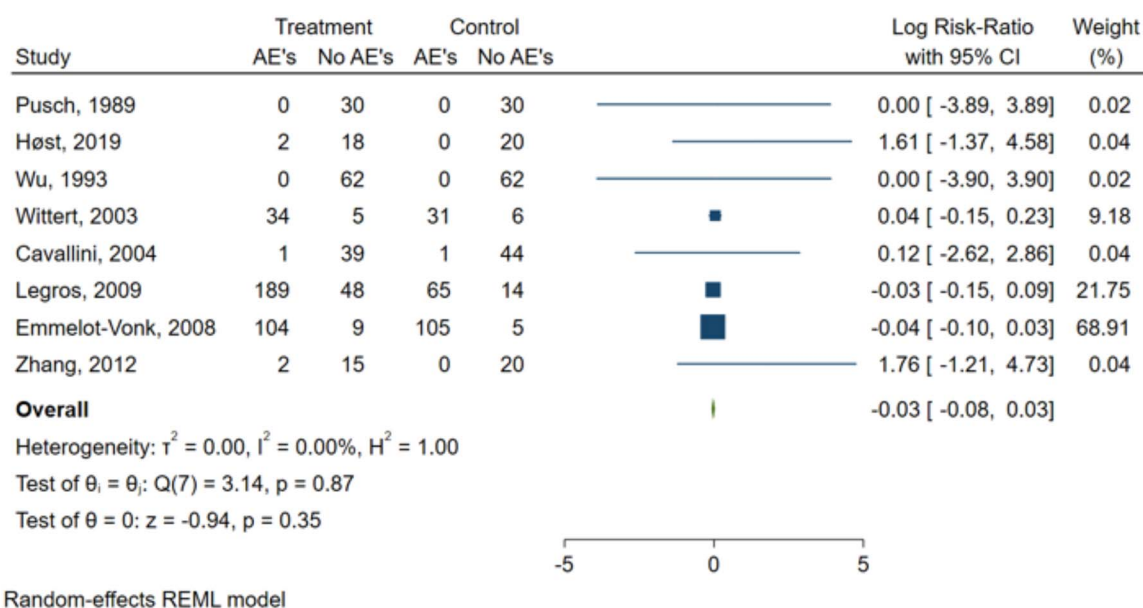
Despite the increasing prescription rates of TRT in past decades, rates at which oral TRT are prescribed have been decreasing.<sup>8-10</sup> In part, this trend can be explained by the decreasing use of MT as a result of its well-established hepatotoxicity. However, the increasing availability of various oTU formulations raises questions as to why there is greater hesitancy to prescribe oral TRT, which may be due to concerns regarding its efficacy and safety. In a review of the current guidelines on the management of TD, most societies either recommend against or advise caution in the use of oTU, citing that its absorption does not reliably produce improvements in serum testosterone levels and its effect is heavily dependent on the intake of food with a high fat content.

In this review of the available literature, it was revealed that studies of oTU administration to men with TD at baseline consistently reported significant improvements in testosterone levels. In all but 1 trial, these improvements resulted in an average TT level within the eugonadal range. However, the results of trials examining men with eugonadal levels of TT at baseline showed varied responses in TT levels following oTU use. While the present review may provide some reassurance relating to the efficacy of oTU use in hypogonadal men, it should be noted that relatively few placebo-controlled trials excluded eugonadal men. As such, further studies may be necessary to investigate the use of oTU in hypogonadal men before concerns regarding its efficacy may be dispelled.

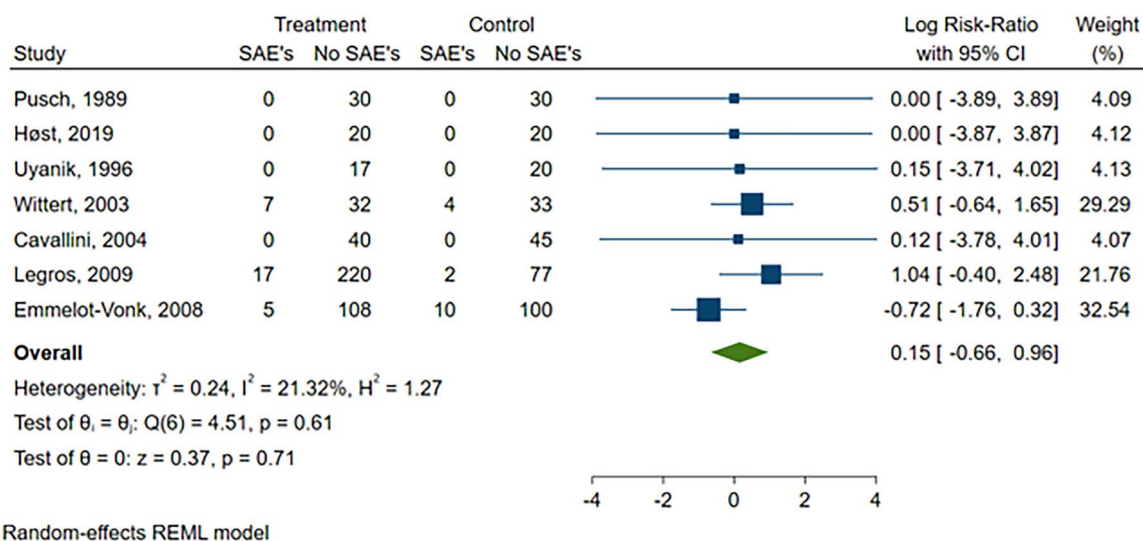
While multiple studies suggested that oTU had no significant effect on hematocrit or hemoglobin levels, the remaining studies analyzed described significant increases. When the studies for which the CI crossed zero, the mean change in hematocrit fell between 0.01% to 2.1%, likely representing a statistically significant, but clinically insignificant change. Only 1 additional trial found a hematocrit increase above this range (Legros et al., 5.2%). However, this increase was only noted for patients treated with the highest study dosage (240 mg/d).<sup>72</sup>

Varied reports on the effect of oTU on lipid profiles were analyzed. Overall, the use of oTU appeared safe, with a majority of studies analyzed reporting no difference in lipid profile following treatment. However, in other trials a significant decrease in total cholesterol and/or HDL was noted, with varied clinical significance. On the contrary, the studies analyzed unanimously reported that there were no significant increases in liver enzymes or PSA. While 2 studies noted a significant increase in prostate volume, these increases were likely clinically insignificant and did not result in simultaneous changes to PSA or IPSS results.

While studies that included boys with CDGP noted a unanimous increase in height velocity following the use of oTU, its effect on other measures of body composition remained varied. Although there were no significant changes in BMI across any study included in this review, a split effect was seen in regard to changes in lean and fat mass. While multiple



**Figure 4.** Forest plot comparing the rate of adverse effects (AEs) between patients receiving oral testosterone undecanoate vs placebo.



**Figure 5.** Forest plot comparing the rate of serious adverse effects (SAE's) between patients receiving oral testosterone undecanoate versus placebo.

studies reported significantly decreased fat mass and increased lean mass following the use of oTU, others were without significant changes. In addition, the clinical significance of these statistically significant changes remains in question.

Although mixed results were reported in regard to the effect of oTU on blood pressure, the majority of studies found that there was no significant effect. Interestingly, White et al. reported internally varied results, with improvements in blood pressure seen for those with hypertension at baseline and increases in blood pressure described for those without hypertension at baseline.<sup>43</sup> Although the results of this review overall suggest that oTU is well tolerated in regard to changes in blood pressure, questions remain regarding the impact of baseline hypertension on this measure.

Most significantly, the reported effects of oTU on symptomatic responses were varied. For sexual symptoms, notably libido and erectile function, the majority of studies included described significant improvements following oTU use. Although some studies described a less overwhelming

subjective clinical response in sexual symptoms following oTU use, it is notable that only 1 study included men with TD. Contrarily, although some studies demonstrated a significant improvement in mood or general well-being with oTU use, an equal number of studies found no statistically significant effect, leaving the impact of oTU on these symptoms unclear.

Last, the rates of adverse effects as described in trials without a placebo-controlled design tended to be <21%. On a further meta-analysis comparing placebo-controlled trials, there was no significant difference between the rates of adverse effects or serious adverse effects in oTU or placebo groups, suggesting that oTU was well tolerated overall.

Limitations of the review included the use of single-arm and retrospective cohort trials, as well as trials with smaller sample sizes. While the inclusion of these data was deemed necessary given the dearth of studies on the observed topic, their inclusion may introduce various sources of bias to the review. In addition, given significant variations in the way in which data were presented between trials regarding



hematologic assays, lipid profiles, liver enzymes, prostate assays, body composition, blood pressure, and symptomatic response, a meta-analysis summarizing these data could not be performed. Another limitation of the review was its exclusion of alternative patient cohorts. Notably, the study excluded data pertaining to female patients. While oral TRT has been used in female patients, specifically in the population of postmenopausal women, numerous systematic reviews have extensively covered the pertinent trials relating to the use of oral TRT in this population.<sup>84-88</sup> An additional population excluded in the results reported above was transgender patients receiving oral testosterone for hormone replacement therapy. Likely due to faults within the search strategy and the more recent emergence of these treatments, studies on this topic that met the inclusion criteria were not retrieved on the initial search.

Further studies examining the use of oral TRT and specifically oTU are needed to provide further information regarding its efficacy and safety. The ideal study on oTU would not only include a large cohort of hypogonadal participants randomized oTU and placebo, but would also include administration of additional formulations of testosterone, including injection and topical therapies at multiple dosages. Participants should be followed for a long study period with periodic assessment intervals at which tests should be performed for TD symptoms, mood, and well-being, and for various laboratory values including lipid profiles, hematologic assays, liver function assays, and hormone assays.

## Conclusion

To the authors' knowledge this is the first systematic review and meta-analysis to include a sufficiently large number of trials comparing oral TRT to placebo to allow for a meta-analysis to be performed and for a discussion of the efficacy and safety of oral TRT to be conducted. The above results suggest that oTU is a well-tolerated option for TD that results in improved TT levels, height velocity, and sexual symptoms in hypogonadal patients, without leading to significant hepatotoxicity, prostatic changes, or worsening hypertension. Despite these findings, the impact of oTU on lean and fat body mass, hematologic assays, and lipid profiles remains unclear. As well, the use of oTU to improve general well-being and mood is yet to be described consistently.

Given the results reported here, the current depiction of oral TRT within guidelines on the management of TD may not accurately represent the current literature. As newer oral agents are formulated and tested, additional trials on the use of oral TRT should be performed and a further discussion on the place of oral TRT in treating varying conditions may be merited.

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**Conflicts of Interest:** Faysal A. Yafi reports being a speaker for Antares Pharma and Clarus Therapeutics, an advisory board member and

consultant for Coloplast, an advisory board member for Cynosure, Promescent, and Sprout, and a research grant primary investigator for Viome. Mohit Khera reports being a consultant for AbbVie, Endo, Halozyme, Tolmar, Marius, Boston Scientific, Coloplast, and Petros.

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