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Association of Testosterone Treatment With Alleviation of Depressive Symptoms in Men
A Systematic Review and Meta-analysis

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IMPORTANCE Countering depressive disorders is a public health priority. Currently, antidepressants are the first-line treatment, although they show modest effects. In men, testosterone treatment is a controversial alternative or adjunct treatment option.

OBJECTIVES To examine the association of testosterone treatment with alleviation of depressive symptoms in men and to clarify moderating effects of testosterone status, depression status, age, treatment duration, and dosage.

DATA SOURCES English-language studies published in peer-reviewed journals identified from PubMed/Medline, Embase, Scopus, PsychINFO, and the Cochrane Controlled Trials Register from database inception to March 5, 2018, using the search terms *testosterone*, *mood*, *administration*, *dosage*, *adverse effects*, *deficiency*, *standards*, *therapeutic use*, *therapy*, *treatment*, and *supplementation*.

STUDY SELECTION Randomized placebo-controlled clinical trials (RCTs) of testosterone treatment that together cover a broad age range and hypogonadal or eugonadal men reporting depressive symptoms on psychometrically validated depression scales.

DATA EXTRACTION AND SYNTHESIS Of 7690 identified records, 469 were evaluated against full study inclusion criteria after removing duplicates, reviews, and studies that did not examine male patients or testosterone. Quality assessment and data extraction from the remaining 27 RCTs were performed.

MAIN OUTCOMES AND MEASURES Primary outcomes were testosterone treatment effectiveness (standardized score difference after treatment), efficacy (proportion of patients who responded to testosterone treatment with a score reduction of 50% or greater), and acceptability (proportion of patients who withdrew for any reason).

RESULTS Random-effects meta-analysis of 27 RCTs including 1890 men suggested that testosterone treatment is associated with a significant reduction in depressive symptoms compared with placebo (Hedges *g*, 0.21; 95% CI, 0.10-0.32), showing an efficacy of odds ratio (OR), 2.30 (95% CI, 1.30-4.06). There was no significant difference between acceptability of testosterone treatment and placebo (OR, 0.79; 95% CI, 0.61-1.01). Meta-regression models suggested significant interactions for testosterone treatment with dosage and symptom variability at baseline. In the most conservative bias scenario, testosterone treatment remained significant whenever dosages greater than 0.5 g/wk were administered and symptom variability was kept low.

CONCLUSIONS AND RELEVANCE Testosterone treatment appears to be effective and efficacious in reducing depressive symptoms in men, particularly when higher-dosage regimens were applied in carefully selected samples. However, given the heterogeneity of the included RCTs, more preregistered trials are needed that explicitly examine depression as the primary end point and consider relevant moderators.

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Depressive disorders, such as major depressive disorder (MDD) and dysthymic disorder, are psychiatric illnesses with devastating personal and social consequences owing to a persistent depressed mood, negative thoughts, and fatigue. The World Health Organization has declared depression to be the leading cause of disability worldwide.[1] Current pharmacologic treatment options show limited effectiveness in countering the disease,[2,3] and approximately 30% of patients do not experience sustained symptomatic remission despite multiple treatment attempts.[4] Although depressive disorders are more prevalent in women, more than 100 million men are currently affected, constituting approximately one-third of all patients with depression.[1,5]

The association between testosterone and depression has been extensively debated because testosterone is a neuroactive steroid hormone influencing mood and appetitive behavior.[6] Several lines of research have examined the potential role of testosterone therapy in alleviating depressive symptoms.[6] Rodent models of depression show that testosterone administration is causally related to increased serotonin release in the dorsal raphe nuclei[7] and facilitates general and antidepressant-induced neuroplasticity in the hippocampal formation.[8,9] Both increased serotonin release and establishment of new neuronal connections are regarded as central mechanisms of action against depression by promoting the adoption of new patterns of thought and experience.[10]

In adult men, a low testosterone level has consistently been associated with increased age and with clinical conditions, such as erectile dysfunction and obesity, that become more prevalent with increasing age.[11-14] Although several studies indicate that men with low testosterone levels also appear to have more depressive symptoms,[15-17] there are a substantial number of conflicting cohort studies in middle-aged and older men that show no association between testosterone level and depressive symptoms[11,18] or that show an association only in subgroups of men[19-21] or subtypes of depression.[22] Studies comparing men with MDD with healthy control participants report mixed findings, with reduced testosterone levels in patients with MDD[23-25] or no differences for patients with MDD,[26-28] although there is some evidence for reduced testosterone levels in patients with dysthymic disorder.[6,19,29]

Although testosterone treatment emerged as a potent therapy for various disorders in hypogonadal men, defined as men with total testosterone levels of 345.82 ng/dL or less (to convert to nanomoles per liter, multiply by 0.0347),[11,30,31] randomized placebo-controlled clinical trials (RCTs) of testosterone treatment in hypogonadal men that examine depressive symptoms have yielded inconsistent results.[20,32-34] Results of RCTs investigating testosterone administration to men with MDD do not support this intervention as an effective antidepressant treatment.[35-38] However, positive results have been reported for some subpopulations of men with depression, such as for men with dysthymic disorder or HIV or for men with treatment-resistant depression or low testosterone levels.[39-42]

Previous meta-analyses of RCTs have identified beneficial associations between testosterone treatment and reduced depressive symptoms in men, with subgroup analyses suggesting that testosterone treatment is most effective in middle-aged, hypogonadal, or HIV-positive men and men with mild depressive illness.[43,44] A recently conducted meta-analysis examining testosterone treatment's association with depression, quality of life, libido, and erectile function in hypogonadal men also identified a beneficial association for testosterone treatment for all 4 domains.[30] Still, testosterone treatment is not recommended as an antidepressant treatment by clinical practice guidelines for depression treatment (National Institute for Health and Care Excellence) or by Endocrine Society clinical practice guidelines for testosterone therapy owing to prevailing uncertainty about its efficacy, age criteria, dosage, ideal duration, and method of application.[31,45]

The Endocrine Society clinical practice guidelines recommend testosterone treatment only in men with symptomatic testosterone deficiency who exhibit unequivocally and consistently low testosterone levels.[31] However, there is currently no testosterone concentration threshold that reliably distinguishes responders from nonresponders to testosterone treatment, suggesting that hypogonadal and eugonadal men may benefit from testosterone treatment with regard to mood.[46] However, the meta-analyses suggesting that testosterone treatment is associated with a reduction of depressive symptoms primarily in hypogonadal men[43,44] did not account for potential publication bias for studies with positive results. Reported effects must be interpreted with caution because publication bias is prevalent in antidepressant research.[3] Furthermore, for a long time there was insufficient evidence to be able to identify evidence-based age criteria for testosterone treatment.[46] The "testosterone trials" addressed the influence of testosterone treatment in various dimensions exclusively in older men and identified a slight improvement in depressive symptoms.[42] Along with the testosterone trials, other recent RCTs have examined the effects of testosterone treatment on depressive symptoms[33,47-49] and call for an updated, methodologically rigorous meta-analysis on the association between testosterone treatment and depressive symptoms in men.

Key Points

Question Is testosterone treatment associated with an alleviation of depressive symptoms in men compared with placebo?

Findings This systematic review and meta-analysis of 27 randomized placebo-controlled clinical trials involving a total of 1890 men found that testosterone treatment was associated with a significant reduction of depressive symptoms, particularly in participants who received higher-dosage regimens.

Meaning The available evidence supports the clinical utility of adjunct testosterone treatment for depressive symptoms in men, but more methodologically rigorous trials are needed to unequivocally determine efficacy, ideal dosage regimens, and other moderators.

Methods

Search Strategy and Selection of RCTs

Candidate studies from peer-reviewed journals were identified via PubMed/Medline, Embase, Scopus, PsychINFO, and

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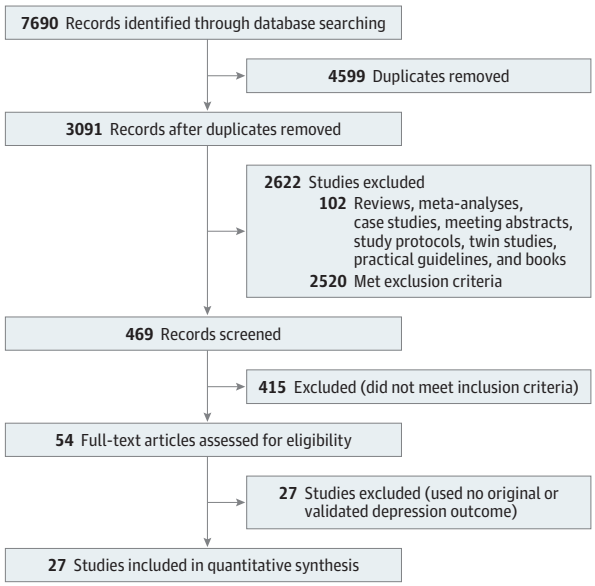
Figure 1. PRISMA Flow Diagram of Study Selection



the Cochrane Controlled Trials Register by using the following search strategy. The applied key terms were *testosterone* AND *mood* together with the corresponding modifiers *administration and dosage*, *adverse effects*, *deficiency*, *standards*, *therapeutic use*, *therapy*, *treatment,* and *supplementation* in the title, abstract, or keywords. The search was restricted to English-language articles published between database inception and March 5, 2018. In sum, 7690 records were extracted. In the following, sample size is presented in parentheses according to the application of stepwise exclusion criteria. The set was refined by removing duplicate entries (3091) and reviews, meta-analyses, case studies, meeting abstracts, study protocols, twin studies, practical guidelines, and books (2989). Subsequently, all studies dealing with animals (1392), women (874), or children (837) and athletic studies (758) and contraceptive studies (728) were excluded. Studies that included non-testosterone treatments (548) and in vitro studies (469) were eliminated. Titles and abstracts of the remaining 469 papers were screened for relevance, including only studies using an RCT design that administered testosterone in men and reporting mood before and after the intervention. All non-RCTs (eg, open-label trials) and studies not dealing with mood (eg, reporting of preintervention depressive symptoms only) were excluded (54). In the final step, 27 studies containing no original or validated psychometric depression outcome were removed (27). An extended description of the search strategy is provided in the eAppendix in the Supplement. Two of us (A.W. and J.B.) further cross-validated candidate studies based on previous meta-analyses and systematic reviews to check whether there existed candidate studies that had not been identified by the systematic search.[30,43,44,50]

Figure 1 shows the sample development throughout the selection process. Study selection and eligibility screening were conducted according to the PRISMA guidelines.[51]

Data Extraction and Preparation

Two of us (A.W. and J.B.) independently searched for literature, extracted data, and performed quality control, and another of us (R.M.) conducted the analysis. Discrepancies about study inclusion were resolved through discussion. When the data were exclusively graphically presented, we used the WebPlotDigitizer[52] to extract the data manually at the highest resolution. A description of the characteristics of the included RCTs is provided in eTable 1 in the Supplement. The following data were extracted or derived from each article: (1) bibliography: first author, title, and year of publication; (2) baseline characteristics: sample size per treatment condition, mean age, HIV infection (yes or no), testosterone status (hypogonadal vs eugonadal), symptom level at baseline, and symptom variability at baseline (coefficient of variation); (3) treatment characteristics: substance, route of administration (intramuscular, transdermal, or oral), and drug regimen (dosage, administration interval, and treatment duration); and (4) outcome characteristics: type of depression measure (Beck Depression Inventory [BDI], Hamilton Depression Rating Scale [HDRS], Montgomery-Åsberg Depression Rating Scale [MADRS], 9-item Patient Health Questionnaire [PHQ-9], Geriatric Depression Scale [GDS], Hospital Anxiety and Depression Scale-Depression [HADS-D], or Bech-Rafaelsen Melancholia Scale [BRMS]), the means and variances of the measures after treatment, the number of participants showing a reduction of depressive symptoms by at least 50% from baseline, and the number of participants lost to follow-up. Baseline testosterone status was classified based on a mean concentration threshold of total testosterone of 345.82 ng/dL or less or free testosterone concentration of 64.84 pg/mL or less (to convert free testosterone to picomoles per liter, multiply by 3.47) following current guidelines.[53,54] Risk of bias for individual studies was assessed by 2 reviewers (A.W. and J.B.) using the Cochrane Collaboration Risk of Bias tool for RCTs (eTable 2 in the Supplement) and Jadad scoring (interrater reliability: intraclass correlation coefficient, 0.64; eTable 3 in the Supplement).[55,56] Baseline depression status (subclinical depression, mild depression, or moderate to severe depression) was classified based on cutoff scores according to psychometric instructions (eTable 4 in the Supplement). Detailed data inspection revealed that 3 of the 27 selected articles reported both a placebo comparator and an active comparator,[34,38,47] whereas only 1 of these 3 studies compared with an established antidepressant.[38] Except for 4 studies that excluded participants taking antidepressants from trials,[32,34,57,58] all remaining articles exclusively reported the effect of testosterone treatment on depressive symptoms compared with placebo in participant populations that were not selected for their abstinence from guideline treatment. Considering that the purpose of the present meta-analysis was to reliably estimate the adjunct effectiveness and efficacy of testosterone treatment for reducing depressive symptoms, not its superiority to treatment-as-usual conditions, we focused on the testosterone treatment-placebo contrast. The final data set was informed by 27 independent studies.

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Statistical Analysis

Owing to substantial variability in the extracted study-level characteristics of all included RCTs, random-effects meta-analyses were performed using the *metafor* package[59] and R, version 3.4.2 statistical software.[60] Three treatment criteria were considered: effectiveness, measured by the standardized placebo-testosterone treatment difference on a depression outcome; efficacy, measured by the total number of patients who had a reduction of 50% or greater of the depression outcome; and acceptability, measured by the proportion of patients who withdrew for any reason. To evaluate treatment effectiveness, Hedges *g* and its sampling variance were estimated (eTable 5 in the Supplement).[61] Four RCTs reported 2 different depression outcomes, thereby providing correlated effectiveness information that depended on the same study-level characteristics.[35-37,62] To enable restricted maximum likelihood–based univariate meta-analyses, the HDRS outcomes of these studies were discarded from the analysis set.[63] However, the results were almost identical when the dependency of different outcomes was explicitly modeled.[64] Efficacy and acceptability were evaluated based on odds ratio (OR). Efficacy was mapped onto effectiveness by means of a Bayesian linear errors-in-variables model.[65] To ensure robustness of all primary analyses to outlying effects, any study with a Cook distance greater than the 50th percentile of the central χ^2_1 distribution was removed from the respective analysis set.[66] The Cochran *Q* test was used to assess the extent of between-study heterogeneity in the respective treatment criterion.

Based on these results, several meta-regression models were finally fitted to investigate the sensitivity of treatment effectiveness or efficacy to different study-level moderators and small study effects (eg, publication bias). The latter was checked by contour-enhanced funnel plots[67,68] and adjusted for by obtaining a precision-effect estimate with SE.[69] Although precision-effect estimate with SE tends to slightly underestimate the true association if the observed effects were generated by questionable research practices, simulations suggest that it provides the most precise estimates in the presence of residual effect heterogeneity and small-study effects.[70]

Results

Meta-analysis of Treatment Effectiveness and Efficacy

Figure 2A[32-42,47-49,57,58,62,71-80] shows the observed effectiveness reported by the 27 studies as standardized differences between placebo and testosterone treatment of the posttreatment depression score and their meta-analytically pooled estimates. The robust estimate (excluding 1 study[34] with an outlying effect; Cook distance, 2.01) suggested that testosterone treatment was accompanied by a significant difference of Hedges *g* of 0.21 SD (SE, 0.05; 95% CI, 0.10-0.32; $z = 3.87$; $P < .001$) in depressive symptoms compared with placebo administration. Based on a reference population of any persons undergoing psychiatric treatment who were diagnosed with depressive disorders,[81] this effect translates, for instance, into a 2.2-point reduction in BDI-II score. Figure 2B and C show that these estimates correspond approximately with a testosterone treatment–associated efficacy of OR, 2.30 (95% CI, 1.30-4.06; log[OR], 0.83; SE, 0.29; 95% CI, 0.26-1.40; $z = 2.87$; $P = .004$) in favor of a clinically relevant reduction in depressive symptoms. These effects exceed the efficacy thresholds for pharmacologic agents for depression therapy proposed by the National Institute for Health and Care Excellence guidelines for treatment-resistant depression (but not treatment-responsive depression)[45,82] and are comparable to reported efficacy measures of current antidepressants.[2,83] Considering that testosterone served as an adjunct medication in many of the analyzed studies (see Data Extraction and Preparation), this finding would support the incremental clinical utility of testosterone treatment in the absence of small-study effects. However, risk-of-bias assessment revealed that few RCTs were at low risk of bias, primarily owing to a lack of details about randomization procedures and allocation concealment and incomplete outcome measures (eTables 2 and 3 in the Supplement). With regard to treatment effectiveness, the portion of true heterogeneity was estimated to amount to an I^2 of 18.7% of the total effect variability (τ, 0.11; $\chi^2_{25} = 31.20$; $P = .18$), which is comparable to other meta-analyses on pharmacologic treatment of mental health outcomes.[84]

Meta-analysis of Treatment Acceptability

The meta-analysis of the 25 studies (eFigure in the Supplement) providing information about the treatment-related loss to follow-up showed no statistically significant difference in risk of attrition when participants received testosterone compared with placebo (OR, 0.79; 95% CI, 0.61 to 1.01; log[OR], −0.24; SE, 0.13; 95% CI, −0.49 to 0.01).

Moderators of Treatment Effectiveness

The inclusion of the outlying study[34] inflated the heterogeneity estimate of the effectiveness meta-analysis to an I^2 of 81.4% (τ, 0.49; $\chi^2_{26} = 96.00$; $P < .001$), which could not only indicate the presence of bias owing to suboptimal reporting and/or effect estimation (eTable 5 in the Supplement) but also interactions between testosterone treatment and moderator variables of the treatment protocol used in that study. To identify such candidate moderators to explain the between-study heterogeneity of testosterone treatment effects, each of the extracted study-level variables was submitted as effect predictors to meta-regression modeling. The results of the naive meta-regression analyses are listed in the **Table** (eTable 6 in the Supplement for robust versions) and suggest that, in particular, the higher testosterone dosage and lower symptom variability at baseline could have moderated the testosterone treatment–related difference in posttreatment depressive symptoms. By contrast, the analyses provided little evidence for a pronounced association with age, baseline testosterone level, depression status, HIV infection, treatment duration, and the route of testosterone administration.

Based on these exploratory analyses, the final precision-adjusted meta-regression model was jointly informed by testosterone dose ($\beta = 0.08$ SD per each additional 100 mg/wk; SE, 0.03) and baseline symptom variability ($\beta = -0.12$ SD per each additional 25% symptom variability; SE, 0.08) and

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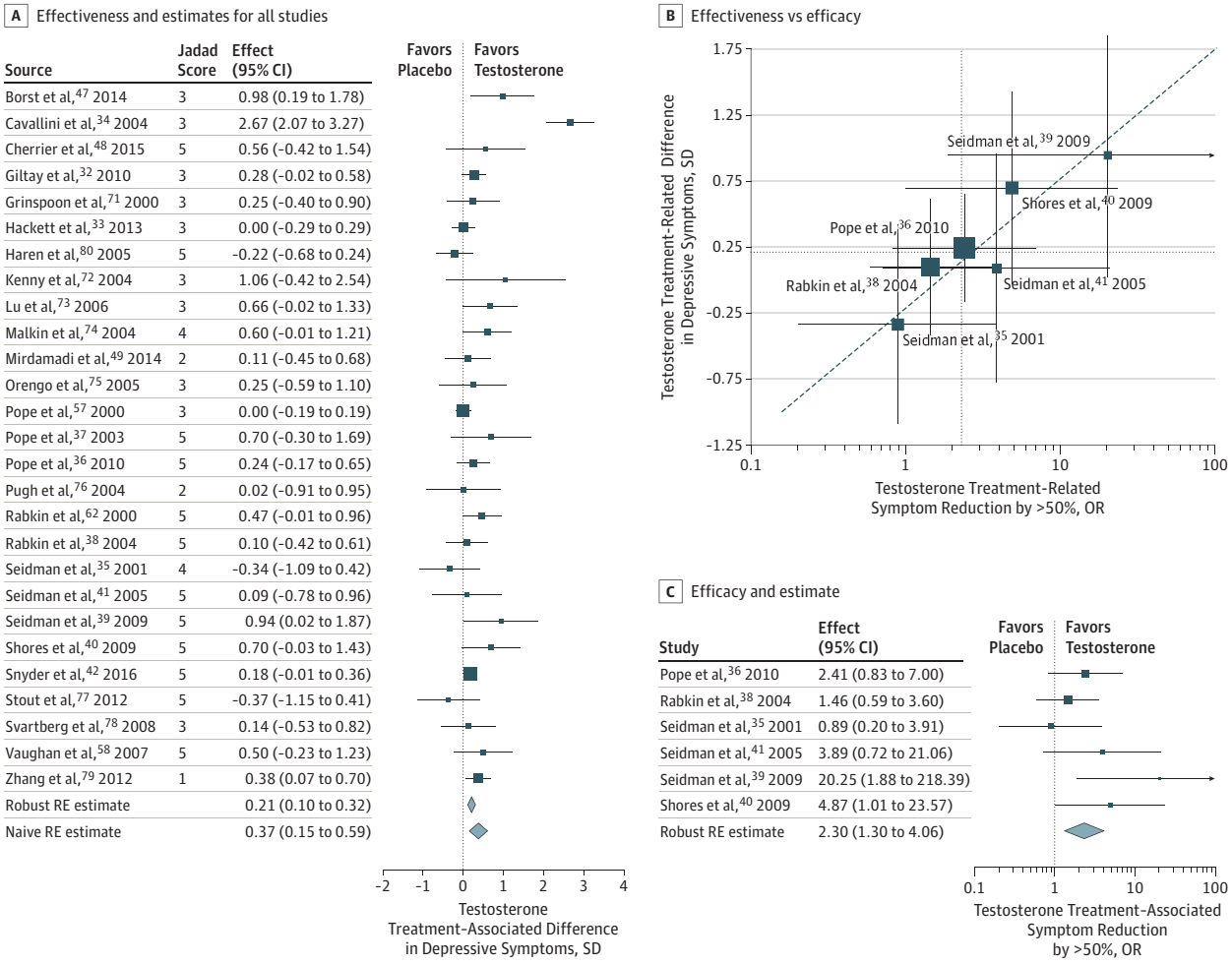
Figure 2. Forest Plots of Treatment Effectiveness and Efficacy



A, Effectiveness of testosterone treatment in each respective study and their meta-analytical estimates. The naive estimate is based on an analysis set including the outlying study; the robust estimate is based on analysis excluding the outlying study.[34] The dotted vertical line signifies the "no efficacy of testosterone treatment" scenario. Square data markers indicate study effects, and their size indicates relative sample size. Error bars indicate 95% CI. Diamond data markers indicate meta-analytical effect estimates. B, Relation between testosterone treatment effectiveness and testosterone treatment efficacy, estimated by Bayesian errors-in-variables modeling. The dashed line indicates the estimated correspondence line of the efficacy and effectiveness outcomes. The vertical dotted line indicates the (robust) meta-analytical effect estimate for efficacy, and the horizontal dotted line indicates the meta-analytical effect estimate for effectiveness. The size of data markers indicates the sample size of each study. C, Efficacy of testosterone treatment (as odds ratios [ORs]) in each respective study and their meta-analytical estimates. In all panels, positive estimates represent depression-alleviating effects of testosterone treatment compared with placebo. RE indicates random effects.

accounted for a total variance portion R^2 = 29.8% (χ^2_2 = 8.71; P = .01) of the estimated true effect heterogeneity. Nonetheless, the residual portion of effect heterogeneity still amounted to an I^2 of 72.0% (τ, 0.41; χ^2_{23} = 66.10; P < .001). The precision-adjusted estimate (Hedges g, 0.23 SD; SE, 0.16; 95% CI, −0.08 to 0.54) is shown in **Figure 3**A and illustrates that the robust estimate of the general effectiveness of testosterone treatment was hardly sensitive to the presence of bias and questionable research practices in the set of analyzed RCTs.

A considerable portion of the heterogeneity attributed to the outlying study[34] was a result of its comparably large dose of administered testosterone (1.12 g/wk) and low symptom variability at baseline (coefficient of variation = 10.7%). Accordingly, testosterone treatment with 500 mg/wk at a symptom variability of 20% was estimated to result in a Hedges g of 0.52 (SE = 0.23; 95% CI, 0.08-0.96). By contrast, the outcome of testosterone treatment with 200 mg/wk at a symptom variability of 50% was estimated to amount to a Hedges g of 0.15 SD (SE, 0.18; 95% CI, −0.21 to 0.51). The robustness of this conceptually important dose-response association is shown in Figure 3B, which highlights that, even in the most conservative bias scenario, the depression-alleviating effect of testosterone treatment remained clinically significant when high testosterone dosages (>500 mg/wk) were administered and symptom variability was kept low (by sampling from homogeneous participant populations).

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Table. Meta-regression of the Effectiveness of Testosterone Treatment on Various Study-Level Moderators

Characteristic	Estimate (SE) [95% CI]	NHST χ^2 (*df*)	*P* Value
Baseline			
Age, y			
40	0.223 (0.198) [−0.166 to 0.612]	0.835 (1)	.36
60	0.393 (0.116) [0.165 to 0.621]		
80	0.562 (0.238) [0.096 to 1.029]		
Testosterone status			
Eugonadal	0.208 (0.221) [−0.225 to 0.641]	1.021 (1)	.31
Hypogonadal	0.475 (0.144) [0.192 to 0.758]		
HIV infection			
Yes	0.276 (0.331) [−0.373 to 0.926]	0.096 (1)	.76
No	0.386 (0.123) [0.144 to 0.627]		
Symptom level			
Severe	0.385 (0.232) [−0.070 to 0.840]	1.194 (2)	.55
Mild	0.277 (0.155) [−0.027 to 0.582]		
Subclinical	0.595 (0.247) [0.112 to 1.078]		
Symptom variability, CV, %			
20	0.615 (0.180) [0.262 to 0.968]	2.935 (1)	.09
50	0.439 (0.116) [0.211 to 0.667]		
100	0.146 (0.169) [−0.185 to 0.478]		
Treatment			
Treatment dosage, g/wk			
0.1	0.166 (0.137) [−0.103 to 0.434]	5.298 (1)	.02
0.3	0.312 (0.108) [0.100 to 0.524]		
1.0	0.823 (0.224) [0.383 to 1.263]		
Treatment duration, wk			
5	0.363 (0.141) [0.086 to 0.640]	0.012 (1)	.91
20	0.370 (0.117) [0.142 to 0.599]		
100	0.408 (0.345) [−0.268 to 1.083]		
Administration			
Intramuscular	0.243 (0.141) [−0.033 to 0.520]	3.352 (2)	.19
Oral	0.851 (0.306) [0.252 to 1.450]		
Transdermal	0.430 (0.222) [−0.006 to 0.865]		

Abbreviations: CV, coefficient of variation; NHST, null hypothesis significance test.

Discussion

To our knowledge, the present meta-analysis is the largest examination to date of the association of testosterone treatment with depressive symptoms in men, including 27 RCTs comprising 1890 men. Replicating and extending previous work,[30,43,44] we show evidence for a moderate antidepressant association of testosterone treatment compared with placebo, identifying an effect size of the overall analysis of Hedges *g* of 0.21. Based on reference ranges for depressive symptoms,[81] this effect is translatable into a clinically relevant symptom reduction by 2.2 points on the BDI-II. The National Institute for Health and Care Excellence guidelines on depression suggest a reduction of 3.0 and 2.0 points on BDI scores to be clinically significant for normal depression and treatment-resistant depression, respectively.[45,82] Furthermore, testosterone treatment revealed an efficacy OR of 2.30, suggesting the potential of testosterone treatment as adjunct therapy for men with depressive disorders. Acceptability of testosterone treatment was high, showing an OR of 0.79 for testosterone treatment-related loss to follow-up when compared with placebo. This outcome suggests that testosterone treatment is rather positively experienced and potential adverse effects seem rare.[46] Endocrine Society clinical practice guidelines also conclude that there are insufficient data to establish a causal link between testosterone treatment and clinical conditions, such as cardiovascular events or prostate cancer.[31] Still, the guidelines do not recommend testosterone treatment in testosterone-deficient men with increased risk for these conditions because much larger postmarketing surveillance studies would be necessary to assess whether testosterone treatment is associated with increased risk of rare adverse drug reactions.[31]

The between-study heterogeneity was of considerable size only when 1 outlying study was included, suggesting the presence of either bias or moderating design factors. In agreement with Elliot et al,[30] we conclude that, based on the Coch-

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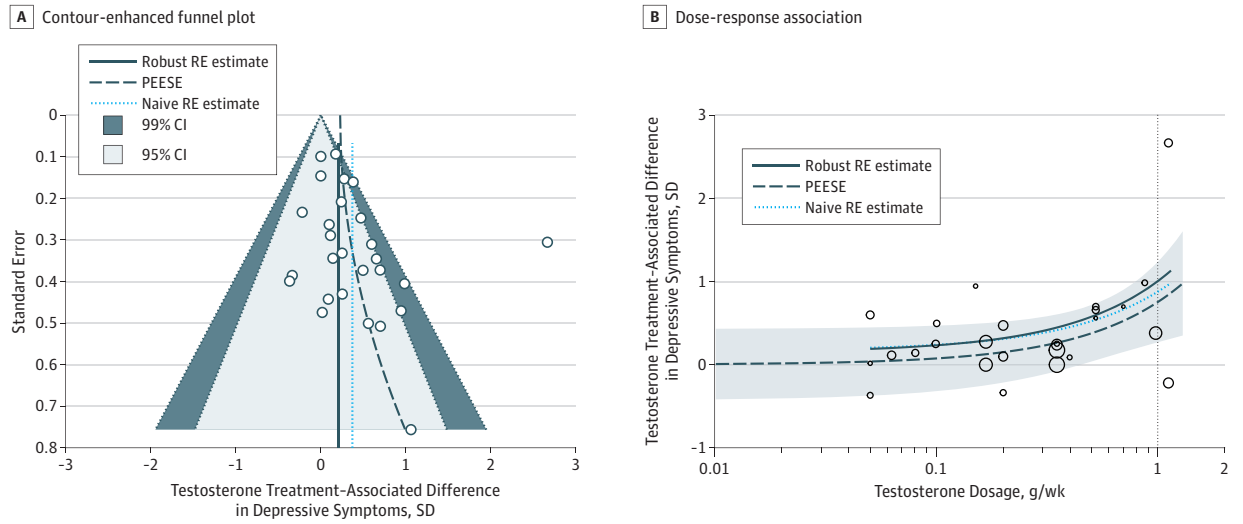
Figure 3. Funnel and Moderator Plots



A, Contour-enhanced funnel plot of observed testosterone treatment effects from all included randomized clinical trials. B, Observed (circles) and estimated (lines) testosterone treatment effectiveness as a function of the administered testosterone dosage per week. The size of the circles in Figure 3B indicates the relative sample size of each study. The shaded area represents the 95% CI of the precision-adjusted estimate (PEESE) of testosterone treatment effectiveness. RE indicates random effects.

rane Risk of Bias assessment of the 27 RCTs, most testosterone treatment studies were at high or unclear risk of bias (see Turner et al,[3] who suggest a publication bias in reporting of antidepressant trials that may lead to a 32% inflation of effect size for antidepressant treatments).

Irrespective of any bias, analysis of potential moderators revealed that dose was a likely moderator, indicating robust effects for dosages higher than 500 mg/wk (Figure 3B). Previous studies failed to detect testosterone dose-response relationships for mood, including for depressive symptoms.[30,85] Our results suggest for the first time, to our knowledge, that better treatment response may require higher dosages, although this finding requires independent replication. However, a previous RCT using a higher-dosage testosterone regimen with an initial dosage of 100 mg/d in men 65 years and older reported increased risk for cardiovascular adverse events.[86] In the testosterone trials, on the other hand, an initial dosage of 50 mg/d was used, and no increased risk for cardiovascular adverse events was identified.[42] The authors of the testosterone trials further concluded that a trial of a much larger number of men for a much longer period would be necessary to determine whether testosterone increases the risk for cardiovascular events.[87] Lower symptom variability at baseline also emerged as a potential effect predictor, demonstrating a better inferential performance of RCTs that sampled from symptomatically homogeneous source populations. Treatment duration was not significantly associated with the testosterone treatment-related reduction in depressive symptoms. Consistently, the time course of testosterone treatment effects shows considerable variation, with studies reporting beneficial effects on depressive symptoms after 6 weeks[39] up to 36 months.[58] This variation suggests that treatment effects may begin within 6 weeks of initiating testosterone treatment. In line with this reasoning, it has been suggested that testosterone treatment-related effects on depressive symptoms could become detectable after 3 to 6 weeks, and maximum effects emerge after 18 to 30 weeks.[88]

Remarkably, initial testosterone status was not a moderator of the effect of testosterone treatment on depressive symptoms. This result contradicts a previously published study showing up to a 3-fold increased incidence of MDD in hypogonadal men.[25] A previous meta-analysis also suggested that only hypogonadal men might benefit from testosterone treatment,[43] but this finding was exclusively informed by a single outlying RCT comprising 76 healthy men with low depressive burden.[80] The present meta-analysis failed to replicate this effect based on a larger sample (944 vs 1890 participants), yielding a more precise estimate of a potential moderation by gonadal status. Accordingly, the previously suggested selective effectiveness of testosterone treatment in hypogonadal men is, we believe, not substantiated by evidence, which aligns with a recent expert consensus questioning treatment decisions based on fixed testosterone threshold levels.[46]

With regard to age, no moderation effect was identified, indicating that younger and older adult men benefit similarly from testosterone treatment. By contrast, the meta-analysis of Amanatkar and colleagues[43] identified a potential detrimental effect of testosterone treatment on mood for men older than 60 years. Again, this effect was driven by the outlying study mentioned above. Thus, our analysis, in conjunction with the testosterone trials[42] and the recently conducted meta-analysis on testosterone treatment effects in hypogonadal men,[30] provides further evidence that testosterone treatment may also be efficacious in reducing depressive symptoms in older men.

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With regard to depression status, there was no evidence of a significant association with testosterone treatment-related reduction in depressive symptoms, although estimates indicate that less severely depressed men profit more, which is in line with previous research.[6] Such an association, however, is likely confounded with symptom variability at baseline in the respective studies, that is, lower variability tended to be accompanied by less severe depressive symptoms and larger testosterone treatment effects. More research is needed based on samples focusing on the testosterone treatment effect in men presenting homogeneously low depressive burden. Based on the analysis of mean scores and distribution for depressive symptoms, 2 of the 27 included RCTs were able to rigorously exclude depressed participants.[57,58] However, those 2 studies reported negligible effects for testosterone treatment on the reduction of depressive symptoms. Formulation was not robustly associated with the observed effect, suggesting the generalizability of testosterone treatment across oral, transdermal, and intramuscular routes of administration, but more research is required to confirm a meaningful absence of such differences.

Finally, the noninferiority of testosterone treatment to other antidepressants for the reduction of depressive symptoms in men remains to be elucidated because 1 study directly compared testosterone treatment with an antidepressant (fluoxetine hydrochloride) and showed no significant difference.[38]

Strengths and Limitations

Although the overall association of testosterone treatment with alleviation of depressive symptoms in men seems to be clinically relevant, the large portion of studies with high or unclear risk of bias as well as the low number of methodologically rigorous RCTs primarily addressing the effect of testosterone treatment in depressed but otherwise healthy men limits the interpretation. Because testosterone treatment has primarily been examined in hypogonadal men who do not necessarily have depression but may have various other somatic or sexual symptoms, larger preregistered RCTs of testosterone treatment defining depression as the primary end point are needed. Furthermore, the superiority of testosterone treatment over current antidepressants could not be assessed because 1 study compared an established antidepressant with testosterone treatment in depressed men.[38] Although previous meta-analyses have indicated that testosterone treatment has antidepressant potential,[30,43,44] the analysis by Elliot et al[30] was restricted to hypogonadal men, and the analyses by Amanatkar et al[43] are exclusively interpretable to the extent to which their findings are sensitive to small-study effects.[3] Against this background, our meta-analysis presents the most comprehensive and elaborate summary of testosterone treatment effects on depressive symptoms in men to date.

Conclusions

Previous research provided evidence that testosterone treatment is effective in reducing depressive symptoms in hypogonadal[30,43] or middle-aged men up to age 60 years.[43] This meta-analysis provides important new evidence that testosterone treatment may also be effective and efficacious for eugonadal and older men when higher testosterone dosages are administered. For acceptability, testosterone treatment was not significantly associated with fewer dropouts than placebo. Safety monitoring in testosterone treatment trials continues to be important owing to a lack of sufficiently powered long-term studies to determine increased risk for adverse events.[87] Because our results as well as previous investigations[30] have indicated that risk of bias is considerable in most studies, we call for large, preregistered RCTs of good quality investigating testosterone treatment's effect in men on depression as the primary outcome.

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