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RESEARCH ARTICLE

Impact of exogenous testosterone on mood: A systematic review and meta-analysis of randomized placebo-controlled trials

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BACKGROUND: In the last decade, there has been a surge of new clinical trials studying the impact of exogenous testosterone on mood. The results of these studies have been inconsistent.

METHODS: Meta-analysis of controlled clinical trials using common depression rating scales was performed.

RESULTS: Sixteen trials with a total of 944 subjects met selection criteria. Meta-analysis of data showed a significant positive impact of testosterone on mood ($z = 4.592$; $P < .0001$). Subgroup analysis showed a significant effect size of 5.279 ($P < .0001$) in the trials with a mean age of <60 years. However, the effect size was not statistically significant in those trials with a mean age of >60 years. The effect size in hypogonadal men was 4.192 ($P < .0001$), whereas the result was not statistically significant in eugonadal men. In addition, the effect size was larger in subthreshold depression compared with major depression. Oral testosterone compared with oral dehydroepiandrosterone, testosterone gel, and intramuscular testosterone did not show a significant result. Larger effect size was observed in the studies of 8 to 24 weeks' duration.

CONCLUSIONS: Testosterone may be used as a monotherapy in dysthymia and minor depression or as an augmentation therapy in major depression in middle-aged hypogonadal men.

KEYWORDS: meta-analysis, subthreshold depression, major depression, hypogonadism, testosterone, dehydroepiandrosterone

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INTRODUCTION

Men do not undergo a sudden cessation of sex steroid production as they age, as women do during their postmenopausal phase. Rather, testosterone levels decline progressively in aging men, at a rate of approximately 0.8% per year.[1] The Baltimore Longitudinal Study of Aging reported prevalence of hypogonadism, defined by 1 total testosterone level of <325 ng/dL (11.3 nmol/L), from relatively low levels for men age <49 to 12%, 19%, 28%, and 49% in men in their 50s, 60s, 70s, and 80s, respectively.[2] In addition, testosterone levels can be diminished by a variety of systemic diseases such as renal failure, cirrhosis, type 2 diabetes mellitus, chronic obstructive pulmonary disease, hemosiderosis, sickle cell disease, protein malnutrition, AIDS, cancers, metabolic syndrome and obesity, medications such as corticosteroids, abuse of drugs such as opiates, alcohol abuse, and mental disorders such as schizophrenia and depression.[3-9] Moreover, not all men with low testosterone are symptomatic. Araujo et al studied prevalence of symptomatic androgen deficiency in a diverse population of 1,475 black, Hispanic, and white men age 30 to 79 years. They defined symptomatic androgen deficiency as total testosterone levels <300 ng/dL or free testosterone levels <5 ng/dL plus presence of low libido, erectile dysfunction, osteoporosis or fracture, or ≥2 of the following symptoms: sleep disturbance, depressed mood, lethargy, and diminished physical performance. They reported that 5.6% of men in the general population met these criteria, and this prevalence was not significantly related to race or ethnic group. However, the percentage of symptomatic men with low testosterone increased markedly with age. A prevalence of 3.1% to 7.0 % in men age <70 increased markedly with age to 18.4% among those in their 70s.[10]

Despite the fact that many men with low testosterone levels are not apparently symptomatic, many others have a partial, gradual, and variable decline in testosterone associated with various somatic, sexual, and behavioral symptoms. These symptoms are characterized by insidious onset and slow progression of diminished sexual desire and erectile quality, decreased muscle mass, increased body fat, decreased bone mineral density potentially resulting in osteoporosis, weakness, fatigue, depressed mood, lack of motivation and energy, lower psychological vitality, and decreased work and sport performances.[10-14] Many of these symptoms are similar to the symptoms of depression. However, the incidence of diagnosed depression in hypogonadal men is much higher than eugonadal men. For example, Shores et al studied 278 men age ≥45 without prior diagnosed depressive illness. They found that the 2-year incidence of depression in men with total testosterone <200 ng/dL was 21.7% compared with 7.1% in the eugonadal men.[15] Also, Aydogan et al reported a 23.1% prevalence rate of depressive symptoms in men with congenital hypogonadotropic hypogonadism compared with 5% in age-matched healthy eugonadal males.[16] Moreover, Khera et al reported that 17.3% of hypogonadal men have moderately severe to severe depressive symptoms.[17] Because depression is fairly common in hypogonadal men and many of the symptoms of hypogonadism are similar to depression, it is important to pay special attention to testosterone levels in men with depressive symptoms. Different levels of testosterone could be associated with the presence of specific clinical symptoms. In a study of 434 men age 50 to 86 years, Zitzmann et al reported that androgen-induced prevalence of loss of libido or vigor increased below testosterone concentrations of 15 nmol/L (432 ng/dL), whereas depression was significantly more present in men with testosterone concentrations below 10 nmol/L (288 ng/dL).[18] However, when Lackner et al studied 675 healthy men age 45 to 60, they could not identify a depression-specific testosterone threshold.[19]

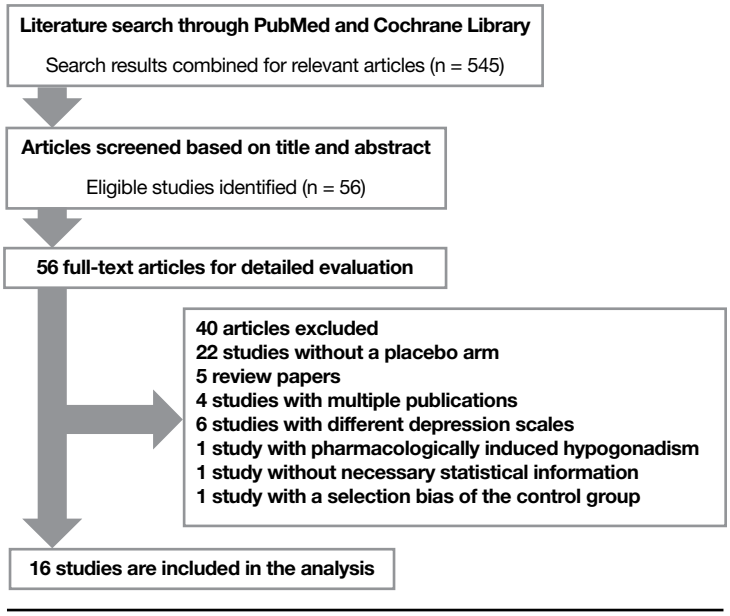
Testosterone has a prominent effect on different aspects of sexual performance. Low testosterone in men is associated with low libido, erectile dysfunction, and anorgasmia.[20] An international, multicenter, one-arm observational study of 1,438 hypogonadal men in 23 countries showed that the percentage of patients with "low" or "very low" levels of sexual desire/libido decreased from 64% at baseline to 10%, and that the percentage of patients with moderate, severe, or extremely severe erectile dysfunction decreased from 67% to 19% after 9 to 12 months of testosterone treatment.[21] A meta-analysis of 17 trials showed that testosterone has a significant effect on libido in hypogonadal men.[22] Another meta-analysis showed that in men with an average testosterone level below 12 nmol/L (346 ng/dL), testosterone treatment moderately improved the number of nocturnal erections, sexual thoughts and motivation, number of successful intercourses, scores of erectile function, and overall sexual satisfaction, whereas exogenous testosterone had no effect on erectile function in eugonadal men compared with placebo.[13] In addition, depression is associated with decreased libido, diminished erectile function in men, and decreased sexual activity.[22] Systematic studies suggest that low libido is present in up to 75% of depressed patients.[22,23] Also, the

Massachusetts Male Aging Study (MMAS) showed that 41% of men with depressive symptoms had moderate to complete erectile dysfunction—twice the level of men who were not depressed.[24] When comparing a group of depressed men on no antidepressant therapy to a control group with normal moods, Rizvi et al showed that hypogonadal men with major depressive disorder (MDD) had lower scores on all domains of sexual function compared with nondepressed men with hypogonadism, concluding that the presence of MDD appears to be a stronger factor than low testosterone as a highly predictive value for sexual outcomes. However, this study indicated that testosterone levels interact with MDD status to affect orgasm and desire.[25]

Depression is associated with lower levels of testosterone. Barrett-Connor et al studied 856 men age 50 to 89 and reported that Beck Depression Inventory (BDI) scores were significantly and inversely associated with bioavailable testosterone, independent of age, weight change, and physical activity. They showed that bioavailable testosterone levels were 17% lower in the men with categorically defined depression than were the levels observed in all other men.[26] Also, Almeida et al studied 3,987 men age 71 to 89, including 203 men with depression. Participants with depression had significantly lower total and free testosterone concentrations than nondepressed men.[27] Therefore, there was always a general trend to use exogenous testosterone in depressed men in order to elevate their mood and energy levels, in addition to correcting sexual dysfunction in these patients.

In the last decade, there has been a surge of new studies investigating the impact of exogenous testosterone on mood. These studies used testosterone as monotherapy or as an augmentation to antidepressants. A review of these studies shows many inconsistencies. Differences in the results of these studies may reflect differences in participant populations (eg, eugonadal vs hypogonadal participants, younger vs older subjects, participants with minor depression vs major depression vs normal mood), duration of study, route of administration (gel vs intramuscular [IM] vs oral), and concomitant medical illness (eg, HIV, Alzheimer's disease).[28] These studies also were small in the number of participants. In order to clarify this confusing picture, we performed a meta-analysis using these studies to compare the impact of exogenous testosterone on these different subpopulations.

FIGURE 1
Flow diagram of the study selection process



METHODS

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocol for reporting of a meta-analysis was followed in this study.[29]

Eligibility criteria

Because depression in some individuals improves fully or partially without the use of any medication,[30] we included only studies that had a placebo arm. Given this criterion, many studies without a control group were eliminated. We tried to include all randomized controlled trials with different types of participants (eg, different age groups with or without hypogonadism, HIV-positive or HIV-negative status), with different level of mood from major depression to subthreshold depression (including minor depression and dysthymia), as well as participants with normal mood, with all types of interventions used in different studies (eg, oral, patch, gel, and IM testosterone). Because dehydroepiandrosterone (DHEA) is a precursor of testosterone, studies investigating DHEA's effects were included in this analysis as well. We also included all

TABLE 1
Summary of included studies in the meta-analysis of testosterone impact on mood

Source	N	Mean age (SD), years	Inclusion criteria	Duration	Androgen dose and route of administration	Conclusions
Pope et al, 2010[28]	95	50.6 (8.2)	HG/MDD on AD	6 weeks	5 g/d T gel	T is not generally effective in depressed men
Giltay et al, 2010[31]	170	52.1 (9.6)	HG/metabolic syndrome	30 weeks	1000 mg IM T at weeks 0, 6, and 18	T may be effective in men with HG with metabolic syndrome
Grinspoon et al, 2000[32]	39	41.6 (1.1)	HG/HIV with wasting	24 weeks	300 mg IM T q 3 weeks	T significantly improved depression inventory scores
Haren et al, 2005[33]	58	68.5 (6)	At least 2 symptoms on ADAM	52 weeks	80 mg bid oral T	Oral T is not effective in older men with HG
Lu et al, 2006[34]	11	69.3 (8.4)	Alzheimer's disease	24 weeks	75 mg/d T gel	T had no effect on BDI
Orengo et al, 2005[35]	12	63 (8.5)	HG/MDD on AD	12 weeks	5 g/d T gel	T had no effect, when compared to placebo
Pope et al, 2000[36]	53	20 to 50 y/o	Normal mood	6 weeks	150 to 600 mg IM T	Most individuals showed minimal changes. Several individuals developed prominent effects
Pope et al, 2003[37]	21	48.9 (8.5)	HG/MDD on AD	8 weeks	10 g/d T gel	T appears to have antidepressant effects in men with HG and MDD
Rabkin et al, 2000[38]	26	38 (7.3)	HIV	6 weeks	Rising dose 200 to 400 mg IM T biweekly	T alleviates depressed mood and restores energy
Rabkin et al, 2004[39]	60	41 (7.7)	HIV	8 weeks	Rising dose 200 to 400 mg IM T biweekly	T is not more effective than placebo
Rabkin et al, 2006[40]	133	44 (9)	HIV/SD	8 weeks	Rising dose 100 to 400 mg/d oral DHEA	DHEA is effective in restoring SD in HIV-positive men
Seidman et al, 2005[41]	26	46.4 (10.8)	MDD on AD	6 weeks	200 mg IM T biweekly	T and placebo augmented mood in patients already treated with an SSRI
Seidman and Roose, 2006[42]	30	52 (8)	HG/MDD	6 weeks	200 mg IM T biweekly	There was no difference between the PG and TRT groups
Seidman et al, 2009[43]	23	50.6 (7)	HG/Dysthymia	12 weeks	200 mg IM T q 10 d	T may be effective in men with HG with late-onset dysthymia
Shores et al, 2009[44]	27	57.1 (5.7)	HG/SD	12 weeks	7.5 mg/d T gel	T may be effective in men with HG with SD
Zhang et al, 2012[45]	160	59.4 (6.3)	HG/positive score on ADAM	24 weeks	120 to 160 mg oral T daily	T significantly improved psychological scores

AD: antidepressant; ADAM: Androgen Deficiency in Aging Male questionnaire; BDI: Beck Depression Inventory; DHEA: dehydroepiandrosterone; HG: hypogonadism; IM: intramuscular; MDD: major depressive disorder; PG: placebo group; SD: subthreshold depression; SSRI: selective serotonin reuptake inhibitor; T: testosterone; TRT: testosterone replacement therapy.

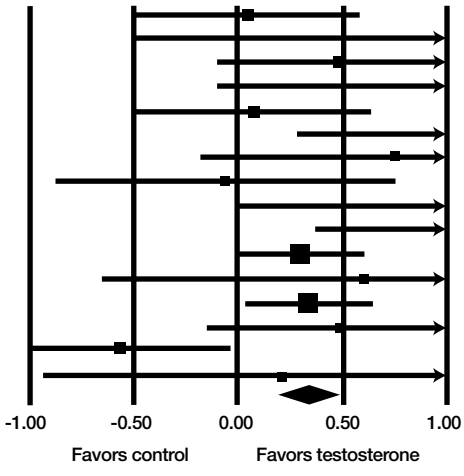
studies with different outcome measures that were commonly used as a depression and mood scale, including the Hamilton Depression Rating Scale (HAM-D), Patient Health Questionnaire–9 (PHQ-9), Beck Depression Inventory (BDI), Geriatric Depression Scale (GDS), Center for Epidemiological Studies Depression Scale (CESD), 36-Item Short Form Health Survey (SF-36), and Montgomery-Åsberg Depression Rating Scale (MADRS).

Information source

PubMed was the primary source of study information. The Cochrane Library was searched to find any missing studies in the primary source. In addition, the reference lists of the retrieved articles and available review articles were hand checked. We also contacted some authors to identify additional studies relevant to this meta-analysis.

FIGURE 2
Meta-analysis of the impact of testosterone on mood

Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P	Relative weight
Pope et al, 2000	0.283	0.039	0.080	–0.516	0.593	0.137	.891	6.65
Pope et al, 2003	0.871	1.189	0.759	–0.519	2.897	1.365	.172	0.70
Pope et al, 2010	0.300	0.484	0.090	–0.104	1.073	1.614	.107	5.90
Rabkin et al, 2000	0.648	1.163	0.420	–0.107	2.434	1.795	.073	1.27
Rabkin et al, 2004	0.286	0.074	0.082	–0.487	0.635	0.259	.795	6.49
Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001	13.20
Seidman et al, 2005	0.475	0.749	0.226	–0.183	1.680	1.576	.115	2.36
Seidman and Roose, 2006	0.415	–0.062	0.173	–0.877	0.752	–0.150	.880	3.08
Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049	1.23
Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007	2.03
Zhang et al, 2012	0.159	0.300	0.025	–0.012	0.611	1.886	.059	21.04
Lu et al, 2006	0.640	0.601	0.409	–0.653	1.855	0.939	.348	1.30
Giltay et al, 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035	20.92
Grinspoon et al, 2000	0.326	0.486	0.106	–0.152	1.125	1.493	.136	5.01
Haren et al, 2005	0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037	7.28
Orengo et al, 2005	0.587	0.211	0.345	-0.939	1.362	0.360	.719	1.54
	0.073	0.335	0.005	0.192	0.478	4.592	.000	



Literature search

Because DSM-IV-TR was published in 2000 and most current testosterone formulations and routes of administration became available only in the last decade, we chose 2000 as the cutoff point for the literature search. We primarily searched PubMed (from January 1, 2000 to November 20, 2012) in 4 domains with these search terms: 1) Androgen [Title/Abstract] and Mood [Title/Abstract], with 182 results; 2) Androgen [Title/Abstract] and Depression [Title/Abstract], with 63 results; 3) Testosterone [Title/Abstract] and Mood [Title/Abstract], with 160 results; and 4) Testosterone [Title/Abstract] and Depression [Title/Abstract], with 140 results. The Cochrane Library and reference list of retrieved articles were also searched for missing articles.

Study selection

Two reviewers collaboratively performed the selection part of this study. All of the search results were reviewed through their title and abstract. Then, all of the relevant articles, including review articles, evaluating the impact of testosterone on mood were marked for more detailed evaluation. Full texts of the relevant articles were retrieved and reviewed. We included randomized controlled trials with our preset depression rating scales (HAM-D, BDI, GDS, MADRS, CESD, PHQ-9, and SF-36). Studies without a placebo arm or with different scales than our preset scales, non-English articles, trials with a bias in methodology, and studies with pharmacologically induced hypogonadism were excluded.

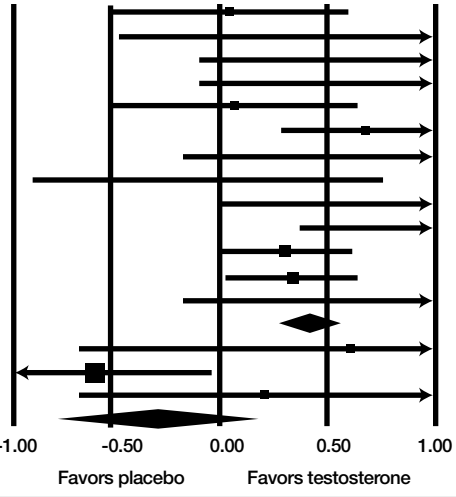
Data extraction

Full texts of the relevant articles were retrieved, and all of the necessary data items were extracted from the full text of these articles and transferred to the designated data extraction sheets. Data items included study design; number of subjects, including completers and noncompleters, and number of subjects in both test and control groups; mean and range of age; funding sources; recruitment method; sample source; duration of study; intervention type, including route of administration, dose, frequency and formulation of androgens; baseline and end-of-study depression rating scores and testosterone levels; concomitant medical illnesses, including HIV, dementia, and hypogonadism; diagnosed mental illnesses, including major depression and subthreshold depression; drug history of subjects, particularly antidepressants; drug abuse, such as opiates; and statistical data.

Duplicate publications were identified by author name, number of subjects, study duration, methodology, and outcomes. Since different laboratories may have different ranges for normal testosterone and different studies may have varying thresholds for hypogonadism, we considered the population of hypogonadism as men-

FIGURE 3
Subgroup meta-analysis based on mean age in the selected studies

Group by comparison	Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P
<60	Pope et al, 2000	0.283	0.039	0.080	–0.516	0.593	0.137	.891
<60	Pope et al, 2003	0.871	1.189	0.759	–0.519	2.897	1.365	.172
<60	Pope et al, 2010	0.300	0.484	0.090	–0.104	1.073	1.614	.107
<60	Rabkin et al, 2000	0.648	1.163	0.420	–0.107	2.434	1.795	.073
<60	Rabkin et al, 2004	0.286	0.074	0.082	–0.487	0.635	0.259	.795
<60	Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001
<60	Seidman et al, 2005	0.475	0.749	0.226	–0.183	1.680	1.576	.115
<60	Seidman and Roose, 2006	0.415	–0.062	0.173	–0.877	0.752	–0.150	.880
<60	Seidman at al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049
<60	Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007
<60	Zhang et al, 2012	0.159	0.300	0.025	–0.012	0.611	1.886	.059
<60	Giltay et al, 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035
<60	Grinspoon et al, 2000	0.326	0.486	0.106	–0.152	1.125	1.493	.136
<60		0.077	0.406	0.006	0.255	0.557	5.279	.000
>60	Lu et al, 2006	0.640	0.601	0.409	–0.653	1.855	0.939	.348
>60	Haren et al, 2005	0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037
>60	Orengo et al, 2005	0.587	0.211	0.345	–0.939	1.362	0.360	.719
>60		0.229	–0.297	0.053	–0.746	0.152	–1.296	.195



tioned in the original study article. Therefore, we did not implement a specific threshold for low testosterone. In addition, we assumed populations with a mean age of ≥60 as the older population.

Data analysis

Because our selected studies had a wide range of methodology and outcome measures (different depression scales) with a diverse range of statistical data, we decided to compute Hedges *g* in each study and measure total effect size by this means. In addition, we compared different subpopulations by computing effect size in each subgroup. We used Comprehensive Meta-Analysis (CMA, version 2) software (Biostat, Inc.) to analyze the data. This software gave us the opportunity to enter different statistical data. In 9 studies, it computed Hedges *g* by response rate, which was defined as a reduction of at least 50% in the depression rating scores from baseline. Data regarding the response rates in the testosterone and placebo groups and the number of subjects were used for these studies. Only the number of participants who completed each study (not the number of participants at the beginning of the study) was entered in this meta-analysis. For 3 studies, data concerning the means of depression scores at the beginning and end of the study, with sample size and *P* value for this change in both the testosterone and placebo groups, were used to compute Hedges *g*. In one study, available Hedges *g* and its variance plus the number of subjects who completed the study (called completers) were entered. In another study, difference in means, *P* value for this change, and number of completers in each testosterone and placebo group were used to compute Hedges *g*. In one study, we used *F* for difference in change between the testosterone and placebo groups, and the number of completers in the testosterone and placebo groups. Hedges *g* in one study was computed based on the available chi-squared value and number of completers.

To assess the risk of publication bias, several tools were used. We used Begg and Mazumdar's rank correlation test and Egger's regression intercept. The statistically significant results in these tests ($P < .05$) suggest that publication bias exists. In addition, we used Classic fail-safe N to indicate the number of null studies required to nullify the observed effect. Moreover, a funnel plot was used to visually depict this bias.

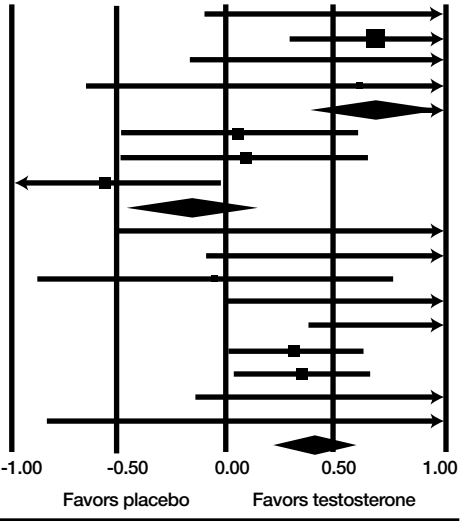
RESULTS

Study flow

Following screening, 545 studies were reviewed. Fifty-six relevant articles were identified and retrieved for

FIGURE 4
Subgroup meta-analysis in hypogonadal vs eugonadal subjects

Group by comparison	Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P
Both	Rabkin et al, 2000	0.648	1.163	0.420	–0.107	2.434	1.795	.073
Both	Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001
Both	Seidman et al, 2005	0.475	0.749	0.226	–0.183	1.680	1.576	.115
Both	Lu et al, 2006	0.640	0.601	0.409	–0.653	1.855	0.939	.348
Both		0.171	0.712	0.029	0.376	1.047	4.153	.000
Eugonadal	Pope et al, 2000	0.283	0.039	0.080	–0.516	0.593	0.137	.891
Eugonadal	Rabkin et al, 2004	0.286	0.074	0.082	–0.487	0.635	0.259	.795
Eugonadal	Haren et al, 2005	0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037
Eugonadal		0.161	–0.165	0.026	–0.482	0.151	–1.024	.306
Hypogonadal	Pope et al, 2003	0.871	1.189	0.759	–0.519	2.897	1.365	.172
Hypogonadal	Pope et al, 2010	0.300	0.484	0.090	–0.104	1.073	1.614	.107
Hypogonadal	Seidman and Roose, 2006	0.415	–0.062	0.173	–0.877	0.752	–0.150	.880
Hypogonadal	Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049
Hypogonadal	Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007
Hypogonadal	Zhang et al, 2012	0.159	0.300	0.025	–0.012	0.611	1.886	.059
Hypogonadal	Giltay et al, 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035
Hypogonadal	Grinspoon et al, 2000	0.326	0.486	0.106	–0.152	1.125	1.493	.136
Hypogonadal	Orengo et al, 2005	0.587	0.211	0.345	–0.939	1.362	0.360	.719
Hypogonadal		0.093	0.390	0.009	0.208	0.572	4.192	.000



Both: trials with both hypogonadal and eugonadal subjects.

more detailed evaluation. The full texts of these studies were reviewed and all studies without a placebo arm (22 articles), with scales other than our preset scales (6 articles), and review articles (5 articles) were excluded. Four of the studies were published in >1 journal. Duplicate articles were also excluded. One study investigated the impact of testosterone on healthy subjects with pharmacologically induced hypogonadism. Because the acute induction was artificial, with different interfering adverse effects of these medications, this study was also excluded. Another study was excluded because it compared hypogonadal men with a control group of eugonadal men. Moreover, 1 small study of 11 subjects with mild cognitive impairment was excluded due to lack of necessary statistical information. Ultimately, 16 studies were identified for inclusion in the meta-analysis.[28,31-45] The selection process is summarized in **FIGURE 1**.

Trials description

All of the 16 selected studies were randomized controlled trials published in English. Of the 16 articles, 3 each were written by Pope, Rabkin, and Seidman and colleagues. The remaining 7 articles were written by various authors. The duration of the intervention was from a minimum of 6 weeks to a maximum of 52 weeks. A total number of 944 subjects age 20 to 80 were included. Four trials were conducted with HIV-infected patients. Nine trials studied the impact of testosterone on hypogonadal men, while 3 trials were conducted on men with normal testosterone levels at baseline. Four trials had a mixture of participants with either low or normal testosterone levels. The intervention type varied in these studies and included 8 trials using IM testosterone injections, 5 trials with transdermal testosterone gel, 2 trials with oral testosterone, and 1 trial with oral DHEA. Depression rating scores were measured based on HAM-D in 12 trials,[28,35-45] BDI in 3 trials,[31,32,34] and GDS in 1 trial.[33] Several studies measured depression rating scores using multiple scales. In this case, we used the HAM-D as the principal scale for data analysis. Most of these trials were funded by pharmaceutical companies and the National Institutes of Health. A summary of the 16 studies in this meta-analysis is shown in **TABLE 1**.

Clinical outcome

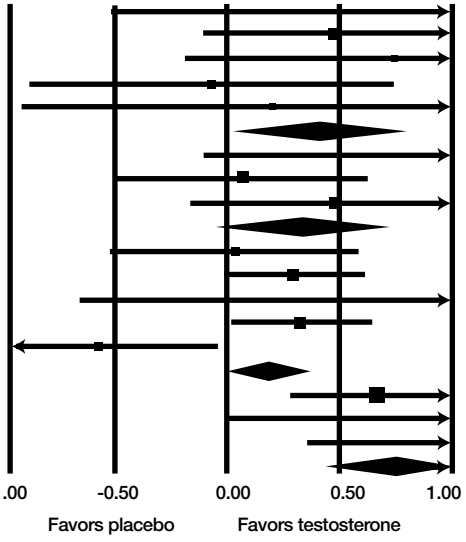
Meta-analysis showed a significant positive impact of testosterone on mood compared with placebo ($z = 4.592$; $P < .0001$) (**FIGURE 2**).

To assess the risk of publication bias across this study, several tests were performed. Begg and Mazumdar's

FIGURE 5

Subgroup meta-analysis based on level of depression

Group by comparison	Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P
MDD	Pope et al, 2003	0.871	1.189	0.759	–0.519	2.897	1.365	.172
MDD	Pope et al, 2010	0.300	0.484	0.090	–0.104	1.073	1.614	.107
MDD	Seidman et al, 2005	0.475	0.749	0.226	–0.183	1.680	1.576	.115
MDD	Seidman and Roose, 2006	0.415	–0.062	0.173	–0.877	0.752	–0.150	.880
MDD	Orengo et al, 2005	0.587	0.211	0.345	–0.939	1.362	0.360	.719
MDD		0.198	0.411	0.039	0.024	0.799	2.080	.038
Mixed	Rabkin et al, 2000	0.648	1.163	0.420	–0.107	2.434	1.795	.073
Mixed	Rabkin et al, 2004	0.286	0.074	0.082	–0.487	0.635	0.259	.795
Mixed	Grinspoon et al, 2000	0.326	0.486	0.106	–0.152	1.125	1.493	.136
Mixed		0.204	0.344	0.042	–0.056	0.744	1.685	.092
NA	Pope et al, 2000	0.283	0.039	0.080	–0.516	0.593	0.137	.891
NA	Zhang et al, 2012	0.159	0.300	0.025	–0.012	0.611	1.886	.059
NA	Lu et al, 2006	0.640	0.601	0.409	–0.653	1.855	0.939	.348
NA	Giltay et al 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035
NA	Haren et al, 2005	0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037
NA		0.096	0.179	0.009	–0.010	0.368	1.859	.063
SD	Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001
SD	Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049
SD	Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007
SD		0.180	0.805	0.032	0.453	1.158	4.480	.000



MDD: major depressive disorder; Mixed: trials with a mixture of participants from MDD to SD; NA: trials without enough data describing the diagnosed depression rate among participants or trials studying testosterone on subjects without any diagnosed depression; SD: subthreshold depression, including dysthymia and minor depression.

rank correlation test and Egger's regression intercept did not show significant evidence for publication bias. Rank order correlation (Kendall tau-b) was 0.35833 with a 2-tailed *P* value of .05287, and the intercept (B0) was 0.87655, 95% CI (–0.65358 to 2.40667) with the 2-tailed *P* value of .23945. However, the funnel plot could not rule out the risk of publication bias. Classic fail-safe N was 81. This means that we would have needed to locate and include 81 null studies (ie, 5.1 missing studies for every selected study) for the effect to be nullified.

Subgroup analyses

We analyzed the data based on age, duration of study, route of administration, severity of depression, HIV status, and hypogonadism status.

Age. Because some overlap exists in age range between selected studies, analysis was based on mean age. Studies were divided into 2 subgroups: age <60 and age ≥60 (older). Three studies with 81 participants were identified in the subgroup of older patients, and the remainder were included in the subgroup of patients age <60. By comparison, we found a significantly large positive effect size of 5.279 ($z = 5.279$; $P < .0001$) in the subgroup of patients age <60. However, the effect size in the older subpopulation was negative and did not reach significance ($z = –1.296$; $P = .195$) (**FIGURE 3**).

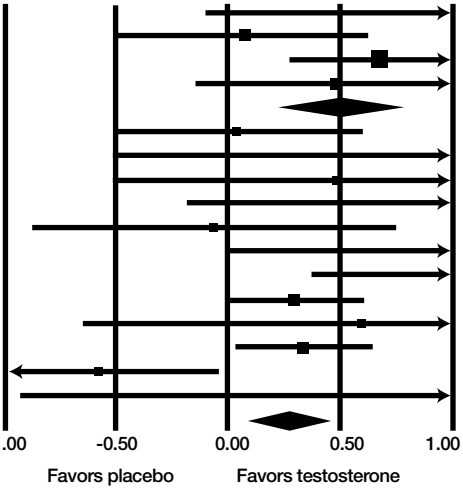
Hypogonadism vs eugonadism. Based on the study's inclusion criteria, trials were divided into 3 categories: hypogonadal, eugonadal, and trials with both subjects. Of 16 trials, 9 trials with 577 hypogonadal subjects and 3 trials with 171 eugonadal subjects were identified. We categorized 4 trials as having a mixture of hypogonadal and eugonadal participants in both categories. By comparison, there was a significant, positive effect size in the hypogonadal subgroup ($z = 4.192$; $P < .0001$) However, effect size in the eugonadal subpopulation was negative and did not reach significance. ($z = -1.024$; $P = .306$) This comparison is summarized in **FIGURE 4.**

Level of depression. Of the 16 selected studies, 5 trials (n = 184) studied the effect of testosterone on subjects with major depressive disorder (MDD) diagnosed based on DSM-IV criteria. Four of these 5 trials[28,35,37,41] used testosterone to augment the effect of other antidepressants, and 1 trial[42] used testosterone as monotherapy. Three trials (n = 83) among these 16 trials studied the impact of testosterone on subthreshold depression, including dysthymia and minor depression.[40,43,44] Shores et al (2009)[44] and Rabkin et al (2006)[40] had the mixture of dysthymia and

FIGURE 6

Subgroup meta-analysis in HIV-positive vs HIV-negative subjects

Group by comparison	Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P
HIV	Rabkin et al, 2000	0.648	1.163	0.420	–0.107	2.434	1.795	.073
HIV	Rabkin et al, 2004	0.286	0.074	0.082	–0.487	0.635	0.259	.795
HIV	Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001
HIV	Grinspoon et al, 2000	0.326	0.486	0.106	–0.152	1.125	1.493	.136
HIV		0.143	0.511	0.020	0.230	0.792	3.570	.000
NA	Pope et al, 2000	0.283	0.039	0.080	–0.516	0.593	0.137	.891
NA	Pope et al, 2003	0.871	1.189	0.759	–0.519	2.897	1.365	.172
NA	Pope et al, 2010	0.300	0.484	0.090	–0.104	1.073	1.614	.107
NA	Seidman et al, 2005	0.475	0.749	0.226	–0.183	1.680	1.576	.115
NA	Seidman and Roose, 2006	0.415	–0.062	0.173	–0.877	0.752	–0.150	.880
NA	Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049
NA	Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007
NA	Zhang et al, 2012	0.159	0.300	0.025	–0.012	0.611	1.886	.059
NA	Lu et al, 2006	0.640	0.601	0.409	–0.653	1.855	0.939	.348
NA	Giltay et al, 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035
NA	Haren et al, 2005	0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037
NA	Orengo et al, 2005	0.587	0.211	0.345	–0.939	1.362	0.360	.719
NA		0.085	0.273	0.007	0.107	0.439	3.223	.001



NA: subjects with negative HIV/AIDS.

minor depression in their participants; however, Seidman et al (2009) only studied this effect in patients diagnosed with dysthymia. Three trials (n = 125) had varieties of participants, from normal mood to diagnosed MDD (defined as Mixed in **FIGURE 5**), and 5 trials (n = 452) did not describe the level of depression in their participants, but those trials predominantly recruited subjects with normal mood to minor depression. As shown in **FIGURE 5**, the strongest effect was observed in subjects with subthreshold depression (z = 4.480; P < .0001). In the category of MDD, the effect size was smaller than that for subthreshold depression but was still was significant and large (z = 2.080; P = .038). The effect of testosterone on the last 2 subgroups was positive but did not reach statistical significance.

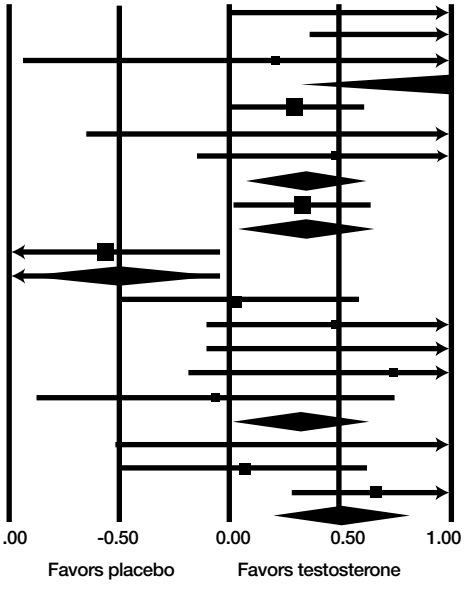
HIV/AIDS. Four trials (n = 258) out of the 16 selected trials studied the impact of testosterone in HIV-positive subjects.[32,38-40] For patients who were HIV positive, the impact of testosterone was slightly larger numerically than for participants with negative HIV status (z = 3.570, P < .0001 in HIV-positive patients vs z = 3.223, P = .001 in HIV-negative patients) (**FIGURE 6**).

Duration of treatment. The 16 selected studies are categorized by 6, 8, 12, 24, 30, and 52 weeks based on their duration of treatment. We compared the impact of testosterone on mood in these 6 subgroups. Five trials (n = 230) in the category of 6 weeks, 3 trials (n = 214) of 8 weeks, 3 trials (n = 62) of 12 weeks, 3 trials (n = 210) of 24 weeks, 1 trial (n = 170) of 30 weeks, and another trial (n = 58) of 52 weeks were compared in this subgroup meta-analysis. The effect size of testosterone in trials with a duration of 6 weeks was positive but nonsignificant (z = 1.926; P = .054). This number peaks at 8 weeks (z = 3.095; P = .002) to 12 weeks (z = 2.944; P = .003), and continues to 24 weeks (z = 2.497; P = .013), and then declines at 30 weeks (z = 2.104; P = .035). However, the impact was negative in the only trial with 52 weeks' duration treated with oral testosterone (z = –2.090; P = .037). The results of this subgroup meta-analysis are summarized in **FIGURE 7**.

Route of administration. Of the 16 selected trials, 8 trials[31,32,36,38,39,41-43] with IM administration of testosterone, 5 trials[28,34,35,37,44] with testosterone gel, 2 trials[33,45] with oral testosterone, and 1 trial[40] with oral DHEA were compared in a subgroup meta-analysis. The number of subjects in each category was 427, 166, 218, and 133, respectively. The effect size was 3.069 (P = .002) in the gel subgroup; z = 2.967 (P = .003) in the IM subgroup; 0.565 (P = .572) in the oral testosterone subgroup; and 3.350 (P = .001) in the oral DHEA subgroup. Oral testosterone, in contrast to oral DHEA, testosterone gel, and IM testosterone, did not show a significant result. The results of this subgroup meta-analysis are summarized in **FIGURE 8**.

FIGURE 7
Subgroup meta-analysis based on the duration of intervention

Group by comparison	Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P
12 weeks	Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049
12 weeks	Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007
12 weeks	Orengo et al, 2005	0.587	0.211	0.345	–0.939	1.362	0.360	.719
12 weeks		0.333	0.979	0.111	0.327	1.631	2.944	.003
24 weeks	Zhang et al, 2012	0.159	0.300	0.025	–0.012	0.611	1.886	.059
24 weeks	Lu et al, 2006	0.640	0.601	0.409	–0.653	1.855	0.939	.348
24 weeks	Grinspoon et al, 2000	0.326	0.486	0.106	–0.152	1.125	1.493	.136
24 weeks		0.139	0.348	0.019	0.075	0.622	2.497	.013
30 weeks	Giltay et al, 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035
30 weeks		0.159	0.336	0.025	0.023	0.648	2.104	.035
52 weeks	Haren et al, 2005	0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037
52 weeks		0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037
6 weeks	Pope et al, 2000	0.283	0.039	0.080	–0.516	0.593	0.137	.891
6 weeks	Pope et al, 2010	0.300	0.484	0.090	–0.104	1.073	1.614	.107
6 weeks	Rabkin et al, 2000	0.648	1.163	0.420	–0.107	2.434	1.795	.073
6 weeks	Seidman et al, 2005	0.475	0.749	0.226	–0.183	1.680	1.576	.115
6 weeks	Seidman and Roose, 2006	0.415	–0.062	0.173	–0.877	0.752	–0.150	.880
6 weeks		0.166	0.320	0.028	–0.006	0.646	1.926	.054
8 weeks	Pope et al, 2003	0.871	1.189	0.759	–0.519	2.897	1.365	.172
8 weeks	Rabkin et al, 2004	0.286	0.074	0.082	–0.487	0.635	0.259	.795
8 weeks	Rabkin et al, 2006	0.201	0.672	0.040	0.279	1.066	3.350	.001
8 weeks		0.162	0.500	0.026	0.183	0.816	3.095	.002



Result of randomized controlled trials not included in this meta-analysis

TABLE 2 summarizes the characteristics of 9 randomized controlled trials not included in this meta-analysis.[16,46-53] Reasons for exclusion were depression scales other than preset scales, presence of perceived bias, lack of useful statistical data, and hypogonadism induced by medication.

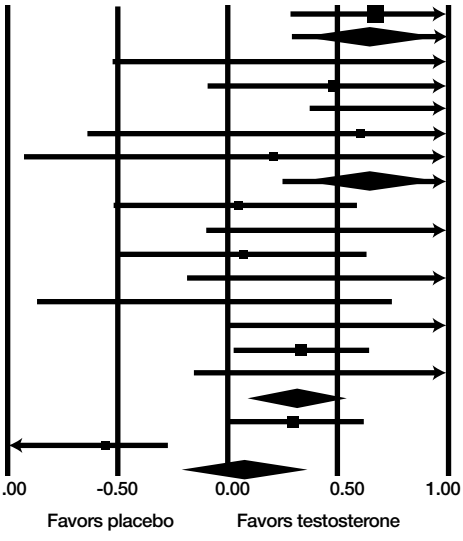
DISCUSSION

This meta-analysis indicates that exogenous testosterone has a robust effect on depressed men with hypogonadism but not on eugonadal men. As the world population is progressively aging, with the help of advanced health care and modern medicine, the prevalence of men with hypogonadism is rising. In addition to the increasing rate of hypogonadism, the rate of depression is several times higher in men with low testosterone compared with eugonadal men. Although testosterone replacement therapy (TRT) has a large positive impact on hypogonadal men, our subgroup meta-analysis showed that this effect is not statistically significant in older men. A major limitation is the inability to separate the ages in several studies. Therefore, we used a mean age to compare subgroups of age <60 with older subpopulations with a mean age ≥60. Hence, 3 trials were set in the subgroup of age <60. In addition to age, there may be other confounds to investigate in order to understand the effects of TRT in older adults. In Lu et al (2006), the study investigated the impact of TRT on the combination of hypogonadal and eugonadal patients with Alzheimer's disease. Haren et al (2005) studied older men (age >60) with low normal testosterone. Finally, Orengo et al (2005) studied the impact on hypogonadal men with major depression. Although this subgroup with a wide range of testosterone levels does not homogeneously reflect subpopulations of older men with hypogonadism, others have shown similar results. Kenny et al (2004) reported that no significant changes from the baseline were found in GDS scores after TRT.[52] In addition, Sih et al (1997) reported no effects after treatment with TRT on the GDS scores in hypogonadal older men.[54] Moreover, Khera et al (2012) studied the impact of testosterone gel on PHQ-9 scores of 849 hypogonadal men in a 12-month single-arm, multicenter observational study in a US-based registry trial.[17] Their subcohort analysis also did not show a clinically meaningful improvement in depression scores in

FIGURE 8

Subgroup meta-analysis based on route of administration

Group by comparison	Study name	Standard error	Std diff in means	Variance	Lower limit	Upper limit	z	P
DHEA	Rabkin et al, 2006	0.201	0.673	0.040	0.279	1.066	3.350	.001
DHEA		0.201	0.673	0.040	0.279	1.066	3.350	.001
Gel	Pope et al, 2003	0.871	1.189	0.759	–0.519	2.897	1.365	.172
Gel	Pope et al, 2010	0.300	0.484	0.090	–0.104	1.073	1.614	.107
Gel	Shores et al, 2009	0.512	1.370	0.262	0.367	2.373	2.678	.007
Gel	Lu et al, 2006	0.640	0.601	0.409	–0.653	1.855	0.939	.348
Gel	Orengo et al, 2005	0.587	0.211	0.345	–0.939	1.362	0.360	.719
Gel		0.215	0.661	0.046	0.239	1.083	3.069	.002
IM	Pope et al, 2000	0.283	0.039	0.080	–0.516	0.593	0.137	.891
IM	Rabkin et al, 2000	0.648	1.163	0.420	–0.107	2.434	1.795	.073
IM	Rabkin et al, 2004	0.286	0.074	0.082	–0.487	0.635	0.259	.795
IM	Seidman et al, 2005	0.475	0.749	0.226	–0.183	1.680	1.576	.115
IM	Seidman and Roose, 2006	0.415	–0.062	0.173	–0.877	0.752	–0.150	.880
IM	Seidman et al, 2009	0.657	1.296	0.432	0.008	2.584	1.973	.049
IM	Giltay et al, 2010	0.159	0.336	0.025	0.023	0.648	2.104	.035
IM	Grinspoon et al, 2000	0.326	0.486	0.106	–0.152	1.125	1.493	.136
IM		0.106	0.316	0.011	0.107	0.524	2.967	.003
Oral	Zhang et al, 2012	0.159	0.300	0.025	–0.012	0.611	1.886	.059
Oral	Haren et al, 2005	0.270	–0.565	0.073	–1.095	–0.035	–2.090	.037
Oral		0.137	0.077	0.019	–0.191	0.346	0.565	.572



DHEA: oral dehydroepiandrosterone; Gel: transdermal gel testosterone; IM: intramuscular testosterone; Oral: oral testosterone.

hypogonadal men age ≥60 compared with hypogonadal men age <60.

The effect size of exogenous testosterone on subthreshold depression, including dysthymia and minor depression, was large and unanimously positive across trials. Among all of the selected trials, 3 trials studied this effect in a homogeneous group of subjects with subthreshold depression. Shores et al (2009) studied the effect of testosterone on hypogonadal men with dysthymia and minor depression. Seidman et al (2009) studied this effect on subjects with diagnosed dysthymia. Rabkin et al (2006) studied this impact on HIV-positive patients with dysthymia or minor depression. In addition, the effect of exogenous testosterone on MDD was statistically significant and positive. Of 5 trials with homogenous subjects diagnosed with MDD, 4 trials studied testosterone to augment the effect of other antidepressants. The calculated effect size individually in these trials was positive in all 4 trials.[28,35,37,41] However, the effect size was negative in the only trial that used 6 weeks of IM testosterone as monotherapy.[42] Because the placebo response in this study was very high, this result needs to be studied in a larger, controlled trial with a longer duration.

Exogenous testosterone had a significant effect on mood among HIV-positive patients. Despite the fact that low baseline testosterone was not set as an inclusion criterion in 3 out of the 4 trials in this subpopulation, the effect size in these patients was larger than that seen in the HIV-negative subpopulation. This result might have occurred because of multiple benefits of treatment with testosterone in these patients. The study by Rabkin et al (2000) indicated that testosterone treatment restores libido and energy, alleviates depressed mood, and increases muscle mass specifically in HIV-positive patients with wasting syndrome. They reported response rates of 74%, 59%, and 58% with testosterone treatment in improving libido, fatigue, and depressed mood, respectively, compared with 19%, 25%, and 14% response rates in the control group, respectively. They also reported an average increase of 2.2 kg in the muscle mass of subjects with wasting syndrome over 12 weeks of treatment with testosterone. However, the effect size of testosterone on HIV-positive patients in the study by Rabkin et al (2004) was much lower than that seen in the 3 other trials conducted with HIV-positive patients. This may have occurred because of the higher (613 [SD = 270] pg/dL) mean baseline testosterone level of participants in the Rabkin 2004 study, compared with participants in the other 3 trials in this subpopulation.

Based on our subgroup meta-analysis, the maximum effect size was observed in studies of 8 weeks' duration. It

TABLE 2
Summary of randomized controlled trials not included in meta-analysis

Study name	N	Age	Duration (weeks)	Inclusion criteria	Intervention	Depression scale	Conclusion	Reason excluded
Cavallini et al, 2004[46]	130	60 to 74	24	HG	Oral T, carnitine	DMS-III	T significantly improved DMS	Different scale
Knapp et al, 2008[47]	61	18 to 60	16	HIV with weight loss	IM T	DASS-21	Improvement in mood scores was not significantly different from placebo group	Different scale
McNicholas et al, 2003[48]	208	31 to 80	12	HG	Gel and Patch T	Questionnaire rating positive and negative mood	No statistically significant changes in T patch, in contrast to gel, which has a significant improvement	Different scale
O'Connor et al, 2004[49]	28	22 to 44	12	Eugonadal	1000 mg single-dose IM T	POMS	T increment was associated with detectable but minor mood changes	Different scale
Dean et al, 2005[50]	371	48 to 68	52	HG	Gel T	Questionnaire rating positive and negative mood	Significant improvement in mood were maintained for up to 12 months of treatment	Different scale
Steidle et al, 2002[51]	406	50 to 70	12	HG	Gel and patch T	Questionnaire rating positive and negative mood	Although all treatments resulted in improvement in mood scores, no significant differences among the treatments were observed	Different scale
Aydogan et al, 2012[16]	40	20 to 26	24	CHH, compared with eugonadal healthy men	IM T	BDI	BDI scores significantly improved after T replacement treatment	Bias in selecting control group
Kenny et al, 2004[52]	11	73 to 87	12	HG/mild to moderate cognitive impairment	IM T	GDS	No significant changes were found in depression scores	Lack of necessary statistical data, such as *P* value
Schmidt et al, 2004[53]	31	18 to 45	12	Eugonadal men	IM T following acute induction of hypogonadism by Lupron (leuprolide)	BDI	Significant effect of T on BDI scores was observed	Acute induction of hypogonadism

BDI: Beck Depression Inventory; CHH: congenital hypogonadotropic hypogonadism; DASS-21: Depression Anxiety Stress Scales–21; DMS: Diagnostic Melancholia Scale; GDS: Geriatric Depression Scale; HG: hypogonadism; IM: intramuscular; POMS: Profile of Mood States; T: testosterone.

was interesting that the effect of 6 weeks of testosterone treatment was not statistically significant. The reason may be the lack of homogenous participants in this subpopulation. However, this result was consistent with studies by Pope et al (2003 and 2010). Both these trials had similar inclusion criteria, including participants with MDD with partial response or resistant to antidepressants and testosterone level <350 pg/dL, but they had almost opposite results. The first study had a significant difference in HAM-D scores, whereas the second study did not have a significant change compared with placebo. The only difference between these 2 studies was the duration and dose of testosterone. The first study was with 8 weeks in duration with 10 g/d of testosterone gel, and the second study was 6 weeks in duration with 5 g/d of testosterone gel. In the study by Pope et al (2010), it is possible that had they continued their trial for 2 more weeks, they would have observed a significant difference in the HAM-D score. The

other interesting result in this subgroup meta-analysis was that treatment duration of 1 year showed a negative effect size. But our meta-analysis was limited in that we had only 1 study in this subgroup—that of Haren et al (2005). This trial was conducted with subjects with low normal testosterone and a mean baseline GDS of 6. Therefore, this effect size cannot be interpreted as a whole. Dean et al (2005) studied the effect of testosterone treatment on negative and positive mood over 12 months of treatment. They reported an improvement in mood scores, which was maintained through month 12.[50]

Our subgroup meta-analysis regarding route of administration showed that the effects of testosterone gel and IM injection are not comparable to oral testosterone because some oral testosterone formulations have proven to have variable absorption and poor bioavailability due to the first-pass effect in the liver.[55] In addition, this subgroup meta-analysis showed that oral DHEA has a slightly larger effect size than testosterone gel and injection. DHEA is classified by the FDA as a nutritional supplement that can be used in both sexes.[40] Our results were based on only 1 trial, by Rabkin et al (2006), studying the effect of this supplement in both men and women with HIV. This slightly larger effect size of DHEA might be because of the slightly larger effect of exogenous testosterone in patients with HIV. More studies investigating the effects of DHEA are needed to observe its effect on depressed individuals.

CONCLUSIONS

The results of this meta-analysis support the use of TRT in middle-aged, depressed men with low testosterone. This treatment can be used as monotherapy in dysthymia and minor depression or as augmentation therapy in MDD in this population. Therefore, we recommend checking total testosterone levels as a screening tool in depressed middle-aged men, particularly in those individuals whose depression is associated with poor morning erection, low sexual desire, and erectile dysfunction.[56,57] In this meta-analysis, 7 of 9 trials conducted with hypogonadal men set their threshold for low total testosterone level at 350 ng/dL. Shores et al (2009) set a threshold of 280 ng/dL, and Zhang et al (2012) defined low testosterone as a total testosterone level of <230 ng/dL. For levels between 230 and 350 ng/dL, they checked free testosterone level and considered a free testosterone level <65 pg/mL as hypogonadism. Within the latest Endocrine Society guidelines, it is recommended that TRT be initiated in men with 2 morning total testosterone levels <280 to 300 ng/dL plus symptoms of androgen deficiency such as low libido, decreased energy, decreased spontaneous erection, and depressed mood.[56]

Because most antidepressants have adverse side effects, these side effects are the major reason for medication discontinuation. An important side effect of most antidepressants is sexual dysfunction. Selective serotonin reuptake inhibitors are the most commonly used medications in depression and are estimated to cause sexual dysfunction in one-third of patients.[58] Because maintenance of satisfying sexual performance in patients with depression is important, TRT—with its dual effects on mood and sexual function—may be a better choice for hypogonadal men. In addition, there were no cases of prostate cancer reported with short-term use of testosterone in 16 selected trials in this meta-analysis. Most of the side effects reported in these trials were minor, comparable with the placebo group, and reversible after discontinuing treatment. As recommended by the Endocrine Society, prostate-specific antigen (PSA) and hematocrit levels should be checked at the beginning of treatment and monitored after 3 to 6 months of treatment. This treatment should be withheld in the case of a PSA level of >4 ng/mL (>3 ng/dL in men at high risk of prostate cancer, such as African American men or men with first-degree relatives with prostate cancer), a hematocrit level >50%, untreated severe obstructive sleep apnea, or uncontrolled or poorly controlled heart failure.[11] Surprisingly, the effects of TRT in hypogonadal men may persist for an extended period of time after the treatment is discontinued. Taniguchi et al followed up 33 men with symptomatic androgen deficiency who had received TRT for 6 months in the past. The mean duration from the last treatment was 55 months. Scores of the International Index of Erectile Function (IIEF-5) and SF-36 were improved significantly in the early stages of treatment and remained unchanged for a long period of time after TRT was discontinued.[59] Therefore, depressed men with low testosterone may experience long-term benefit from a short trial of TRT. ■

DISCLOSURES: Dr. Seo is an employee of AbbVie. Drs. Amanatkar, Chibnall, Manepalli, and Grossberg report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

REFERENCES

1. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 2002;87:589-598.
2. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001;86:724-731.
3. Dandona P, Rosenberg MT. A practical guide to male hypogonadism in the primary care setting. Int J Clin Pract. 2010;64:682-696.
4. Kalyani RR, Gavini S, Dobs AS. Male hypogonadism in systemic disease. Endocrinol Metab Clin North Am. 2007;36:333-348.
5. Dandona P, Dhindsa S, Chaudhuri A, et al. Hypogonadotrophic hypogonadism in type 2 diabetes, obesity and the metabolic syndrome. Curr Mol Med. 2008;8:816-828.
6. Fernandez-Egea E, Garcia-Rizo C, Miller B, et al. Testosterone in newly diagnosed, antipsychotic-naive men with nonaffective psychosis: a test of the accelerated aging hypothesis. Psychosom Med. 2011;73:643-647.
7. Gorobets LN, Matrosova MI. Specialties of prolactin secretion and peripheral reproductive sex hormones in patients with of first episode of schizophrenia [in Russian]. Zh Nevrol Psikhiatr Im S S Korsakova. 2010;110:17-22.
8. Levenson JL. Psychosomatic medicine. In: Tasman A, Key J, Lieberman JA, et al, eds. Psychiatry. London, United Kingdom: Wiley; 2008:2505.
9. Schweiger U, Deuschle M, Weber B, et al. Testosterone, gonadotropin, and cortisol secretion in male patients with major depression. Psychosom Med. 1999;61:292-296.
10. Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. J Clin Endocrinol Metab. 2007;92:4241-4247.
11. Itoh N, Tsukamoto T. Clinical aspects of partial androgen deficiency of aging male (PADAM) [in Japanese]. Clin Calcium. 2003;13:1432-1437.
12. Tracz MJ, Sideras K, Boloña ER, et al. Clinical review: testosterone use in men and its effects on bone health: a systematic review and meta-analysis of randomized placebo-controlled trials. J Clin Endocrinol Metab. 2011;91:2011-2016.
13. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol (Oxf). 2005;63:381-394.
14. Boloña ER, Uraga MV, Haddad RM, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc. 2007;82:20-28.
15. Shores MM, Sloan KL, Matsumoto AM, et al. Increased incidence of diagnosed depressive illness in hypogonadal older men. Arch Gen Psychiatry. 2004;61:162-167.
16. Aydogan U, Aydogdu A, Akbulut H, et al. Increased frequency of anxiety, depression, quality of life, and sexual life in young hypogonadotropic hypogonadal males and impacts of testosterone replacement therapy on these conditions. Endocr J. 2012;59:1099-1154.
17. Khera M, Bhattacharya RK, Blick G, et al. The effects of testosterone supplementation on depression symptoms in hypogonadal men from the Testim Registry in the US (TRiUS). Aging Male. 2012;15:14-21.
18. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab. 2006;91:4335-4343.
19. Lackner J, Rücklinger E, Schatzi G, et al. Are there symptom-specific testosterone thresholds in aging men. BJU Int. 2011;108:1310-1315.
20. Guyton AC, Hall JE. Reproductive and hormonal functions of the male (and function of the pineal gland). In: Guyton AC, Hall JE, eds. Textbook of medical physiology. Philadelphia, PA: Saunders; 2000:922-928.
21. Zitzmann M, Mattern A, Hanisch J, et al. IPASS: a study on the tolerability and effectiveness of injectable testosterone undecanoate for treatment of male hypogonadism in a worldwide sample of 1,438 men. J Sex Med. 2013;10:579-588.
22. Seidman SN, Roose SP. Sexual function and depression. Curr Psychiatry Rep. 2001;3:202-208.
23. Nofzinger EA, Thase ME, Reynolds CF 3rd, et al. Sexual function in depressed men. Assessment by self-report, behavioral, and nocturnal penile tumescence measures before and after treatment with cognitive behavior therapy. Arch Gen Psychiatry. 1993;50:24-30.
24. Araujo AB, Durante R, Feldman HA, et al. The relationship between depressive symptoms and male erectile dysfunction: cross sectional results from the Massachusetts Male Aging Study. Psychosom Med. 1998;60:458-465.
25. Rizvi SJ, Kennedy SH, Ravindran LN, et al. The relationship between testosterone and sexual function in depressed and healthy men. J Sex Med. 2010;7:816-825.
26. Barrett-Connor E, Von Mühlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. J Clin Endocrinol Metab. 1999;84:573-577.
27. Almeida OP, Yeap BB, Hankey GJ, et al. Low free testosterone concentration as a potentially treatable cause of depressive symptoms in older men. Arch Gen Psychiatry. 2008;65:283-289.
28. Pope HG Jr, Amiaz R, Brennan BP, et al. Parallel-group placebo-controlled trial of testosterone gel in men with major depressive disorder displaying an incomplete response to standard antidepressant treatment. J Clin Psychopharmacol. 2010;30:126-134.
29. Liberati A, Altman DG, Tetzlass J, et al. The PRISMA statement for reporting systematic reviews and meta-analysis of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62:e1-34.
30. Posternak MA, Zimmerman M. Short-term spontaneous improvement rates in depressed outpatients. J Nerv Ment Dis. 2000;188:799-804.
31. Giltay EJ, Tishova YA, Mskhalaya GJ, et al. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. J Sex Med. 2010;7:2572-2582.
32. Grinspoon S, Corcoran C, Stanley T, et al. Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. J Endocrinol Metab. 2000;85:60-65.
33. Haren MT, Wittert GA, Chapman IM, et al. Effects of oral testosterone undecanoate on visuospatial cognition, mood, and quality of life in elderly men with low-normal gonadal status. Maturitas. 2005;50:124-133.
34. Lu PH, Masterman DA, Mulnard R, et al. Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. Arch Neurol. 2006;63:177-185.
35. Orengo CA, Fullerton L, Kunik ME. Safety and efficacy of testosterone gel 1% augmentation in depressed men with partial response to antidepressant therapy. J Geriatr Psychiatry Neurol. 2005;18:20-24.
36. Pope HG Jr, Kouri EM, Hudson JI. Effects of supraphysiologic doses of testosterone on mood and aggression in normal men. Arch Gen Psychiatry. 2000;57:133-140.
37. Pope HG Jr, Cohane GH, Kanayama G, et al. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. Am J Psychiatry. 2003;160:105-111.
38. Rabkin JG, Wagner GJ, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. Arch Gen Psychiatry. 2000;57:141-147.
39. Rabkin JG, Wagner GJ, McElhiney MC, et al. Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: a placebo-controlled trial. J Clin Psychopharmacol. 2004;24:379-385.
40. Rabkin JG, McElhiney MC, Rabkin R, et al. Placebo-controlled trial of dehydroepiandrosterone (DHEA) for treatment of nonmajor depression in patients with HIV/AIDS. Am J Psychiatry. 2006;163:59-66.
41. Seidman SN, Miyazaki M, Roose SP. Intramuscular testosterone supplementation to selective serotonin reuptake inhibitor in treatment-resistant depressed men: randomized placebo-controlled clinical trial. J Clin Psychopharmacol. 2005;25:584-588.
42. Seidman SN, Roose SP. The sexual effects of testosterone replacement in depressed men: randomized placebo-controlled clinical trial. J Sex Marital Ther. 2006;32:267-273.
43. Seidman SN, Orr G, Raviv G, et al. Effects of testosterone replacement in middle-aged men with dysthymia: a randomized placebo-controlled clinical trial. J Clin Psychopharmacol. 2009;29:216-221.
44. Shores MM, Kivlahan DR, Sadak TI, et al. A randomized double-blind placebo-controlled study of testosterone treatment in hypogonadal older men with subthreshold depression (dysthymia or minor depression). J Clin Psychiatry. 2009;70:1009-1016.
45. Zhang X, Liu Z, Hu X, et al. Androgen replacement therapy improves psychological distress and health-related quality of life in late onset hypogonadism patients in Chinese population. Chin Med J (Engl). 2012;125:3806-3810.
46. Cavallini G, Caracciolo S, Vitali G, et al. Carnitine versus androgen administration in the treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. Urology. 2004;63:641-646.
47. Knapp PE, Storer TW, Herbst KL, et al. Effects of a supraphysiological dose of testosterone on physical function, muscle performance, mood, and fatigue in men with HIV-associated weight loss. Am J Physiol Endocrinol Metab. 2008;294:E1135-E1143.
48. McNicholas TA, Dean JD, Mulder H, et al. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvement in body composition and sexual function. BJU Int. 2003;91:69-74.
49. O'Connor DB, Archer J, Wu FC. Effects of testosterone on mood, aggression, and sexual behavior in young men: a double-blind, placebo-controlled, cross-over study. J Clin Endocrinol Metab. 2004;89:2837-2845.
50. Dean JD, Carnegie C, Rodzvilla J, et al. Long-term effects of Testim 1% testosterone gel in hypogonadal men. Rev Urol. 2005;7:87-94.
51. Steidle C, Schwartz S, Jacoby K, et al; North American AA2500 T Gel Study Group. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metabol. 2002;88:2673-2681.
52. Kenny AM, Fabregas G, Song C, et al. Effects of testosterone on behavior, depression and cognitive function in older men with mild cognitive loss. J Gerontol A Biol Sci Med Sci. 2004;59:75-78.
53. Schmidt PJ, Berlin KL, Danaceau MA, et al. The effects of pharmacologically induced hypogonadism on mood in healthy men. Arch Gen Psychiatry. 2004;61:997-1004.
54. Sih R, Morley JE, Kaiser FE, et al. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab. 1997;82:1661-1667.
55. Jockenhövel F. Testosterone therapy—what, when and to whom. Aging Male. 2004;7:319-324.
56. Bhasin S, Cunningham GR, Hayes FJ, et al; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95:2536-2559.
57. Wu FC, Tajar A, Beynon JM, et al; EMAS Group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010:363:123-135.
58. Seidman SN, Roose SP, Rosen RC. Sexual dysfunction and pharmacological treatments: biological interactions. In: Charney DS, Nestler EJ, eds. Neurobiology of mental illness. New York, NY: Oxford University Press; 2009:1332.
59. Taniguchi H, Kawa G, Kinoshita H, et al. Symptomatic change in Japanese hypogonadal patients several years after androgen replacement therapy. Aging Male. 2011;14:190-194.