A Randomized, Double-Blind, Placebo-Controlled Study of Testosterone Treatment in Hypogonadal Older Men With Subthreshold Depression (Dysthymia or Minor Depression)

Molly M. Shores, M.D.; Daniel R. Kivlahan, Ph.D.; Tatiana I. Sadak, Ph.C.; Ellen J. Li, M.D.; and Alvin M. Matsumoto, M.D.

Objective: Hypogonadism and subthreshold depression are common conditions in elderly men. The objective of this study was to examine the effect of testosterone treatment in older, hypogonadal men with subthreshold depression.

Method: A randomized, double-blind, placebo-controlled study was conducted at a university-affiliated Veterans Affairs Medical Center among men aged 50 years or older (N = 33) with screening total testosterone levels of ≤ 280 ng/dL and subthreshold depression (dysthymia or minor depression, according to DSM-IV). Recruitment for the study was conducted from November 2002 through May 2005. Participants received either 7.5 g of testosterone gel or placebo gel daily for 12 weeks, followed by a 12-week open-label extension phase during which all subjects received 7.5 g of testosterone gel. The primary outcome measure was the change in the Hamilton Rating Scale for Depression (HAM-D) score from baseline to the end of the double-blind phase. Secondary outcome measures were remission of subthreshold depression (defined a priori as a HAM-D score ≤ 7) and changes in the Hopkins Symptom Checklist depression scale, the Medical Outcomes Study 36-Item Short-Form Health Survey, and the short-form 16-item Quality of Life Enjoyment and Satisfaction Questionnaire.

Results: At the end of the double-blind phase, testosterone-treated men had a greater reduction in HAM-D scores (p = .024) and a higher remission rate of subthreshold depression (52.9% vs. 18.8%, p = .041) than did placebo-treated men, but there were no differences in other secondary outcome measures between groups. At the end of the open-label phase, the testosterone group had sustained improvement, the control group improved, and there were no differences between groups in any outcome measures.

Conclusion: These results suggest that testosterone replacement may be efficacious treatment for subthreshold depression in older men with hypogonadism. Larger studies are needed to corroborate these findings.

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Corresponding author and reprints: Molly M. Shores, M.D., VA Puget Sound Health Care System, 1660 S. Columbian Way, S-182GRECC, Seattle, WA 98108 (e-mail: mxs@u.washington.edu).

Androgen deficiency, as defined by a low serum testosterone level, is a common condition in elderly men that increases with age, occurring in 30% of men over age 70 and 50% of men over age 80.[1] Symptomatic androgen deficiency, or hypogonadism, is less common but still affects a substantial number of men, with a prevalence of approximately 20% in men aged 70 years or older.[1] Manifestations of hypogonadism include decreased muscle and bone mass, increased total body and abdominal fat, and insulin resistance.[2] Some symptoms of hypogonadism also occur in depression, such as dysphoria, irritability, anorexia, fatigue, decreased concentration, and decreased libido. The overlap of hypogonadism with depressive illness remains unclear but may be substantial, particularly since both hypogonadism and depressive illness are common in elderly men with chronic medical illness.[2,3] Several epidemiologic studies found an association between low testosterone and depressive illness,[4,5] and other studies found that low testosterone in older men is associated more often with subthreshold depressive disorders, such as dysthymia

or minor depression,[6,7] than with major depressive disorder. Few placebo-controlled studies have been conducted of testosterone treatment in hypogonadal, depressed men, and the potential role of testosterone in the treatment of depressive illness remains unclear at this time.[8]

Subthreshold depressive disorders (minor depression or dysthymia) are clinically significant disorders that do not meet full criteria for major depressive disorder.[9–12] These disorders are common in primary care settings and in elderly patients, with prevalence rates ranging from 8% to 27%.[9–17] Although subthreshold depression is a less severe depressive disorder than major depressive disorder, it is associated with multiple adverse outcomes, including structural brain alterations (e.g., prefrontal lobe atrophy), decreased function and quality of life, and increased morbidity, mortality, and health care utilization and costs.[17–20] However, despite the high prevalence and morbidity of subthreshold depression, most studies of depression in the elderly have examined major depressive disorder rather than subthreshold depressive disorders. There are currently no evidence-based treatment guidelines for subthreshold depression in the elderly because there is insufficient evidence available to develop these guidelines.

Given that many older adults with clinically significant depressive disorders have subthreshold depression, more studies are needed to examine treatment options for subthreshold depression in elderly patients. Our study sought to address the need for further studies of subthreshold depression and of testosterone treatment in depressive illness by conducting a randomized double-blind placebo-controlled trial of testosterone treatment in hypogonadal older men with subthreshold depression. We examined subthreshold depression because it is the most common type of depressive illness in the elderly and appears to be more closely associated with hypogonadism than does major depressive disorder. Our hypothesis was that testosterone replacement would significantly decrease depressive symptoms and improve quality of life in hypogonadal older men with subthreshold depression.

METHOD

The study design consisted of a 12-week, randomized, double-blind, placebo-controlled trial of testosterone gel or placebo gel, followed by a 12-week, open-label extension phase for which all subjects were eligible. The open-label extension phase was included to provide a replication of treatment effects in the wait-list control condition and to enhance recruitment.

Inclusion Criteria

Men were eligible for inclusion if they were aged 50 years or older and had a screening serum total testosterone level of ≤ 280 ng/dL, the lower limit of the normal range. The screening testosterone level was obtained prior to the baseline testosterone level that was obtained at entry into the study. Eligible subjects met DSM-IV[21] criteria for either dysthymia or minor depression (per Appendix B of DSM-IV) on the basis of a structured clinical interview. Subjects who had previously been treated with antidepressants were eligible if they had been on a stable antidepressant dose for 3 months and did not meet criteria for major depressive disorder.

Exclusion Criteria

Men were excluded if they had a history of prostate, breast, or testicular cancer; hospitalization within the previous month; prostate-specific antigen (PSA) level of ≥ 3.0 ng/mL; or an abnormal digital rectal exam. Psychiatric exclusions included current treatment with benzodiazepines or antipsychotics, substance dependence, schizophrenia, bipolar disorder, dementia, or psychiatric instability or suicidality.

Recruitment

Computerized clinical records were used to identify potential subjects who had testosterone levels obtained as part of routine clinical care. Potential subjects were those who were ≥ 50 years of age and had testosterone levels of ≤ 280 ng/dL. Approval to contact potential subjects was obtained from their primary care providers. Recruitment was conducted from November 2002 through May 2005 at an urban, academically affiliated Veterans Affairs Medical Center (VAMC). The University of Washington Human Subjects Committee, the institutional review board of the VAMC, approved the study.

Outcome Measures

The primary outcome measure was the change in the 17-item Hamilton Rating Scale for Depression (HAM-D)[22] score from baseline to the end of the double-blind phase. Remission of depression was a secondary outcome and was defined a priori as a HAM-D score of ≤ 7.[23] We did not define treatment response as a 50% decrease in the HAM-D score (a conventional definition for studies of major depressive disorder) because the men in the study had relatively low HAM-D scores at baseline (mean baseline HAM-D score of 13). Secondary outcome measures were change in total score on the Hopkins Symptom Checklist (SCL) depression scale,[24,25] a 20-item self-report depression scale; the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36)[26]; and the short-form (16-item) Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[27] Higher scores on the SCL indicate more severe depression, while higher scores on the SF-36 and Q-LES-Q indicate higher function and quality of life. The Cumulative Illness Rating Scale for Geriatrics (CIRS-G)[28] was used to estimate medical morbidity on the basis of medical record review and interview. The CIRS-G has been validated in geriatric populations and quantifies general medical morbidity in 14

organ systems. The CIRS-G score is the number of illnesses multiplied by the average severity of the illness.

Procedures

Potential subjects were screened initially for cognitive impairment with the short Blessed Orientation-Memory-Concentration Test[29] and for substance dependence and minor depression or dysthymia with a structured interview using DSM-IV criteria. An interview and chart review were conducted to assess current medications and medical illnesses. A blood sample was drawn to assess PSA level and hematocrit. At the baseline visit, eligible subjects were administered the HAM-D by a psychiatrist (M.M.S.) or a master's level research nurse (T.I.S.) and completed the self-rated measures (SCL, SF-36, and Q-LES-Q). Sera were obtained and stored at –70°C for subsequent assay for hormone measurements. Subjects were randomly assigned to receive either placebo gel or testosterone gel by a research pharmacist who was blinded to the subjects' ratings and assessments. Randomization was done via a computer random-number-generator program for a 1:1 ratio assignment. All raters were blinded to the subjects' treatment status during the double-blind phase. In the treatment condition, the daily dosage of testosterone gel was 7.5 g. This dosage of testosterone gel has been shown to adequately replace testosterone in elderly hypogonadal men.[30] Follow-up phone visits with all subjects occurred at week 6 and week 18 to monitor for compliance and side effects of medication. Follow-up clinic visits occurred at week 12 (end of the double-blind phase) and week 24 (end of the open-label extension phase) and consisted of blood draws, psychometric ratings, and review of medical status.

Laboratory Assays

Laboratory assays were performed in a research laboratory (A.M.M.). Total testosterone and sex hormone–binding globulin (SHBG) were measured using a time-resolved Delfia fluoroimmunoassay (PerkinElmer Life and Analytical Sciences, Waltham, Mass.).[31] For total testosterone, the intra-assay and interassay coefficients of variation were 3.7% and 8.2%, respectively, and the lower limit of detection was 0.4 nmol/L. For SHBG, the intra-assay and interassay coefficients of variation were 1.3% and 5.1%, respectively, and the lower limit of detection was 0.5 nmol/L. All samples were run in triplicate. To minimize interassay variability, all testosterone levels (i.e., baseline, week 12, and week 24) for a particular subject were measured in the same assay. Free testosterone was calculated from total testosterone, SHBG, and albumin using the Södergard equation, which provides accurate estimates of free testosterone comparable to those measured directly by equilibrium dialysis.[32]

Statistical Analysis

In all analyses of primary and secondary outcomes, we used an intent-to-treat approach, and the last-observation-carried-forward (LOCF) method was applied for missing data. Although the LOCF method has limitations,[33] we believe that this methodology was the most conservative way to analyze the data. All statistical tests were 2-tailed, with $\alpha = .05$, and results are reported as the mean (standard deviation). To evaluate the success of randomization, the placebo and testosterone groups were compared at baseline with an independent t test for analysis of continuous measures. At the end of the double-blind phase, we examined pretreatment to posttreatment differences within groups. Then we compared differences between groups using a general linear model with repeated measures. Age was included in the model as a covariate because the men treated with testosterone were by chance significantly younger than the placebo-treated men. Then, we used a χ^2 analysis to compare the difference in remission of depression between groups, in which remission was defined as a HAM-D score ≤ 7. At the end of the open-label extension phase, we examined pretreatment to posttreatment differences within groups from baseline to week 24. Finally, we compared differences between groups using a general linear model with repeated measures, with age included as a covariate in the model. Statistical analyses were conducted using SPSS, version 16.0 (SPSS Inc., Chicago, Ill.).

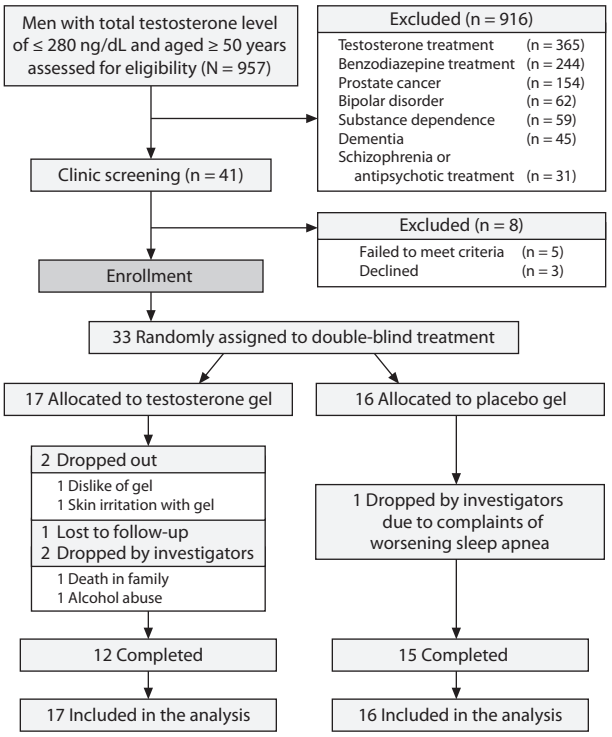
RESULTS

Subject Recruitment and Retention

From computerized medical records, 957 men were identified with testosterone levels measured as part of their clinical care. The primary indications for obtaining testosterone levels were for evaluation of sexual dysfunction, osteoporosis, follow-up of prior low serum testosterone levels, geriatric rehabilitation, genitourinary conditions, cancer, and endocrine conditions. High medical and psychiatric comorbidity in the population resulted in exclusion of many potential subjects. Nine hundred sixteen men were excluded due to one or more of the following: current testosterone treatment (n = 365), benzodiazepine treatment (n = 244), prostate cancer (n = 154), bipolar disorder (n = 62), substance dependence (n = 59), dementia (n = 45), and schizophrenia or antipsychotic treatment (n = 31).

Forty-one patients underwent screening assessment; 3 (7.3%) declined to enter the study, and 5 (12.2%) failed to meet the inclusion criteria for subthreshold depression. Thirty-three men were randomly assigned to treatment, with 17 subjects assigned to testosterone gel and 16 assigned to placebo gel. Six subjects dropped out of the study within 6 weeks of entry, and only baseline values were available for these subjects. One subject was dropped from the placebo arm due to complaints of worsening sleep apnea. In the testosterone arm, 4 subjects stopped the protocol, 1 each for the following reasons: dislike of the smell of the gel, skin irritation from the gel, psychiatric instability after a death in the family, and concurrent alcohol abuse (that had been

Figure 1. Flow Diagram of the Study of Hypogonadal Older Men With Subthreshold Depression



denied in the initial interview). One additional subject was lost to follow-up. The men who dropped out were younger, with a mean (SD) age of 54.0 (3.6) years versus 60.5 (6.7) years for the completers (p = .029), and had a higher baseline free testosterone level than did the study completers (8.4 vs. 6.0 ng/dL; p = .043). Otherwise, there were no significant differences between the completers and the dropouts. Figure 1 illustrates the flow of subjects through the study.

Baseline Characteristics

The men randomly assigned to testosterone were younger (mean [SD] age = 57.1 [5.7] vs. 61.7 [7.0] years; p = .044) and had a greater prevalence of dysthymia (70.6% vs. 37.5%; p = .056) than did the placebo-treated men. There were no other significant differences between the groups randomly assigned to testosterone or placebo on any of the baseline measures (p > .10). There was a high degree of medical morbidity, with an average of 3 to 4 chronic medical conditions in both treatment groups (Table 1). Six men were on stable antidepressant dosages (n = 3 in each group).

Double-Blind Placebo-Controlled Phase (baseline to week 12)

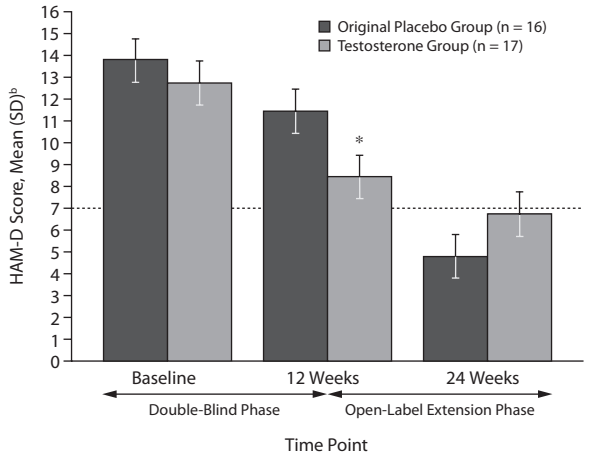
For pretreatment to posttreatment differences within groups, testosterone-treated men had a significant increase in free testosterone levels (p = .052), with a mean free testosterone level of 10.6 ng/dL at the end of the double-blind treatment phase, a decrease in HAM-D scores (p = .001), and a trend for improvement in the SCL (p = .070) (Figure 2). The placebo-treated men had a decrease in free testosterone levels (p = .060), with a mean free testosterone level of 5.1 ng/dL and a decrease in HAM-D scores (p = .038) but no significant changes in other measures pretreatment to posttreatment.

Table 1. Baseline Characteristics of Study Subjects Randomly Assigned to Testosterone or Placebo[a]

Variable	Testosterone (n = 17)	Placebo (n = 16)	p Value
Age, y	57.1 (5.7)	61.7 (7.0)	.044[b]
Body mass index, kg/m^2	33.2 (4.5)	32.9 (8.2)	.888
Total no. of comorbid illnesses	5.5 (3.1)	5.3 (4.3)	.848
Total testosterone, ng/dL	311 (127)	274 (98)	.541
Free testosterone, ng/dL	7.0 (2.1)	5.9 (2.0)	.620
CIRS-G score	6.1 (3.5)	5.4 (4.2)	.614
Type of depression			.056
Dysthymia, n (%)	12 (70.6)	6 (37.5)	
Minor depression, n (%)	5 (29.4)	10 (62.5)	
HAM-D score	12.7 (3.4)	13.8 (4.4)	.449
SCL score	28.5 (18.4)	26.6 (16.1)	.755
SF-36 mental score	39.1 (12.0)	43.7 (11.4)	.265
SF-36 physical score	44.7 (8.0)	43.0 (7.9)	.558
Q-LES-Q score	48.3 (10.4)	54.7 (13.5)	.136

[a]Values are given as mean (SD) unless noted otherwise.
[b]Statistically significant p value.
Abbreviations: CIRS-G = Cumulative Illness Rating Scale for Geriatrics, HAM-D = Hamilton Rating Scale for Depression, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SCL = Hopkins Symptom Checklist depression scale, SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey.

Figure 2. Hamilton Rating Scale for Depression (HAM-D) Scores for the Entire Sample (N=33)[a]



[a]In an intent-to-treat analysis, testosterone-treated men had a significantly greater decrease in HAM-D scores than did placebo-treated men at the end of the double-blind phase (week 12). At the end of the extension phase (week 24), depressive symptoms were significantly lower in both groups than they were at the start of the study, but there were no significant differences between groups.
[b]The dashed horizontal line depicts the level for remission of depression, which was defined a priori as HAM-D ≤ 7.
*Indicates statistical significance (p = .024) for the testosterone group at week 12.

Table 2. Changes in Outcome Measures From Baseline to Week 12 in Older Hypogonadal Men Treated With Placebo or Testosterone in a Double-Blind Manner[a]

Outcome Measure	Testosterone Group at Baseline (n = 17)	Testosterone Group at Week 12 (n = 17)	Placebo Group at Baseline (n = 16)	Placebo Group at Week 12 (n = 16)	p Value
Total testosterone, ng/dL	291 (108)	449 (282)	267 (98)	232 (82)	.004[b]
Free testosterone, ng/dL	6.3 (2.1)	10.6 (6.6)	5.9 (2.0)	5.1 (1.5)	.003[b]
HAM-D score	12.7 (3.4)	8.4 (5.0)	13.8 (4.4)	11.4 (4.4)	.024[b]
SCL score	28.5 (18.4)	25.0 (15.4)	26.6 (16.1)	24.9 (17.7)	.959
SF-36 mental score	39.1 (12.0)	43.8 (12.0)	43.7 (11.4)	45.2 (12.0)	.691
SF-36 physical score	44.7 (8.0)	45.5 (7.7)	43.0 (7.9)	45.3 (7.2)	.865
Q-LES-Q score	48.3 (10.4)	50.1 (11.1)	54.7 (13.5)	53.4 (13.7)	.657
Depression remission, n (%)	…	9 (52.9)	…	3 (18.8)	.041[c]

[a]Values are given as mean (SD) unless noted otherwise.
[b]Statistically significant p value for between-group differences in a general linear model with repeated measures controlling for age.
[c]Statistically significant p value in a χ^2 analysis.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SCL = Hopkins Symptom Checklist depression scale, SF-36 = Medical Outcomes Study 36-Item Short-Form Health Survey.
Symbol: … = not applicable.

For between-group differences, testosterone-treated men had significantly higher total and free testosterone levels ($p \leq .004$) and a greater decrease in HAM-D scores ($p = .024$) than did the placebo-treated men in a general linear model with repeated measures controlling for age. Testosterone-treated men also had a greater remission of depression of 52.9% compared to 18.8% in the placebo group ($p = .041$) (Table 2). Similar results were found when type of depressive illness (dysthymia or minor depression) was entered as a covariate in the model. When we examined correlates of treatment response by baseline severity of HAM-D scores, a lower baseline HAM-D score correlated with remission of depression by Spearman ρ ($r = -0.470$, $p = .006$). There were no significant differences between groups on quality-of-life measures or the self-rated depression scale, the SCL. Finally, we repeated the analysis including only the completers and found similar results, namely, that the testosterone-treated men had a greater decrease in HAM-D scores than the placebo-treated men ($p = .015$) and had greater remission of depression of 75% vs. 20% ($p = .004$). There were no adverse effects reported in either group, and patients reported that they were adherent with treatment.

Open-Label Extension Phase (week 13 to week 24)

During the extension phase, all subjects received 7.5 g/day of testosterone gel in an open-label manner. From baseline to the end of the extension phase, the men originally treated with testosterone had a significant decrease in HAM-D scores ($p < .001$) and improvement in quality of life ($p = .040$)—and a trend for improvement in the SCL ($p = .096$). From baseline to the end of the extension phase, the group originally treated with placebo and then with testosterone in an open-label manner had a significant decrease in HAM-D scores ($p < .001$) and the SCL ($p = .011$) and a trend for improvement in quality of life ($p = .082$). At the end of the extension phase, there were no significant between-group differences in any of the outcome measures or in the remission rate of depression between the original testosterone group and the original placebo group (58.8% vs. 68.8%, respectively; $p = .554$) (Figure 2). However, testosterone levels increased more in the original testosterone group compared to the original placebo group, despite the same dosage of testosterone gel. This result was due to 2 outliers who had high total testosterone levels of 1750 to 1840 ng/dL at week 24. We repeated our analyses excluding these 2 men and found that there were no significant differences in testosterone levels or outcome measures between groups.

DISCUSSION

In this double-blind placebo-controlled study, men treated with testosterone gel had a greater decrease in HAM-D scores and a greater remission of subthreshold depression than did placebo-treated men, with the beneficial effects of testosterone treatment persisting during the extension phase. There were no significant differences between groups on self-rated measures of depression or quality-of-life measures. The finding of a greater difference between groups on clinician-rated vs. self-rated measures of depression is consistent with a meta-analysis of treatment trials of geriatric depression[34] that found greater improvements in clinician-rated than in self-rated depression measures. It is also possible that the quality-of-life measures (SF-36 and Q-LES-Q) in this study were insensitive to detecting changes in quality of life due to hormonal status. For example, a recent testosterone study[35] found significant differences in a quality-of-life scale reflective of hormonal status but found no changes in the SF-36.

Prior epidemiologic studies in older men have found that testosterone levels are inversely related to mood,[4,5] that low testosterone levels are associated with prevalent depression in analyses adjusted for medical morbidity,[36] and that low testosterone levels are a risk factor for incident depressive illness.[37,38] Several plausible biologic mechanisms may explain the association between low testosterone and

depressive illness. First, androgen receptors, which are activated by testosterone and its metabolites (estradiol and dihydrotestosterone), are located throughout the brain, including the hypothalamus, mamillary bodies, nucleus basalis of Meynert, hippocampus, and cerebral cortex.[39–43] Second, testosterone alters serotonergic activity via increases in serotonin $5HT_{1A}$ and $5HT_{2A}$ receptor density and mRNA expression and by alterations in serotonin uptake transporter levels.[44,45] Finally, testosterone has other central effects, such as decreases in corticotropin-releasing hormone promoter activity[46] and increases in cerebral blood flow in prefrontal regions.[47]

However, despite epidemiologic and basic science studies that suggest an association between low testosterone levels and depressive illness in men, there have been few studies that have examined the effect of testosterone treatment on mood. In hypogonadal men without depression, testosterone treatment improved general well-being and positive mood[30,48,49] in non–placebo-controlled studies. However, there were no differences in mood in placebo-controlled studies of testosterone in hypogonadal men.[50] In eugonadal depressed men, testosterone significantly decreased depressive symptoms[51,52] in non–placebo-controlled studies. However, there were no differences in depression in placebo-controlled studies of testosterone in eugonadal depressed men.[53,54] In hypogonadal depressed men, augmentation with testosterone for treatment-resistant depression significantly decreased depressive symptoms in an open-label study[55] and a placebo-controlled study.[56] Testosterone also decreased depression in hypogonadal, depressed, HIV-positive men,[57,58] while in other placebo-controlled studies[59–61] of hypogonadal depressed men, testosterone did not differ from placebo. Limitations of the studies that did not find a difference between testosterone and placebo include an inadequate testosterone dose[59] and high placebo response rates of 41% to 52%.[60,61] In summary, there are few placebo-controlled trials of testosterone for depression in men, and the only placebo-controlled studies with positive findings were those that examined men who had both hypogonadism and depression.[48–50]

Several factors may have contributed to the results of the current study. These factors include the duration of the trial, the gel formulation of testosterone, and that the men in the study had hypogonadism, subthreshold depression, and chronic medical conditions. First, the duration of the double-blind phase was longer (12 weeks) than the typical duration (6–8 weeks) of studies of testosterone treatment in depression.[53,54,60,61] The longer duration may have decreased the placebo response rate because a subject who initially responded to placebo would have a longer time to relapse back into depression. Second, the use of a gel formulation of testosterone rather than intramuscular (IM) testosterone may have decreased the placebo response rate because IM medications may have a higher placebo response rate,[61] perhaps due to greater psychological effects of an injection. For example, in the only placebo-controlled trial of testosterone treatment in major depressive disorder,[61] the placebo response rate for an IM placebo injection was 41.2%. In contrast, in the current study, the placebo response rate for placebo gel was only 18.8%. Another potential advantage of the gel formulation of testosterone is that it provides near–steady-state levels of testosterone[62] that are more physiologic than the wide fluctuations in testosterone that are associated with IM or oral testosterone. The steady-state physiologic levels of testosterone may have improved treatment response given that wide fluctuations in testosterone levels have been reported to be associated with dysphoria, especially at the nadir of testosterone levels.

Third, the men in this study had both hypogonadism and depression at baseline, and this is the only group of men who have shown beneficial response to testosterone in placebo-controlled studies. We hypothesized that men with low testosterone levels would be more likely to respond to testosterone treatment than would men with normal testosterone levels on the basis of several studies that noted threshold effects with testosterone and mood. Specifically, these studies noted that below a threshold level of testosterone, there was an increased prevalence of depressive illness or a negative correlation between testosterone and depressive symptoms, while above the threshold level there was no correlation between testosterone and mood.[30,36,37,48] Finally, the subjects in our study had a high degree of medical comorbidity, with an average of 3 to 4 chronic medical conditions, suggesting that testosterone treatment may be more efficacious for men with chronic medical illness. This possibility is supported by several positive trials of testosterone treatment in HIV-positive men[57,63,64] who are chronically medically ill.

This study has several limitations. One is the small sample size. Recruitment was slow due to the exclusion of many subjects. The difficult recruitment process could lead to concerns that there are not very many older men who have both hypogonadism and subthreshold depression. However, many men were excluded due to the high degree of psychiatric morbidity and psychotropic medication use in the VA population. Some of these conditions were exclusions because they may have complicated interpretation of the results. For example, benzodiazepines were an exclusion because efficacy of testosterone could have been masked by benzodiazepine side effects of sedation and fatigue. However, benzodiazepines are not contraindications to testosterone treatment, and, thus, in routine clinical practice (as opposed to a clinical trial), benzodiazepine treatment would not preclude treatment with testosterone. In addition, nearly 40% of the men were excluded due to concurrent testosterone treatment, which also limited our sample size.

Another limitation was the differential dropout between treatment arms, with 5 dropouts from the testosterone arm and 1 from the placebo arm. The greater number of dropouts in the testosterone arm appeared to be due to chance and

was not associated with any serious adverse effects. We included the dropouts from the testosterone arm in an LOCF analysis and continued to observe significant differences between the testosterone and placebo groups in HAM-D scores. However, since we included the 5 men in the testosterone arm who had only baseline data, it is possible that we underestimated the beneficial effects of testosterone. Another limitation is that we did not have frequent in-clinic visits. However, it is possible that the less frequent visits reduced the placebo response rate in our study. In addition, the less frequent visits are more consistent with practice patterns in a primary care setting where many hypogonadal men with subthreshold depression may be evaluated.

Despite these limitations, there are several strengths to our study, including the randomized, double-blind, placebo-controlled design; inclusion of men with both low testosterone levels and subthreshold depression; and performance of triplicate measurements of testosterone, which improves the reliability of the measures.

In conclusion, this is the first study of which we are aware that has examined testosterone replacement in older, hypogonadal men with subthreshold depression. We found that men with subthreshold depression who were treated with testosterone had a significantly greater decrease in HAM-D scores than did placebo-treated men and that this response was maintained in the extension phase. In addition, men with lower HAM-D scores at baseline had a higher remission rate. These results suggest that testosterone may be most effective in patients with mild depressive symptoms, such as minor depression or dysthymia, or in men who have partially responded to antidepressant treatment but have not yet fully remitted from their depression. However, the routine use of testosterone cannot be advocated at this time, given the limited number of placebo-controlled studies and the small sample size of this study. Replication of these results in a larger sample will be important given the small size of this study. In addition, although there have been no studies that have found an association between testosterone levels[65] or testosterone treatment and incident prostate cancer, this possibility remains a concern.[66] Finally, it will also be important to examine different patient populations and potential subgroup factors that may predict greater responsiveness to testosterone. In particular, testosterone treatment studies in men with chronic medical illness are needed since most studies of testosterone treatment of depressive illness in older men have included primarily healthy men.

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