Testosterone Replacement Therapy for Hypogonadal Men With Major Depressive Disorder: A Randomized, Placebo-Controlled Clinical Trial

Stuart N. Seidman, M.D.; Erica Spatz, B.A.; Christie Rizzo, B.A.; and Steven P. Roose, M.D.

Background: Symptoms of male hypogonadism include low libido, fatigue, and dysphoria and are alleviated with testosterone replacement. The prevalence of major depressive disorder (MDD) in hypogonadal men is not known, nor is the antidepressant efficacy of testosterone replacement in depressed, hypogonadal men.

Method: A 6-week double-blind, placebo-controlled clinical trial was conducted in 32 men with DSM-IV MDD and a low testosterone level, defined as total serum testosterone ≤ 350 ng/dL. Patients were randomly assigned to receive weekly 1-mL intramuscular injections of either testosterone enanthate, 200 mg, or sesame seed oil (placebo). The primary outcome measure was the 24-item Hamilton Rating Scale for Depression (HAM-D).

Results: Thirty patients were randomly assigned to an intervention; 13 received testosterone, and 17 received placebo. Mean ± SD age was 52 ± 10 years, mean testosterone level was 266.1 ± 50.6 ng/dL, and mean baseline HAM-D score was 21 ± 8. All patients who received testosterone achieved normalization of their testosterone levels. The HAM-D scores decreased in both testosterone and placebo groups, and there were no significant between-group differences: reduction in group mean HAM-D score from baseline to endpoint was 10.1 in patients who received testosterone and 10.5 in those who received placebo. Response rate, defined as a 50% or greater reduction in HAM-D score, was 38.5% (5/13) for patients who received testosterone and 41.2% (7/17) for patients who received placebo. Patients receiving testosterone had a marginal but statistically significant improvement in sexual function (p = .02).

Conclusion: In this clinical trial with depressed, hypogonadal men, antidepressant effects of testosterone replacement could not be differentiated from those of placebo.

(J Clin Psychiatry 2001;62:406–412)

Received July 6, 2000; accepted Nov. 30, 2000. From the Department of Psychiatry, College of Physicians and Surgeons of Columbia University; and the New York State Psychiatric Institute, New York.

Supported in part by a grant from the Office of Clinical Trials of Columbia Presbyterian Medical Center, New York (Dr. Seidman), and from the National Alliance for Research in Schizophrenia and Depression (NARSAD), Great Neck, N.Y. (Dr. Seidman).

Financial disclosure: Dr. Seidman is a consultant for Pfizer and has received honoraria from Forest Labs, Pfizer, SmithKline Beecham, and Organon. Dr. Roose is a consultant for, has received honoraria from, and is on the speakers bureau for Pfizer.

The authors thank Harold A. Sackeim, Ph.D.; D. P. Devanand, M.D.; Jonathan Stewart, M.D.; and S. Holly Lisanby, M.D., for comments on the manuscript and Linda Fitzsimons, R.N.; Elizabeth Adorno, R.N.; Bobba Moody, M.S.W.; Renee Doolity, R.N.; and Nancy Turret, M.S.W., for their care of the patients participating in the study.

Reprint requests to: Stuart N. Seidman, M.D., New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, 1051 Riverside Dr. Unit 98, New York, NY 10032.

Hypogonadism, defined as testosterone level ≤ 350 ng/dL, affects approximately 5% of adult men under 50 years of age and nearly one third of men over 80 years of age.[1,2] Hypogonadal men commonly report loss of libido, irritability, dysphoria, and fatigue.[3–5] Numerous placebo-controlled testosterone replacement trials have consistently demonstrated that systemic testosterone administration in hypogonadal men leads to an increase in sexual interest and activity.[6–8] Improved energy, mood, and quality of life have also been reported in these studies, although these domains have not generally been systematically assessed.[6–9] Despite the phenomenological overlap between hypogonadism and depressive illness, there has been relatively little systematic research on the specific relationship between hypothalamic-pituitary-gonadal (HPG) axis function and major depressive disorder (MDD).

In the early psychiatric literature, there were numerous anecdotal reports that testosterone (and other androgen) administration, irrespective of baseline testosterone level, had an ameliorative effect on depressive and sexual symptoms.[4,10] In 1889, Brown-Sequard reported that self-injections of the extracts of crushed animal testicles were "rejuvenating" for sexual and mental functions.[11] Thousands of men received similar injections, and following the isolation of testosterone in 1932, testosterone became a widely prescribed treatment for the reversal of senescence

and "depression." Although numerous investigators reported that the majority of "depressed" men responded immediately and dramatically to androgen treatment and subsequently relapsed when treatment was discontinued,[12] interpretation of such studies was limited by the lack of systematic assessment, standardized diagnoses, and placebo control. Open clinical trials of androgen administration to men who met DSM criteria for MDD also suggested that androgens might have antidepressant properties in chronically depressed men,[13] selective serotonin reuptake inhibitor (SSRI)-refractory hypogonadal men,[14] and moderately depressed human immunodeficiency virus (HIV)-seropositive men.[15,16] Finally, although there are no published randomized controlled trials using testosterone in MDD, there have been published randomized controlled trials using the oral androgens mesterolone and dehydroepiandrosterone (DHEA) for depressed eugonadal men. Although the total number of patients studied was small, cumulatively these data suggested that androgens have mood-elevating properties in some depressed men, particularly those with chronic, low-grade depressive illnesses.[17] There is, however, little evidence to suggest a robust antidepressant effect comparable to that of well-established antidepressant medication. Moreover, although there are anecdotal reports of dramatic MDD resolution following testosterone replacement,[18,19] normalization of testosterone level in hypogonadal men has never been studied systematically as an antidepressant treatment.

The relationship between hormone axis functioning and depressive illness is complex and bidirectional. Abnormalities in the hypothalamic-pituitary-thyroid (HPT) axis (e.g., reduced thyroid-stimulating hormone response to thyrotropin-releasing hormone) and the hypothalamic-pituitary-adrenal (HPA) axis (e.g., hypercortisolism) are markers of MDD and may affect illness course and/or treatment response.[20] For example, normalization of serum cortisol level has been reported to be of some clinical utility in depression.[21–23] In addition, a retrospective analysis of data from a large clinical trial suggests that estrogen replacement therapy may augment antidepressant efficacy in postmenopausal women.[24]

The best-studied hormone–affective disorder model has been one in which depressive illness is assumed to be secondary to a hormone-deficit state and remits after normalization of the endocrinological abnormality. The prototype of this model is hypothyroidism: the clinical consensus is that in the setting of comorbid hypothyroidism and MDD, effective treatment and maintenance of euthyroidism lead to MDD remission and may obviate the need for specific antidepressant treatment.[20]

Given that the symptoms of hypogonadism overlap with those of MDD, we hypothesized that, similar to the model of hypothyroid-induced MDD, hypogonadism may induce MDD that can be reversed by testosterone replacement. To test this hypothesis, we conducted a randomized, double-blind clinical trial comparing weekly intramuscular testosterone enanthate at replacement doses with placebo in hypogonadal men with MDD.

METHOD

Study Design

Depressed men ≥ 35 years of age were recruited, primarily via newspaper advertisements that offered free treatment in a research study. At screening, demographic information; medical, psychiatric, and substance abuse history; and a single sample of plasma for measurement of total testosterone by radioimmunoassay were obtained. A trained clinician completed the Structured Clinical Interview for DSM-IV (SCID).[25] Inclusion criteria were current MDD and serum total testosterone level ≤ 350 ng/dL. Patients who met diagnostic criteria for bipolar illness, schizophrenia, or substance abuse or dependence (current or within the last year); had current psychotic symptoms or active suicidal ideation; or had a serious or unstable medical illness were excluded. Patients over 50 years of age had a prostate-specific antigen (PSA) level determined and a digital rectal exam of the prostate. Patients with PSA level ≥ 4.0 and/or whose digital rectal exam showed abnormalities were excluded. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute, and written informed consent was obtained from all patients before protocol-specified procedures were carried out. Eligible men were told that they had a low testosterone level and MDD and that testosterone replacement was not known to be effective for MDD. Participants did not receive compensation.

Baseline assessment included a repeat of the SCID, the 24-item Hamilton Rating Scale for Depression (HAM-D),[26] physical examination, electrocardiogram, complete blood cell count, clinical chemistry (Chem-20), and blood thyroid and luteinizing hormone levels. Patients completed the following self-report instruments: the Beck Depression Inventory (BDI),[27] the Derogatis Sexual Performance Scale, Male Version (DSPS-M),[28] and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[29]

Enrolled patients were randomly assigned to an intervention and were seen weekly for 6 weeks. At every visit, patients received an intramuscular injection of either 1 mL testosterone enanthate, 200 mg, in sesame seed oil base or 1 mL sesame seed oil (placebo). Injections were administered by a registered nurse who had no other involvement with the study. Testosterone and placebo nonresponders were offered 6 weeks of open treatment with testosterone enanthate, 400 mg i.m., every 2 weeks. During the blinded phase, no concomitant psychotropic medications were allowed.

A blinded psychiatrist (S.N.S.) assessed depressive symptoms at each visit with the 24-item HAM-D,[26] the Clinical Global Impressions scale (CGI),[30] and a modified

Table 1. Demographic Characteristics of the Treatment Groups[a]

Characteristic	Testosterone (N = 13)	Placebo (N = 17)
Age, y, mean (range)	53.6 (42–71)	49.7 (35–64)
Baseline testosterone level, ng/dL, mean (range)	269.5 (134–331)	263.5 (168–338)
Baseline HAM-D score, mean (SD)	22.23 (5.1)	20.1 (4.7)
Baseline BDI score, mean (SD)	23.5 (8.6)	19.3 (7.0)
Baseline DSPS-M score		
Sect. 1 mean (SD)	14.2 (5.3)	14.6 (7.5)
Sect. 2 mean (SD)	8.3 (7.6)	10.8 (9.0)
Sect. 3 mean (SD)	6.5 (7.2)	8.3 (7.6)
Duration of current MDE, mo, median (range)	22 (3–130)	26 (1–109)
No. of prior MDEs		
0	8	14
1–2	4	1
≥ 3	1	2
Depressive subtype		
Melancholic	1	3
Atypical	5	3

[a]Abbreviations: BDI = Beck Depression Inventory; DSPS-M = Derogatis Sexual Performance Scale, Male Version; HAM-D = Hamilton Rating Scale for Depression; MDE = major depressive episode.

Treatment Emergent Symptom Scale (TESS)[31] in which all known side effects of testosterone were added as items. Another trained clinical rater who was blind to the intervention and who had no other clinical contact with the patient administered the HAM-D, the CGI, and the Hamilton Rating Scale for Anxiety (HAM-A)[32] at baseline and endpoint. Patients completed the BDI and the DSPS-M weekly and the Q-LES-Q at baseline and endpoint. Serum total testosterone level testing was repeated at endpoint.

Statistical Methods

For comparison of baseline variables, categorical data were analyzed using chi-square, and continuous data were analyzed using t tests. A revised intent-to-treat analysis was performed using all evaluable patients, i.e., those who were randomly assigned to an intervention and subsequently assessed at least once. The baseline-endpoint change scores were used in the appropriate statistical model, usually a 1-way analysis of variance (ANOVA) or Fisher exact test. The primary outcome variable was the change in total 24-item HAM-D score from baseline (i.e., the day of the first injection) to endpoint (i.e., 1 week after the last injection), measured using the HAM-D completed by the independent, blinded rater. Additional efficacy variables included the following: the percentage of patients who were classified as responders at endpoint, defined as ≥ 50% HAM-D decrease from baseline; change in the BDI score; change in the DSPS-M sexual function subscale scores; and change in Q-LES-Q subscale scores. All statistical tests were 2-tailed, with an α level of ≤ .05.

RESULTS

Patient Population

We screened 107 men, and 32 (30%) met entry criteria and were randomly assigned to receive either testosterone or placebo. Two enrolled men, both randomly assigned to testosterone, did not return for the first visit following random assignment and were administratively dropped from the study and not included in the analyses. Demographic and clinical characteristics of the 30 patients randomly assigned to an intervention who returned for at least one follow-up visit are shown in Table 1; there were no statistically significant differences between testosterone and placebo groups. The mean ± SD age of the enrolled patients was 51.9 ± 10.2 years (range, 35–71 years), and mean serum testosterone level was 266.1 ± 50.6 ng/dL (range, 134–338 ng/dL). For most patients (73%), the current major depressive episode was the first depressive episode. The median duration of the current episode was 26 months (range, 1–130 months), and 8 patients (27%) had received treatment for the current depressive episode.

Twenty-nine of the 30 patients completed the 6-week trial. One patient who had been randomly assigned to placebo had a myocardial infarction 3 weeks after random assignment and was removed from the study. No other adverse events occurred. There were no new symptoms reported on the expanded TESS in either treatment group.

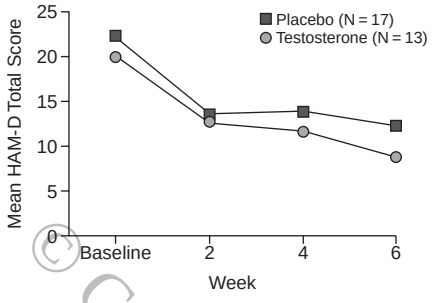
Testosterone Levels

At the end of the 6-week blinded treatment phase, all patients who were randomly assigned to receive testosterone had testosterone levels in the upper normal range (mean = 981.3 ng/dL), with a mean increase from baseline of 711.8 ng/dL. There were no significant associations between baseline level, final level, or change in testosterone level and change in depressive symptoms. Patients who received placebo had no significant change in testosterone level (mean final testosterone level = 297.7 ng/dL).

Depression Severity

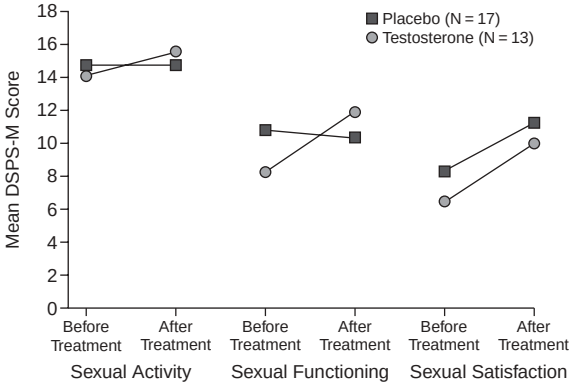
Changes from baseline to endpoint among patients in the testosterone and placebo groups are shown in Figure 1. The HAM-D and BDI scores decreased in both the testosterone and placebo groups, and there was no significant between-group difference. Reductions in group mean HAM-D and BDI scores from baseline to endpoint were 10.1 and 8.8, respectively, among the patients who received testosterone and 10.5 and 7.2 among those who received placebo. Response rate, defined as a 50% or greater reduction in HAM-D, was 38.5% (5/13) for those who received testosterone and 41.2% (7/17) for those who received placebo. Identical response rates were achieved using HAM-D ratings from the treating physician or using CGI response criteria of "much improved" or "very much improved."

Figure 1. HAM-D Total Score by Treatment Group and Visit (week)[a]



[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

Figure 2. Derogatis Sexual Performance Scale, Male Version (DSPS-M) Subscale Scores Before and After 6-Week Blinded Treatment



Sexual Function

Changes from baseline to endpoint in DSPS-M subscores are shown in Figure 2. Sexual activity (section 1 of the DSPS-M), sexual function (section 2), and sexual satisfaction (section 3) changed little over the 6-week treatment. Changes in mean DSPS-M sections 1, 2, and 3 from baseline to endpoint were 1.4, 3.6, and 3.5, respectively, among the patients who received testosterone and 0.0, –0.4, and 2.9 among those who received placebo. These change scores were 0.1, 0.1, and 2.3 in responders (irrespective of treatment received) and 0.0, 2.1, and 3.8 in nonresponders. The DSPS-M summary score increased more among those who received testosterone (8.4) than among those who received placebo (2.5) ($F = 5.90$, $df = 1,38$; $p = .02$). There was no association between response status and change in sexual function.

Quality of Life Scores

As measured by the Q-LES-Q, life satisfaction improved overall, but was minimally affected by treatment group and most influenced by response status. The mean increase in the Q-LES-Q global life satisfaction summary score from baseline to endpoint was 6.7 ± 12.3 among the patients who received testosterone and 3.8 ± 11.9 among those who received placebo. The mean Q-LES-Q score increase was 10.4 ± 10.6 among responders and only 0.9 ± 8.7 among nonresponders ($F = 19.69$, $df = 1,11$; $p = .001$).

DISCUSSION

In a parallel-group, double-blind, randomized trial including 30 men who had low total testosterone level and MDD, testosterone replacement and placebo were indistinguishable in antidepressant effects. Overall, approximately 40% of enrolled patients responded during double-blind treatment, with virtually no distinction between testosterone and placebo groups. Therefore, we cannot reject the null hypothesis, and it appeared that the improvement we observed was independent of testosterone treatment.

Depressed men who received testosterone had a significant increase in self-reported sexual functioning, particularly in the DSPS-M subscale score that measures sexual activity. This improvement occurred irrespective of the change in other depressive symptoms, and testosterone replacement apparently had more influence on sexual functioning than did depressive remission (which was not associated with a change in sexual functioning). It is well recognized that testosterone replacement is associated with improved libido and arousal and restoration of sleep-related erectile function.[33] We have shown that the presence of MDD does not prevent the pro-sexual effect of testosterone replacement, although we cannot exclude the possibility that comorbid MDD diminishes this effect.

Our finding that testosterone replacement was not more effective than placebo in the treatment of MDD was unexpected: clinical consensus is that treatment of reversible medical conditions should precede specific treatment of MDD, and we expected that MDD in the presence of low testosterone level would follow the MDD-hypothyroidism model. There are a number of reasons why this study might not have been able to detect a specific antidepressant effect of testosterone. First, hypogonadism was defined by a single determination of total testosterone level, using the liberal criterion of 350 ng/dL. With this definition of hypogonadism, it is likely that the enrolled group was endocrinologically heterogeneous. Future studies should employ a wider array of HPG measures, including free testosterone levels and the recently described trait marker of androgen receptor function (CAG isotype),[34] as well as a greater focus on the specific etiology of hypogonadism. Second, because men with severe MDD[35] or chronic depression[36] develop HPG blunting, hypogonadism in such men may be an MDD "epiphenomenon," and the condition less likely to be affected by testosterone replacement. Third, the potential antidepressant effects of exogenous androgen administration may be independent

of baseline HPG functional status or idiosyncratic. Fourth, testosterone replacement may improve mood in only a subgroup of depressive conditions in men (e.g., late-onset dysthymia, mild MDD). Finally, the placebo response rate (41%) was relatively high. This high rate might be related to the nature of the treatment (e.g., injection, the suggestive possibilities inherent to the expectation of receiving testosterone) or may be a characteristic of the hypogonadal state or trait. Coupled with the relatively small sample size, which raises the possibility of a type II error, this trial had the statistical power to detect only a large effect size; a small effect would be easily missed. Also, it should be remembered that in about one third of randomized controlled trials with well-established antidepressants, these agents are no more efficacious than placebo.[37]

The relationship between HPG functioning and MDD in men is poorly characterized, and the psychiatric impact of exogenous testosterone has never been systematically studied in depressed men. Testosterone secretion appears to be blunted, particularly at night, among some men with severe MDD[35,38] and normalizes after MDD remission.[39] There is some evidence that testosterone secretion is more blunted among older men with MDD compared with older men without MDD.[17] Wexler and colleagues[40] have reported that in a group of 18 men with MDD, the 9 men who exhibited a high level of right ear advantage on dichotic listening tests (which is a reliable measure of cerebral laterality) had a significantly lower total testosterone level than the others; testosterone level was negatively correlated with symptom severity in these men and positively correlated with symptom severity in the others.

In the only systematic study of the mood effects of testosterone replacement, Wang and colleagues[3] followed 51 profoundly hypogonadal men aged 22 to 60 years during 2 to 6 months of double-blind testosterone replacement. Testosterone level at baseline was below 250 ng/dL, and many of the patients had been withdrawn from testosterone replacement for 6 weeks to enter the study. On self-report positive mood scales, there was a significant increase in self-reported friendliness, energy level, and well-being, usually evident by 3 weeks and persisting through 6 months of replacement. On self-report negative mood scales, there was a significant decrease in nervousness, irritability, sadness, and anger.[3]

In the past 2 decades, to our knowledge there have been 10 androgen *treatment* trials for depression in men in which investigators used DSM diagnoses and systematically followed depressive symptoms; there have been no androgen *replacement* trials in depressed men. Most studies used the oral androgen mesterolone, which is a derivative of dihydrotestosterone (DHT) and therefore lacks the non-DHT actions of testosterone (i.e., testosterone-specific and estrogenic activity). Itil and colleagues[13,41] performed 3 mesterolone trials. First, they administered variable doses of mesterolone to 17 depressed men openly for 3 weeks, and found that 8 (47%) improved, particularly in mood and anxiety level.[41] Then, in a randomized, double-blind 4-week trial, they administered low-dose mesterolone (i.e., 75 mg/day) or placebo to 38 eugonadal dysthymic men and found that mesterolone led to improvement in symptoms such as anxiety, lack of drive, lack of desire, and impaired satisfaction.[41] Finally, they administered high-dose mesterolone (i.e., 450 mg/day) or placebo in a 6-week randomized trial to 52 eugonadal men (mean age = 40 years) with dysthymia, unipolar depression, or bipolar depression.[13] Both the mesterolone and placebo groups improved significantly, and there was no difference between the conditions.

Vogel and colleagues[42] administered mesterolone openly for 7 weeks to 13 eugonadal men (mean age = 39 years) with refractory, chronic unipolar depression. Eleven responded, most by the second week, with a mean HAM-D decrease (in these 11) from 21.1 to 5.6. The same investigators, in a 12-week randomized, double-blind trial, gave mesterolone or amitriptyline to 34 chronically depressed, eugonadal men aged 27 to 62 years.[43] Mesterolone was as effective as amitriptyline in reducing depressive symptoms.

Wolkowitz and colleagues[44] openly administered physiologic doses of DHEA to 6 elderly men and women with MDD and low DHEA levels and reported that mood and aspects of memory improved significantly. In a follow-up study,[45] these investigators randomly assigned 12 men and 10 women with MDD (all but 7 on antidepressant medication) to receive DHEA or placebo for 6 weeks. Mean HAM-D score decreased 30.5% in the DHEA-treated patients and 5.3% in the placebo-treated patients; about half of those receiving DHEA had a "clinically meaningful" response.[45] Response of male patients was not reported separately. This is particularly relevant, since it has recently been shown in a placebo-controlled trial that DHEA replacement enhances mood and libido in women with adrenal insufficiency.[46] Finally, DHEA had significant antidepressant efficacy in a 12-week double-blind, randomized, crossover, placebo-controlled clinical trial that included 12 men who had midlife-onset dysthymia.[47]

Rabkin and colleagues[15] openly administered physiologic doses of exogenous testosterone for 8 weeks to 34 HIV-seropositive men who had testosterone levels below 500 ng/dL and MDD or dysthymia. Mean HAM-D score decreased from 18.5 to 3.0 at week 8, as did symptom inventories for depressive, anxious, and somatic symptoms. Seidman and Rabkin[14] administered testosterone replacement to 5 men who had SSRI-resistant MDD and testosterone level below 350 ng/dL. In this 6-week open trial, all 5 achieved remission, with a mean HAM-D score decrease from 19.2 to 4.0. Of the 4 patients who were followed after the trial, 3 relapsed when treatment was discontinued.

Although our double-blind data do not support testosterone replacement at physiologic doses as more efficacious than placebo for MDD, our clinical impression is that some men, particularly those with milder depressive symptoms, may obtain an antidepressant benefit from testosterone administration that cannot be maintained after testosterone is discontinued. Notably, following the double-blind phase in this study, we offered nonresponders open treatment with testosterone, 400 mg every 2 weeks, for 4 weeks. Of those who received open treatment with testosterone, 40% (2/5) of acute-phase testosterone nonresponders subsequently responded in the open phase (with the different, moderately supraphysiologic, dosing schedule); 75% (6/8) of acute-phase placebo nonresponders responded in the open phase. Our impression of the variable and possibly idiosyncratic antidepressant effects of testosterone is in keeping with the growing experience of other investigators using exogenous testosterone.[48,49] Whether testosterone has a role in antidepressant therapy for specific populations of depressed individuals (e.g., hypogonadal, dysthymic, medication-resistant) and in which form (e.g., supraphysiologic doses, augmentation to antidepressant medication) remain to be established.

This study reaffirms the need for systematic clinical research to determine the therapeutic utility of androgen administration in male depression. Although exogenous testosterone is currently being used by some clinicians for refractory MDD, this was the first systematic study of testosterone in depressed men, and efficacy was not supported in the double-blind, placebo-controlled phase. Further clinical research should address the therapeutic potential of testosterone administration as an antidepressant augmentation in a variety of clinical subpopulations and/or at different doses. Broad clinical use of this potentially harmful agent should await further systematic research.

Drug names: amitriptyline (Elavil and others), testosterone enanthate (Delatestryl and others).

REFERENCES

1. Vermeulen A, Kaufman JM, Giagulli VA. Influence of some biological indexes on sex hormone binding globulin and androgen levels in aging or obese males. J Clin Endocrinol Metab 1998;81:1821–1826
2. Gray A, Berlin JA, McKinlay JB, et al. An examination of research design effects on the association of testosterone and male aging: results of a meta-analysis. J Clin Epidemiol 1991;7:671–684
3. Wang C, Alexander G, Berman N, et al. Testosterone replacement therapy improves mood in hypogonadal men: a clinical research center study. J Clin Endocrinol Metab 1996;81:3578–3583
4. Rubinow DR, Schmidt PJ. Androgens, brain, and behavior. Am J Psychiatry 1996;153:974–984
5. Kemper TD. Social Structure and Testosterone. New Brunswick, NJ: Rutgers University Press; 1990
6. Anderson RA, Bancroft J, Wu FC. The effects of exogenous testosterone on sexuality and mood of normal men. J Clin Endocrinol Metab 1992;75: 1503–1507
7. Burris AS, Banks SM, Carter CS, et al. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. J Androl 1992;13:297–304
8. Luisi M, Franchi F. Double-blind group comparative study of testosterone undecanoate and mesterolone in hypogonadal male patients. J Endocrinol Invest 1980;3:305–308
9. Plymate S. Hypogonadism. Endocrinol Metab Clin North Am 1994;23: 749–772
10. Altschule MD, Tillotson KJ. The use of testosterone in the treatment of depressions. N Engl J Med 1948;239:1036–1038
11. Freeman ER, Bloom DA, McGuire EJ. A brief history of testosterone. J Urol 2001;165:371–373
12. Reiter T. Testosterone implantation: the method of choice for treatment of testosterone deficiency. J Am Geriatr Soc 1965;13:1003–1012
13. Itil TM, Michael ST, Shapiro DM, et al. The effects of mesterolone, a male sex hormone in depressed patients: a double blind controlled study. Methods Find Exp Clin Pharmacol 1984;6:331–337
14. Seidman SN, Rabkin JG. Testosterone replacement therapy for hypogonadal men with SSRI-refractory depression. J Affect Disord 1998; 48:157–161
15. Rabkin JG, Rabkin R, Wagner GJ. Testosterone treatment of clinical hypogonadism in patients with HIV/AIDS. Int J STD AIDS 1997;8:537–545
16. Grinspoon S, Corcoran C, Stanley T, et al. Effects of hypogonadism and testosterone administration on depression indices in HIV-infected men. J Clin Endocrinol Metab 2000;85:60–65
17. Seidman SN, Walsh BT. Testosterone and depression in aging men. Am J Geriatr Psychiatry 1999;7:18–33
18. Rinieris PM, Malliaras DE, Batrinos ML, et al. Testosterone treatment of depression in two patients with Klinefelter's syndrome. Am J Psychiatry 1979;136:986–988
19. Heuser I, Hartmann A, Oertel H. Androgen replacement in a 48, XXYY-male patient [letter]. Arch Gen Psychiatry 1999;56:194–195
20. Prange AJ Jr. Psychoendocrinology: commentary. Psychiatr Clin North Am 1998;21:491–505
21. Thakore JH, Dinan TG. Cortisol synthesis inhibition: a new treatment strategy for the clinical and endocrine manifestations of depression. Biol Psychiatry 1995;37:364–368
22. Murphy BE, Dhar V, Ghadirian AM, et al. Response to steroid suppression in major depression resistant to antidepressant therapy. J Clin Psychopharmacol 1991;11:121–126
23. Wolkowitz OM, Reus VI, Manfredi F, et al. Ketoconazole administration in hypercortisolemic depression. Am J Psychiatry 1993;150:810–812
24. Schneider LS, Small GW, Hamilton SH, et al, for the Fluoxetine Collaborative Study Group. Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Am J Geriatr Psychiatry 1997;5: 97–106
25. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-I/P, Version 2.0). New York, NY: Biometric Research, New York State Psychiatric Institute; 1995
26. Williams JBW. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry 1988;44:742–747
27. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
28. Derogatis LR, Laban MP. Psychological assessment measures of human sexual functioning in clinical trials. Int J Impot Res 1998;10:13–20
29. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: a new measure. Psychopharmacol Bull 1993;29: 321–326
30. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
31. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. Dept Health Human Services publication (ADM) 91-338. Rockville, Md: National Institute of Mental Health, Psychopharmacology Research Branch; 1991
32. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
33. Seidman SN. Hormonal aspects of sexual dysfunction: the therapeutic use of exogenous androgens in men and women. Curr Psychiatry Rep 2000;2: 215–222
34. Seidman SN, Araujo AB, Roose SP, et al. Testosterone level, androgen receptor polymorphism, and depressive symptoms in middle-aged men. Biol Psychiatry. In press
35. 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
36. Seidman SN, Devanand DP, Roose SP. Testosterone level in late life male dysthymia [abstract]. Neuropsychopharmacology 2000;23:S147
37. Thase ME, Howland RH, Friedman ES. Treating antidepressant nonresponders with augmentation strategies: an overview. J Clin Psychiatry 1998;59(suppl 5):5–12
38. Steiger A, von Bardeleben U, Guldner J, et al. The sleep EEG and nocturnal hormonal secretion studies on changes during the course of depression and on effects of CNS-active drugs. Biol Psychiatry 1993;17:125–137
39. Rupprecht R, Rupprecht C, Rupprecht M, et al. Different reactivity of the hypothalamo-pituitary-gonadal-axis in depression and normal controls. Pharmacopsychiatry 1988;21:438–439
40. Wexler BE, Mason JW, Giller EL. Possible subtypes of affective disorder suggested by differences in cerebral laterality and testosterone: a preliminary report. Arch Gen Psychiatry 1989;46:429–433
41. Itil TM, Herrmann WM, Blasucci D, et al. Male hormones in the treatment of depression: effects of mesterolone. Prog Neuropsychopharmacol 1978;2:457–467
42. Vogel W, Klaiber EL, Broverman DM. A comparison of the antidepressant effects of a synthetic androgen (mesterolone) and amitriptyline in depressed men. J Clin Psychiatry 1985;46:6–8
43. Vogel W, Klaiber EL, Broverman DM. Roles of the gonadal steroid hormones in psychiatric depression in men and women. Prog Neuropsychopharmacol 1978;2:487–503
44. Wolkowitz OM, Reus VI, Roberts E, et al. Dehydroepiandrosterone (DHEA) treatment of depression. Biol Psychiatry 1997;41:311–318
45. Wolkowitz OM, Reus VI, Keebler A, et al. Double-blind treatment of major depression with dehydroepiandrosterone (DHEA). Am J Psychiatry 1999;156:646–649
46. Arlt W, Callies F, Van Vlijmen JC, et.al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 1999;341: 1013–1020
47. Bloch M, Schmidt PJ, Danaceau MA, et al. Dehydroepiandrosterone treatment of midlife dysthymia [see comments]. Biol Psychiatry 1999;45: 1533–1541
48. Yates WR. Testosterone in psychiatry. Arch Gen Psychiatry 2000;57: 155–156
49. Pope HG Jr, Kouri EM, Hudson JI. Effects of supraphysiologic doses of testosterone on mood and aggression in normal men: a randomized controlled trial. Arch Gen Psychiatry 2000;57:133–140