Testosterone Therapy in Late-Life Major Depression in Males

Paul J. Perry, Ph.D.; William R. Yates, M.D.; Richard D. Williams, M.D.; Arnold E. Andersen, M.D.; John H. MacIndoe, M.D.; Brian C. Lund, Pharm.D.; and Timothy L. Holman, M.A.

Background: Major depression associated with aging in males may improve with anabolic/androgenic steroid therapy. The efficacy and safety of testosterone therapy in the treatment of depression in elderly hypogonadal males is inconclusive. The following study identifies a subgroup of elderly depressed males who may benefit from testosterone therapy.

Method: Participants included 16 elderly eugonadal males with major depressive disorder (DSM-IV criteria) and a Hamilton Rating Scale for Depression (HAM-D) score > 18. Following a single-blind 2-week placebo lead-in, patients were randomly assigned to treatment with either a physiologic dose of testosterone cypionate (TC), 100 mg/week, or supraphysiologic dose of 200 mg/week IM for 6 weeks. Psychometric testing was carried out at entry into the study, at the TC injection baseline, and every 2 weeks thereafter. Tests included an objective measurement, the HAM-D, and the Buss-Durkee Hostility Inventory.

Results: One patient meeting inclusion criteria responded during the placebo lead-in; thus, 15 patients were randomly assigned to treatment (100 mg/week, N = 8; 200 mg/week, N = 7). There was a 42% decrease in the mean HAM-D scores from 20.1 to 11.9 ($p < .0001$). However, the majority of the change was due to improvement in the 10 late-onset (≥ 45 years old) depression patients, whose mean HAM-D score decreased from 19.8 to 9.3 (53%), versus the 5 early-onset depression patients, whose mean HAM-D score decreased from 20.8 to 17.0 (18%) ($p = .0110$). The TC dose did not affect the response. Similar HAM-D decreases of 43% and 41% occurred for the respective 100- and 200-mg/week doses. The HAM-D responder analysis found that none of 5 early-onset patients had HAM-D response, whereas 6 (60%) of 10 late-onset patients responded ($p = .025$). Similarly, none of the early-onset patients experienced a remission whereas 5 (50%) of the late-onset patients were categorized as remitters ($p = .053$). Correlations between the peak and mean total testosterone concentrations and HAM-D change scores suggested that only minimal TC doses were required to produce an antidepressant effect.

Conclusion: These data suggest that testosterone therapy would best be limited to men with late-onset depression. The findings suggest that short-term therapy with TC is safe. Long-term treatment safety is unknown. Psychiatrists using testosterone therapy should ascertain that patients have been recently valuated for prostate cancer. If testosterone therapy is initiated, serial serum prostate-specific antigen sampling should be used for monitoring patients' prostate status.

(J Clin Psychiatry 2002;63:1096–1101)

Received Sept. 5, 2001; accepted May 22, 2002. *From the Division of Clinical Pharmacy, College of Pharmacy (Drs. Perry and Lund), the Department of Psychiatry (Drs. Perry, Andersen, and Holman), the Department of Urology (Dr. Williams), and the Department of Internal Medicine (Dr. MacIndoe), University of Iowa, Iowa City; and the Department of Psychiatry, College of Medicine, University of Oklahoma at Tulsa, Tulsa (Dr. Yates).*

Supported by grant RR00059 from the General Clinical Research Centers Program, National Center for Research Resources, National Institutes of Health, Bethesda, Md.

Corresponding author and reprints: Paul J. Perry, Ph.D., S415 Pharmacy Bldg., University of Iowa, Iowa City, IA 52242 (e-mail: paul-perry@uiowa.edu).

Menopause is a well-described syndrome of somatic and psychological symptoms associated with a decline in circulating estrogenic hormones.[1] Data from a variety of disciplines, including endocrinology, urology, and gerontology, suggest the existence of a similar syndrome in men, referred to as "andropause," "male climacteric," "viropause," or "low-testosterone syndrome."[2] *Andropause* has been defined by at least one investigator as "an indefinite syndrome . . . [in middle-aged and elderly men] . . . composed of several constellations of physical, sexual, and emotional symptoms brought about by a complex interaction of hormonal, psychological, situational, and physical factors."[3(p921)] Psychological changes associated with andropause include dysphoria, anxiety, and irritability.

It has been hypothesized that the dysphoria, or more importantly major depression associated with andropause or aging in males, may improve with anabolic/androgenic steroid therapy. The safety and efficacy of testosterone therapy in the treatment of depression in elderly hypogonadal males are limited to preliminary research. There are suggestions that testosterone therapy improved energy and mood, but no attempt was made to quantify these improvements.[4,5] For example, patients receiving testos-

terone therapy were described as having "a general increase in sense of well-being."[4] A preliminary study in middle-aged hypogonadal men found testosterone enanthate, 400 mg IM every 2 weeks, effective in relieving depression resistant to selective serotonin reuptake inhibitor (SSRI) antidepressant therapy.[6] However, a controlled trial found that testosterone enanthate, 200 mg IM weekly, was no more effective than placebo in treating major depressive disorder in middle-aged hypogonadal men.[7] One randomized study in younger, apparently eugonadal patients administered dihydroepiandrosterone (DHEA) at 90 mg/day or placebo for 6 weeks in depressed patients with a mean age of 44 years. In this study, 5 of 11 DHEA patients versus none of the placebo patients responded.[8] These data suggest at least some possible efficacy for the use of testosterone therapy in treating major depressive disorder in males. A recent exhaustive review of the present literature on testosterone therapy suggested that testosterone is an ineffective treatment for depression in eugonadal males while it is of possible benefit in hypogonadal males.[9] The following open-label study describes the effect of testosterone therapy in a group of elderly males with major depressive disorder (DSM-IV).[10]

METHOD

Using an open-label design, a patient population of 16 males > 50 years old (mean ± SD age = 61.3 ± 7.6 years) with major depressive disorder[10] was randomly treated with either a physiologic dose of testosterone cypionate (TC), 100 mg/week IM, or supraphysiologic dose of 200 mg/week IM for 6 weeks. *Hypogonadal* was defined as a free testosterone (fT) level below the lower limit of normal. For patients 20 to 39 years old, the normal range is 0.88 to 2.7 ng/mL (95% CI); for patients 40 to 59 years old, the normal range is 0.72 to 2.3 ng/dL (95% CI); and for patients greater than 59 years old, the range is 0.56 to 1.9 ng/dL (95% CI).[11] According to the package insert for the Coat-A-Count free testosterone assay,[12] these norms were based on 472 healthy males in whom gonadal disease was not suspected or was excluded by additional laboratory testing. Eugonadal patients were defined by having fT concentrations within the normal range for their age group. Patients were required to have a 24-item Hamilton Rating Scale for Depression (HAM-D)[13] score of > 18 and be antidepressant-free for at least 1 year prior to entry. Additional inclusion criteria were a negative transrectal ultrasound, normal digital rectal prostate examination (DRE), and a prostate-specific antigen (PSA) of < 3 ng/mL. Psychiatric exclusion criteria included current use of antidepressant drugs, delusions or hallucinations, active suicidal ideation, active substance abuse, antisocial personality disorder, and/or a history of violent behavior or sexual abuse. Laboratory exclusion criteria include thyroid-stimulating hormone > 7 μIU/mL, cholesterol > 240 mg/dL, triglycerides > 250 mg/dL, hemoglobin > 17 g/dL, hematocrit > 47%, any liver function test > 200% of normal, and a creatinine > 1.5 mg/dL. Additionally, diabetic patients and patients receiving anticoagulants or antiseizure medication were excluded.

After giving informed consent, each patient received 2 weekly placebo IM doses of TC cottonseed oil vehicle. At the end of the 2-week lead-in period, subjects were reevaluated. Those meeting inclusion criteria were randomly assigned to 1 of 2 different doses of TC—100 mg/week IM, a physiologic replacement dose, or 200 mg/week IM, a supraphysiologic dose—for a period of 6 weeks. Nonresponding patients were offered a standard tricyclic antidepressant alternative treatment of oral nortriptyline, 1 mg/kg/day, adjusted to a blood level of 60 to 150 ng/mL for 6 weeks. If nortriptyline was contraindicated in the patient, an SSRI antidepressant was utilized. All patients were followed up by telephone monthly for 6 months following the end of the active treatment section of the study.

PSA, hematocrits, and vital signs were monitored at baseline and weekly throughout the study. Complete blood cell counts, liver function tests, and measures of lipids, serum free and total testosterone, estradiol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were conducted at entry, baseline, and biweekly throughout the TC injection portion of the study. Thyroid function and urinary free cortisols were determined at entry and after 6 weeks of testosterone injections or discontinuation from the study. Prostate monitoring included transrectal ultrasound volume determinations (baseline and termination) using a Kretz instrument and laboratory measurement of total and free PSA (weekly). All hormone samples were collected between 7 a.m. and 9 a.m. since the use of standardized times reduces sampling variability due to circadian changes. All patients were followed up by telephone monthly for 6 months after the end of the active treatment section of the study. No significant problems were reported by any of the patients.

Psychometric testing was carried out at entry into the study, at the TC injection baseline, and every 2 weeks thereafter. These tests included an objective measurement, the HAM-D, and the Buss-Durkee Hostility Inventory (BDHI).[14]

The medical criteria for discontinuation from the study included systolic blood pressure > 165 mm Hg or diastolic blood pressure > 95 mm Hg on 2 successive visits, the deterioration of a known preexisting medical condition, the appearance of a new significant medical problem, 2 consecutive weekly liver function tests greater than 200% of the upper limit on the chemistry panel sampled, and development of any abnormal tests felt to prohibit continued safe participation, including an increase in the fasting glucose to 150% of the upper limit on the chemistry panel. If the PSA increased more than 1.0 ng/mL on 2 consec-

utive weekly draws, treatment was terminated. No patients were discontinued from the study because of these criteria.

All plasma samples were stored at –20ºC (–4ºF) until assay. Serum LH, FSH, total testosterone (tT), and fT were determined with Coat-A-Count kits.[14] The lower limits of detection were 4 ng/dL, 0.015 ng/dL, 0.15 mIU/mL, and 0.10 mIU/mL for tT, fT, LH, and FSH, respectively. For the fT assay, the interassay and intraassay coefficients of variation were 11.2% and 5.5%, respectively. For 3 standardized fT samples, the mean and standard deviations were 0.19 ± 0.02 ng/dL, 1.37 ± 0.12 ng/dL, and 3.27 ± 0.49 ng/dL. For 3 standardized total testosterone samples, the mean and standard deviations were 86 ± 10 ng/dL, 571 ± 41 ng/dL, and 1152 ± 50 ng/dL. For the LH assay, the interassay and intraassay coefficients of variation were 7.5% and 4.5%, respectively. For 3 standardized LH samples, the standard deviations were 1.8 ± 0.2 mIU/mL, 17.5 ± 1.3 mIU/mL, and 71.5 ± 4.6 mIU/mL. For the FSH assay, the interassay and intraassay coefficients of variation were 5.3% and 4.6%, respectively. For 3 standardized FSH samples, the mean and standard deviations were 6.1 ± 0.4 mIU/mL, 10.2 ± 0.5 mIU/mL, and 29.7 ± 1.5 mIU/mL.

Sample Size Consideration

A series of 10 males 55 years of age or older with major depressive disorder (DSM-IV) were administered the standard rating scale for depression, the HAM-D. The mean score was 20.9 ± 3.5. A 25% or 5-point change on the HAM-D was the minimum change that we regarded as significant. Using these a priori criteria, the power analysis determined that an N of 10 patients per TC dose group for TC dose would produce a statistically significant finding with a power of 0.80, beta of .20 at a 2-tailed alpha level of .02.

Statistics

Within-group changes in continuous measures were analyzed using paired t tests. Between-group change scores were compared using unpaired t tests. In addition, a responder analysis was conducted for the primary outcome measure. Response was defined as a decrease in HAM-D score ≥ 50%, while remission was defined as an endpoint HAM-D score ≤ 7. Response rates between groups were compared using a chi-square test. p Values below .05 were considered significant.

RESULTS

Twenty-eight patients were screened, but only 16 met the inclusion criteria. Of the 12 subjects excluded, 10 were screen failures while the other 2 discontinued before the first actual TC injection due to elevated lipids upon recheck in 1 and elevated glucose upon recheck prior to randomization in the other. One patient responded during the placebo lead-in, with the baseline HAM-D score decreasing from 18 to 5. The remaining 15 patients (mean ± SD age = 61.1 ± 7.9 years) randomly assigned to treatment were treated with TC, 100 (N = 8) or 200 (N = 7) mg/week, for a total of 6 weeks. All 16 patients meeting inclusion criteria were categorized as eugonadal due to the mean of their 2 pretreatment fT concentrations being above the lower limit of normal for their age group (mean = 1.6 ± 0.5 ng/dL, range 1.2–2.6 ng/dL). In fact, all of the fT concentrations were within the normal range of 0.88 to 2.7 ng/dL for men aged 20 to 39 years. Table 1 presents the baseline demographic data on the remaining 15 patients.

Table 1. Demographic Data for 15 Subjects Treated With Testosterone Cypionate, 100 or 200 mg/week[a]

Variable	Value
Age, y	61.1 ± 7.9
Early onset of major depression (< 45 y), N (%)	5 (33)
Baseline measures	
HAM-D score	20.1 ± 2.7
Buss-Durkee, aggression score	11.5 ± 7.1
Buss-Durkee, hostility score	17.7 ± 5.5
Free testosterone, ng/dL	1.5 ± 0.4
Total testosterone, ng/dL	485.9 ± 164.6
Luteinizing hormone, mIU/mL	1.5 ± 1.4
Follicle-stimulating hormone, mIU/mL	4.1 ± 1.9
Prostate-specific antigen, ng/mL	1.0 ± 0.6
Total cholesterol, mg/dL	197.9 ± 18.9
HDL cholesterol, mg/dL	48.2 ± 10.2
LDL cholesterol, mg/dL	122.1 ± 21.9
Triglycerides, mg/dL	150.5 ± 100.7
Hematocrit, %	43.4 ± 2.7
Systolic blood pressure, mm Hg	127.3 ± 14.5
Diastolic blood pressure, mm Hg	81.9 ± 7.9
Pulse, bpm	70.1 ± 8.3

[a]Values shown as mean ± SD unless otherwise noted.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Overall, testosterone therapy increased the mean weekly tT concentrations from 505 ± 148 ng/dL to 694 ± 240 ng/dL (paired t = 3.299, df = 14, p = .0053), while the fT concentrations increased from 1.6 ± 0.5 ng/dL to 2.3 ± 0.7 ng/dL (paired t = 5.071, df = 14, p = .0002). There was no significant difference from a statistical standpoint because of the large standard deviations between the mean weekly serum tT concentrations for the 100-mg/week (661 ± 244 ng/dL) and 200-mg/week doses (733 ± 247 ng/dL). Likewise, there was no significant difference from a statistical standpoint between the final fT concentrations for the 100-mg/week (2.3 ± 0.7 ng/dL) and 200-mg/week doses (2.5 ± 0.4 ng/dL). Regardless of the dose, the median number of weeks required to suppress basal LH to undetectable levels was 2. Ten of 14 patients in whom LH levels were available had suppressed FSH levels within 2 weeks. The median number of weeks required for the 100-mg/week and 200-mg/week TC doses to suppress FSH levels were 3 and 4, respectively. Eight of 12 patients in whom FSH levels were available had suppressed levels at week 4.

Table 2. Hamilton Rating Scale for Depression (HAM-D) Outcome Measures

	HAM-D Score			Group Statistic[a]		
Group	Baseline	Endpoint	Change	Unpaired t	df	p Value
Onset of depression				2.965	13	.0110
Early, (N = 5)	20.8 ± 3.3	17.0 ± 4.2	–3.8 ± 4.1			
Late, (N = 10)	19.8 ± 2.5	9.3 ± 5.6	–10.5 ± 4.1			
Dosage of testosterone cypionate				0.181	13	.8591
100 mg/wk	20.3 ± 2.7	11.8 ± 7.0	–8.5 ± 6.1			
200 mg/wk	20.0 ± 3.0	12.0 ± 5.9	–8.0 ± 4.2			

[a]Comparison of change in HAM-D score between patients with early- and late-onset depression and between patients receiving 100 and 200 mg/week of testosterone cypionate.

Determining the minimum effective testosterone dose is critical due to adverse effect concerns. Because there was considerable biweekly variability in the testosterone levels regardless of the dose, the peak total and free concentrations were contrasted. As was the case with the week 6 fT and tT concentrations, there was no difference between the peak concentrations for the 2 doses. The peak mean tT concentration during the 6 weeks for the 100-mg/week dose was 791 ± 199 ng/dL versus 961 ± 299 ng/dL for the 200-mg/week dose ($t = 1.3080$, $df = 13$, $p = .21$). The peak mean fT concentration during the 6 weeks for the 100-mg/week dose was 3.0 ± 0.76 ng/dL and 3.4 ± 0.8 ng/dL for the 200 mg/week dose ($t = 0.9367$, $df = 13$, $p = .37$).

The change scores on the HAM-D are presented in Table 2. For the 15 patients, there was a 42% decrease in the mean HAM-D scores from 20.1 to 11.9 (paired $t = 6.220$, $df = 14$, $p < .0001$). Six of the patients had ≥ 50% decrease in HAM-D score, while 5 had a final HAM-D score of ≤ 7. However, the majority of the change was due to improvement in the 10 late-onset (≥ 45 years old) depression patients, whose mean HAM-D score decreased from 19.8 to 9.3 (53%), versus the 5 early-onset depression patients, whose HAM-D decreased from 20.8 to 17.0 (18%) (unpaired $t = 2.965$, $df = 13$, $p = .0110$). The TC dose did not affect the response. Similar HAM-D decreases of 43% and 41% occurred with the 100- and 200-mg/week doses, respectively. Additionally, for the 10 late-onset patients, similar HAM-D decreases of 64% and 45% occurred with the 100 and 200 mg/week doses. Of the nonresponding patients, 3 opted for a 6-week course of antidepressant treatment. The 2 patients treated with nortriptyline, at 50 mg/day and 75 mg/day, had their HAM-D score decrease from 25 to 9 and 18 to 8, respectively. The first patient had early-onset depression, while the second had late-onset depression. The third patient, who was treated with sertraline, 50 mg/day, experienced a HAM-D score decrease from 20 to 12. He was categorized as having early-onset depression.

The correlations between the peak and mean tT concentrations and HAM-D change scores were determined for the late-onset patients. As presented in Figures 1A and 1B, the variables correlated in a negative direction.

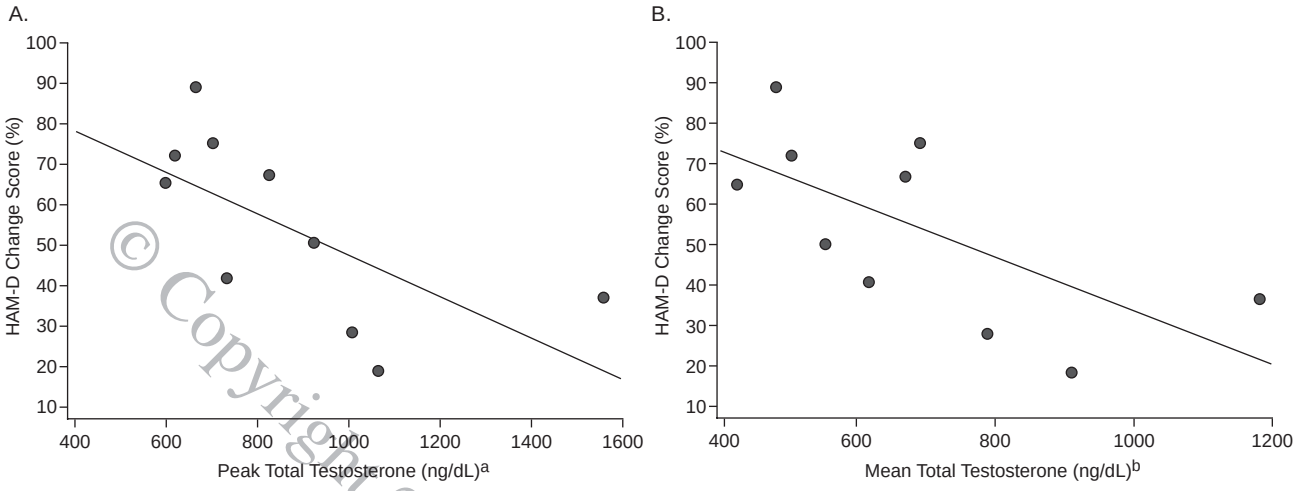
Since there was a difference in response between the early-onset and late-onset patients, the hormonal baseline states of the 2 groups were contrasted. There were no differences in the baseline hormonal profiles for the early-onset and late-onset patients. For the early- versus late-onset patients, the respective mean baseline tT, fT, LH, and FSH values were 501 versus 507 ng/dL, 1.5 versus 1.5 ng/dL, 1.1 versus 1.6 mIU/mL, and 4.4 versus 4.0 mIU/mL. Likewise, there were no differences in the baseline hormonal profiles for the 100- and 200-mg/week patient treatment groups. For the 100- versus the 200-mg/week treatment groups, the respective mean tT, fT, LH, and FSH values were 462 versus 555 ng/dL, 1.5 versus 1.6 ng/dL, 1.0 versus 2.0 mIU/mL, and 3.5 versus 4.7 mIU/mL.

The HAM-D responder analysis found that none (0%) of 5 early-onset patients had HAM-D response, while 6 (60%) of 10 late-onset patients responded ($\chi^2 = 5.000$, $p = .025$). Similarly, none of the early-onset patients experienced a remission, whereas 5 (50%) of the late-onset patients were categorized as remitters ($\chi^2 = 3.750$, $p = .053$). Finally, the dose did not affect the response rate.

The potential for TC to cause agitation among the patients was monitored using the BDHI. Patient scores on both the baseline BDHI aggression and BDHI hostility ratings indicated that the patients randomly assigned to the 200-mg/week dose had higher baseline aggression (15.7 ± 3.3 vs. 7.9 ± 6.6) and hostility (22.1 ± 2.3 vs. 13.9 ± 4.4) ratings than those assigned to the 100-mg/week dose. However, the 100-mg/week aggression (–0.3 ± 3.3) and hostility (–0.5 ± 4.5) change scores and the 200-mg/week aggression (–2.1 ± 3.8) and hostility (–2.3 ± 4.8) change scores dose did not differ significantly at the end of the treatment phase.

The distributions of abnormal clinical laboratory test values and vital signs are reported in Table 3. Regardless of dose, the PSA level increased from 1.0 ± 0.6 to 1.2 ± 0.7 ng/mL (paired $t = 2.682$, $df = 14$, $p < .02$). While being treated, none of the patients' PSA levels exceeded 3.0 ng/mL, which was the PSA exclusion limit for entry into the study. As expected, the hematocrit increased from 43.4 ± 2.7 to 46.0 ± 2.4 (paired $t = 3.348$, $df = 14$, $p < .01$). This change was not a function of dose. The alkaline phosphatase decreased from 68.8 ± 13.4 to

Figure 1. Relationship of Hamilton Rating Scale for Depression (HAM-D) Change Score to Perturbation of (A) Peak Total and (B) Mean Total Testosterone Concentration



[a]Peak total testosterone concentration = 98.7–(0.051 × HAM-D change score); $r^2 = 0.43$, p = .04.
[b]Mean total testosterone concentration = 99.3–(0.066 × HAM-D change score); $r^2 = 0.43$, p = .04.

Table 3. Significant Changes in Baseline Clinical Chemistries and Vital Signs Following Testosterone Treatment (N = 15)

Measure	N	%
Prostate-specific antigen > 3.0 ng/mL	0	0
Total cholesterol > 240 mg/dL	1	7
HDL cholesterol < 35 mg/dL	1	7
LDL cholesterol > 160 mg/dL	1	7
Triglycerides > 250 mg/dL	0	0
Hematocrit > 47%	4	27
Systolic blood pressure > 165 mm Hg	0	0
Diastolic blood pressure > 95 mm Hg	0	0
Pulse > 90 bpm	3	20

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

62.5 ± 12.6 U/L (paired t = 3.348, df = 13, p < .0005). Once again, the change was not a function of dose. The other safety measures did not change significantly overall or as a function of dose. These parameters included total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, lactic dehydrogenase, γ-glutamyl transpeptidase, alanine transaminase, aspartate transaminase, systolic blood pressure, diastolic blood pressure, and pulse. With respect to individual patients, only 1 patient was discontinued from the treatment phase of the study, but this was a result of restlessness and edema, not a change in laboratory test results or vital signs.

DISCUSSION

Depression alone is sufficient reason for clinical attention and treatment. Depression in geriatric males carries an additional burden of the highest suicide rate of all demographic groups.[15] Of affective disorder patients hospitalized for suicidality, 8.6% will eventually die by suicide.[16] Psychological autopsies identify depression in approximately 70% of suicides.[17] Of these suicides, the highest rates in the United States are in men > 65 years.[18] The rates continue to increase after the age of 65 years, doubling by age 85. This rate of suicide is 4 to 10 times greater than in females of similar age.[17] Furthermore, this trend is consistent among different nations and cultures.[19] Of countries reporting suicide data to the World Health Organization, the highest male suicide rate was in the ≥ 75-year-old group in all but 1 country.[20] Thus if testosterone therapy offers a protective effect against the development of late-life depression in hypogonadal and eugonadal males, suicide rates ought to be beneficially impacted.

However, the treatment data in both eugonadal and hypogonadal males are minimal and equivocal regarding an effect of testosterone therapy in major depression.[6–8] Our data suggest an effect, although the conclusion comes with a significant caveat. Testosterone therapy appears useful only in males whose first onset of depression is after age 45. This observation requires replication in both male and female patients with major depression.

The peak and mean tT concentrations and HAM-D change scores correlated in a negative direction for the late-onset patients. From the standpoint of determining the minimal effective testosterone dose for treating late-onset depression, this is an important finding. This relationship suggests only minimal testosterone doses are required to produce an antidepressant effect in these late-onset patients. Although similar analyses for the mean and peak fT versus the HAM-D change scores did not reach significance, the negative direction of the relationship remained consistent. Importantly, lower baseline fT and tT concen-

trations did not predict response to testosterone therapy as previously suggested.[9] The HAM-D change scores did not correlate with the baseline tT or fT concentrations.

The only worrisome finding in the safety data was the slight increase in the PSA levels. However, this concern is of no clinical significance. None of the patients experienced a PSA increase above 3.0 ng/mL, which was the exclusion criterion limit for the study. Additionally, at the study doses, there was no indication that there was a dose-response relationship between the percent change in the mean fT and tT concentrations and the mean change in the PSA concentrations. The patients who experienced the antidepressant response had the smallest perturbations of their tT concentrations. These findings are nearly similar to our experience in 31 healthy volunteers (21–39 years old) who were administered TC at 100, 250, or 500 mg/week for 12 weeks.[21] No significant changes occurred in the prostate volume or serum PSA levels at any dose of TC. Thus, these data indicate that a 6-week exposure to a physiologic replacement dose of TC of 100 mg/week will not produce clinically significant changes in the prostate.

In conclusion, there is a need for a double-blind placebo-controlled study of testosterone therapy for depression in elderly males. Our study suggests it would best be limited to men with late-onset depression. Clinicians treating elderly men should consider having testosterone levels measured to determine if a testosterone deficiency is a potential contributing factor for the depression. Additionally, it might be helpful to consider testosterone as an augmentation strategy for elderly men who respond partially to standard antidepressant therapy. Our study suggests short-term therapy with testosterone is safe. Long-term treatment safety is unknown. Psychiatrists using testosterone therapy should ascertain that patients have been recently evaluated for prostate cancer, and if testosterone therapy is initiated, the PSA assay should be used for monitoring patients' prostate status.

Drug names: nortriptyline (Aventyl, Pamelor, and others), sertraline (Zoloft), testosterone cypionate (Depo-Testosterone and others).

REFERENCES

1. Carr BR, Bradshaw KD. Disorders of the ovary and female reproductive tract. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. Harrison's Principles of Internal Medicine. New York, NY: McGraw Hill; 1998: 2102–2123
2. Sternbach H. Age-associated testosterone decline in men: clinical issues for psychiatry. Am J Psychiatry 1998;155:1310–1318
3. Urban RJ. Neuroendcrinology of aging in the male and female. Endocr Metab Clin North Am 1992;21:921–931
4. Tenover JS. Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab 1992;75:1092–1098
5. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. J Clin Endocr Metab 1997;82:3793–3796
6. Seidman SN, Rabkin JG. Testosterone replacement therapy for hypogonadal men with SSRI-refractory depression. J Affect Disord 1998;48: 157–161
7. Seidman SN, Spatz E, Rizzo C, et al. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. J Clin Psychiatry 2001;62:406–412
8. Wolkowitz OM, Reus VI, Keebler A, et al. Double-blind treatment of major depression with dehydroepiandrosterone. Am J Psychiatry 1999;156: 646–649
9. Margolese HC. The male menopause and mood: testosterone decline and depression in the aging male: is there as link? J Geriatr Psychiatry Neurol 2000;134:93–101
10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
11. Ooi DS, Innanen VT, Wang D, et al. Establishing reference intervals for DPC's free testosterone immunoassay. Clin Biochem 1998;31:15–21
12. Coat-A-Count [package insert]. Los Angeles, Calif: Diagnostic Products Corporation; 1995
13. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
14. Buss AH, Durkee A. An inventory for assessing different kinds of hostility. J Consult Psychol 1957;21:343–349
15. Palsson S, Skoog I. The epidemiology of affective disorders in the elderly: a review. Int Clin Psychopharmacol 1997;12(suppl 7):S3–S13
16. Bostwick JM, Pankratz VS. Affective disorders and suicide risk: a reexamination. Am J Psychiatry 2000;157:1925–1932
17. Meehan PJ, Saltzman LE, Sattin RW. Suicides among older United States residents: epidemiologic characteristics and trends. Am J Pub Health 1991;81:1198–2000
18. Guze SB, Robins E. Suicide and primary affective disorders. Br J Psychiatry 1970;117:437–438
19. Pearson JL, Conwell Y. Suicide in late life: challenges and opportunities for research. Int Psychogeriatr 1995;7:131–135
20. Nicol-Smith L. Causality, menopause, and depression: a critical review of the literature. BMJ 1996;313:1229–1232
21. Cooper CS, Perry PJ, Spark AET, et al. Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. J Urology 1998;159:441–443