

# The Aging Male: Androgens, Erectile Dysfunction, and Depression

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In contrast to women, men do not experience a sudden cessation of gonadal function comparable to menopause. However, there is a progressive reduction in hypothalamic-pituitary-gonadal (HPG) axis activity in aging men: testosterone levels decline and there is a loss of the circadian rhythm of testosterone secretion. Such progressive HPG-axis hypofunctioning is thought to be responsible for some signs and symptoms that are common in elderly men such as fatigue, reduced muscle and bone mass, sexual dysfunction, and depression. Yet, such presumed hypogonadal sequelae have not been correlated with testosterone levels. Unlike the profound effects of replacement therapy in young men with frank hypogonadism, testosterone replacement in men with age-related mild hypogonadism is not apparently effective in reversing these symptoms. This article reviews the relationship between androgens, sexual function, and depression in aging men. (*J Clin Psychiatry* 2003;64[suppl 10]:31–37)

The age-related decline in hypothalamic-pituitary-gonadal (HPG) axis function in men is commonly referred to as *andropause*. The term, which is identified with *menopause*, is similar in etymology more so than process; most men do not experience the cessation of steroid hormone production and the complete loss of reproductive capacity that occur during menopause. Nevertheless, there are significant endocrinological changes that do occur in aging men. In this review, we first provide a brief overview of male HPG physiology and the evidence for age-related HPG changes. Then, we focus specifically on the relationship between declining androgen levels, depression, and sexual dysfunction.

## ANDROGEN PHYSIOLOGY

Testosterone is the most potent and abundant androgen. The hypothalamus secretes gonadotropin-releasing hormone, which stimulates the anterior pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Figure 1). In men, LH stimulates Leydig's cells in the testes to synthesize and secrete testosterone; approxi-

mately 7 mg of testosterone are secreted daily. Secretion occurs in pulsatile bursts (about 6 per day), with a morning peak and an early evening trough, and is regulated through negative feedback on the hypothalamus and pituitary.<sup>1</sup>

The bioavailability of testosterone is determined by the extent to which the steroid is bound to plasma proteins. In the circulation, approximately 98% of testosterone is bound to sex hormone-binding globulin (SHBG) and albumin; only 2% of the hormone is considered "free" and thus biologically available. For clinical purposes, serum testosterone is routinely measured as total testosterone, which comprises both the bound and unbound forms. In target cells, testosterone can be converted to 2 active metabolites: dihydrotestosterone (DHT) and estradiol. There is tissue variability in the concentration of the metabolic enzymes responsible for this conversion, 5 $\alpha$ -reductase and aromatase, respectively, and differential sensitivity to each of these metabolites. All 3 steroids have distinct roles in the development of sexually dimorphic structures and functions.

Nearly all of the known effects of androgens involve receptor-mediated genomic mechanisms,<sup>2</sup> although more recent studies suggest that androgens also may have direct effects at the cell membrane and modulate the activity of other receptors or second messenger systems.<sup>3,4</sup> Both testosterone and DHT bind to the androgen receptor, which is distributed widely but selectively throughout the developing and adult brain and spinal cord.<sup>5</sup> Once the hormone binds to the receptor, the steroid-receptor complex binds to specific sequences of genomic DNA, which influences messenger RNA production and modulates the synthesis of a wide array of enzymatic, structural, and receptor proteins. The androgenic effects of gonadal steroids are either

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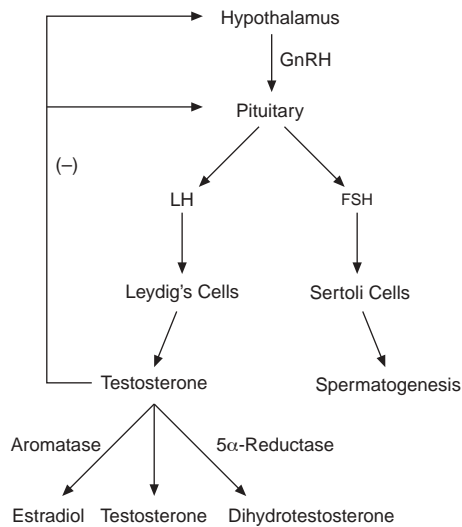
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Figure 1. The Hypothalamic-Pituitary-Gonadal Axis in Men



Abbreviations: FSH = follicle-stimulating hormone, GnRH = gonadotropin-releasing hormone, LH = luteinizing hormone.

organizational, which occur early in development when hormone exposure permanently alters the structure and function of androgen-sensitive tissues, or activational, which occur throughout life and involve acute temporary actions of steroid hormones.<sup>6</sup> Organizational effects of gonadal steroids influence the development of hormone-sensitive tissues that can be activated by gonadal steroids later in life.<sup>5</sup> Thus, the short-term effects that androgens have on adult sexual behavior and mood are activational, but such effects may have been determined by the prenatal hormonal milieu.

### AGE-RELATED CHANGES IN THE HYPOTHALAMIC-PITUITARY-GONADAL AXIS

In 1991, Gray et al.<sup>7</sup> conducted a meta-analysis to evaluate the literature on the age-related changes in testosterone levels among men. The analysis was designed to determine the source of discrepancies among previous study results and included the evaluation of sample characteristics (i.e., selection, health status, medication usage) and design characteristics (i.e., time of blood sampling, hormone assessment technique, hormone assessment quality). Of the 88 articles evaluated, 44 met specific rigorous inclusion criteria for predefined subgroups.

The mean subgroup size was 25 subjects and the average “mid-age” of the subgroups was 56 years. There were 12 subgroups with mean ages older than 80 years, and more than 75% of these subgroups were composed of subjects who had comorbid illnesses and were taking medications. One hundred fifty-seven mean testosterone

level measurements were obtained from the subgroups. Most samples were drawn in the morning and assessed using radioimmunoassay.

The overall weighted mean testosterone level was  $479 \pm 1.2$  ng/dL; however, levels varied considerably depending on the sample and methodological characteristics examined (Table 1). Likewise, general linear modeling revealed a significant relationship between testosterone level and age ( $R^2 = 0.29$ ;  $p < .0001$ ) and showed that some of the sample and methodological variables, including patient selection, health status, time of blood sampling, and type of hormone assessment, significantly affected this relationship (Table 1). Finally, in a multiple regression analysis, the best predictors of both testosterone level (i.e., higher) and the slope of the age-related decline (i.e., steeper) were good general health and morning serum sampling.

Similar results have recently been reported from a cross-sectional study<sup>8</sup> of Austrian men aged 20 to 89 years ( $N = 526$ ), which demonstrated gradual declines in testosterone levels. The extent of the decline depended on health status; total testosterone and free testosterone levels were higher among men in the “superhealthy” group compared with their age-matched counterparts in less healthy groups. Finally, in the 2 large longitudinal studies<sup>9,10</sup> that assessed testosterone levels over 8–10 years in middle-aged men, both demonstrated that the within-subject decline was even steeper than the cross-sectional declines, i.e., 1% to 3% decline per year. Overall, these findings confirm that testosterone level declines with age, although the clinical significance of this decline is not known.

### ANDROGEN EFFECTS ON SEXUAL FUNCTION

In the human male, certain components of sexual function are clearly androgen dependent.<sup>11</sup> For example, increasing androgen levels at puberty are associated with the onset of nocturnal emission, masturbation, dating, and infatuation. Boys who experience precocious puberty often develop an earlier interest in sexuality and erotic fantasies in parallel with an increase in testosterone level.<sup>6</sup> Postpubertal onset of hypogonadism (i.e., low testosterone level) is characterized by loss of libido and loss of sleep-associated and/or spontaneous erections.<sup>12</sup> Sexual desire, sexual thoughts, and the intensity of sexual feelings in hypogonadal men can be restored with testosterone replacement.<sup>13–15</sup> Finally, testosterone suppression in eugonadal men leads to reduced sexual desire and activity and a decrease in spontaneous and fantasy-driven erections.<sup>16</sup>

The clinical consensus is that there is a testosterone threshold below which some aspects of sexual function, particularly fantasy-driven erections and arousal, are impaired.<sup>11,16,17</sup> There is, however, little or no evidence of a correlation between sexual function and testosterone level in the normal range of circulating androgens,<sup>11</sup> and exogenous androgen administration is apparently not

Table 1. Mean Testosterone Levels by Study Characteristics: Results From a Meta-Analysis of 44 Studies<sup>a</sup>

Subject Characteristic	Subgroup	(% of all studies) <sup>b</sup>	Testosterone Level (ng/dL)	R <sup>2</sup> Value <sup>c</sup>
Patient selection	Residents of geriatric institutions	(3)	368	0.80
	Patients	(34)	473	0.05
	Volunteers	(34)	525	0.18
Health status	No illness excluded	(11)	474	0.0
	All illnesses excluded	(25)	486	0.44
	Endocrine illnesses excluded	(40)	500	0.25
Medication use	No medication excluded	(3)	357	NR
	Endocrine medication excluded	(27)	449	NR
	All medication excluded	(24)	495	NR
Methodological Characteristic	Subgroup	(% of all studies) <sup>b</sup>	Testosterone Level (ng/dL)	R <sup>2</sup> Value <sup>c</sup>
Timing of blood sampling	Afternoon/evening only	(2)	414	0.85
	Not specified	(18)	473	0.64
	Morning only	(73)	480	0.32
	Mixed times	(7)	500	0.64
Type of assessment technique	Competitive protein binding	(10)	447	0.40
	Radioimmunoassay	(77)	478	0.25
	Other	(13)	549	0.69
Quality of assessment technique	Poor to fair	(27)	465	NR
	Average/acceptable	(27)	469	NR
	Good	(29)	479	NR
	Excellent	(4)	480	NR
	No information	(13)	557	NR

<sup>a</sup>Adapted from the meta-analysis by Gray et al.<sup>7</sup>

<sup>b</sup>Includes only those subgroups for which testosterone levels were reported; thus, percentages may not add to 100.

<sup>c</sup>R<sup>2</sup> = the amount of variance in testosterone levels explained by age.

Abbreviation: NR = not reported.

Table 2. Testosterone Therapy for Erectile Dysfunction: Results of a Meta-Analysis<sup>a</sup>

Comparison	Number of Studies	Number of Patients	Response Rate (% ± SE)
Etiology of hypogonadism			
Primary	9	117	64 ± 4
Secondary	9	120	44 ± 3
Delivery method			
Intramuscular	7	238	51 ± 3
Oral	4	62	53 ± 6
Transdermal <sup>b</sup>	4 <sup>b</sup>	42	81 ± 6

<sup>a</sup>Data from Jain et al.<sup>22</sup>

<sup>b</sup>Three studies used scrotal and 1 used nonscrotal transdermal delivery systems.

effective for treating decreased libido or erectile dysfunction in eugonadal men.<sup>18,19</sup>

### Androgen Replacement Therapy for Erectile Dysfunction

The prevalence of hypogonadism in men presenting with erectile dysfunction is low, with reported rates ranging from 1% to 35%.<sup>20</sup> Even so, hormone assessment is the most common diagnostic evaluation,<sup>21</sup> and testosterone replacement therapy is the third most common medication treatment for erectile dysfunction.<sup>22</sup> Numerous studies have evaluated the efficacy of androgen therapy for erectile dysfunction in hypogonadal<sup>13,15,23–28</sup> and eugonadal men.<sup>14,18,19,29,30</sup> This literature has been extensively reviewed.<sup>17,25,31–34</sup>

**Hypogonadal men.** Using meta-analytic techniques, Jain et al.<sup>22</sup> assessed the utility of androgen replacement for erectile dysfunction. Studies were included if testosterone was the only method of therapy for erectile dysfunction, and the report provided clear definitions of the treatment response. The literature search (MEDLINE, 1966–1998) identified 73 articles containing the terms *impotence/erectile dysfunction* and *testosterone/androgen replacement therapy*. Sixteen of the articles met the inclusion criteria and were used for data abstraction. The overall response rate was 57% (± 3%). Secondary analyses were performed to compare the etiology (i.e., primary vs. secondary) of hypogonadism and the method (i.e., intramuscular vs. transdermal vs. oral) of hormone administration. The results of the secondary analyses are summarized in Table 2. Response rates were significantly higher among men with primary versus secondary hypogonadism ( $p < .001$ ) and for transdermal versus intramuscular or oral delivery ( $p < .001$ ). Five of the 16 studies included in the meta-analysis were randomized, controlled, crossover studies. In these studies, the mean response rate in the testosterone arm was 65% compared with 17% in the placebo arm, representing a 48% hormone-to-placebo difference indicative of an effect size that is likely to be of substantial clinical significance.

**Eugonadal men.** There are few randomized controlled trials of testosterone replacement therapy for erectile dysfunction among eugonadal men. In general, these studies

have demonstrated that physiologic doses of testosterone are no more effective than placebo for erectile dysfunction, lead to a modest increase in sexual interest, and do not lead to a change in self-reported measures of mood. O'Carroll and Bancroft<sup>18</sup> administered testosterone to men with erectile dysfunction (N = 10) and hypoactive sexual desire (N = 10). Although there was no demonstrable effect of testosterone on erectile function, the authors reported a statistically significant improvement in sexual desire in the hypoactive sexual desire group, but did not report the number of men who had a clinically significant improvement. This finding has not been replicated. Schiavi et al.<sup>19</sup> enrolled 18 eugonadal men with erectile dysfunction (age range, 46–67 years) in a 6-week, double-blind, placebo-controlled, crossover study to compare the effects of bi-weekly intramuscular injections of testosterone or placebo on sexual behavior and mood. During the testosterone phase, there was a significant increase in the frequency of ejaculation compared with the placebo phase. Testosterone did not have demonstrable effects on patient ratings of erectile function, sexual satisfaction, or mood.

These results suggest that exogenous testosterone may increase the frequency of sexual activity without improving erectile function or mood.<sup>19</sup> Overall, these data suggest that androgen *replacement* improves sexual desire and some aspects of erectile function in hypogonadal men. In contrast, exogenous androgen administration to eugonadal men does not appear to improve erectile dysfunction but may have some positive effect on hypoactive sexual desire.

## ANDROGENS AND DEPRESSION

The psychiatric symptoms of hypogonadism overlap with symptoms of depression and include low libido, fatigue, loss of confidence, and irritability.<sup>1</sup> Initial interest in this relationship focused on whether men with major depressive disorder (MDD) had HPG-axis abnormalities. However, most studies that assessed this relationship were methodologically flawed. Specific limitations include the following: endocrinological studies of hypogonadal men did not include methodologically rigorous neuropsychiatric assessments,<sup>13–15,26–28,30</sup> and the few psychiatric studies in which HPG-axis functioning was assessed in men with MDD generally did not use rigorous endocrinological methods<sup>1,11</sup> and did not focus on older men or on milder depressive syndromes.<sup>35,36</sup> Overall, in most clinical studies that have assessed neuroendocrine functioning in men with MDD, there has been only limited evidence that men with MDD—at any age—have significant HPG dysfunction, although evidence does support a blunting of early-morning LH and testosterone release in melancholic men.<sup>35,36</sup>

### Testosterone Levels and Depression in Men

**Epidemiologic studies.** There were 3 large epidemiologic studies in which the association between measures of

male HPG-axis function and depressive symptoms was examined.<sup>37,39,41</sup> The Veterans' Experience Study<sup>37,38</sup> comprised a representative sample of Vietnam-era veterans (mean age = 38 years). Subjects were administered a structured interview for depression (Diagnostic Interview Schedule [DIS]) and provided morning blood samples for testosterone assay. Overall, testosterone level was only weakly and negatively associated with depression ( $r = -.02$ ).<sup>37,38</sup> In a later reanalysis of these data, Booth et al.<sup>38</sup> showed that the relationship between testosterone level and DIS-diagnosed depression was nonlinear: below 600 ng/dL, men with lower testosterone levels were more likely to be depressed; above 600 ng/dL, men with higher testosterone levels were more likely to be depressed. Still, the correlations were relatively low, and the clinical significance remains unclear.

The Massachusetts Male Aging Study (MMAS)<sup>39</sup> was a community-based sample of men aged 40 to 70 years (N = 1709). Participants completed a self-report depression inventory, the Center for Epidemiologic Studies Depression (CES-D) scale, and provided a morning blood sample for hormone measurement. In a multiple logistic regression analysis, serum testosterone levels were not associated with erectile dysfunction (OR = 0.92; 95% CI = 0.82 to 1.03) or CES-D–diagnosed depression (OR = 0.90; 95% CI = 0.75 to 1.09).<sup>39</sup> However, in further MMAS analyses,<sup>40</sup> we included an androgen receptor (AR) genetic polymorphism. The AR gene has a polymorphic CAG repeat sequence encoding a variable-length glutamine chain in the N-terminal transactivation domain of the AR protein. We found that in the MMAS cohort there was a significant interaction between AR CAG repeats, testosterone level, and CES-D scores, suggesting that these HPG-axis state and trait features may interact to produce depressive symptoms; that is, whereas neither testosterone level nor AR isotype alone were associated with CES-D–defined depression (CES-D score  $\geq 16$ ), in a model using all 3 variables, AR isotype and testosterone together predicted depression (significant effect for the interaction term).<sup>40</sup> Thus, this AR trait marker may define a vulnerable group in which depression is expressed when testosterone levels fall below a particular threshold.

In the Rancho Bernardo Study,<sup>41</sup> adult residents of a southern California community were enrolled in a study of heart disease risk factors. In a 10-year follow-up study that included 82% of the surviving community residents, 856 men aged 50 to 89 years (mean age = 70 years) completed the Beck Depression Inventory (BDI) and had a morning blood sample drawn for hormone assays. Multiple linear regression analysis revealed a significant inverse correlation between BDI score and free, but not total, testosterone levels ( $B = -0.302 \pm 0.11$ ,  $p = .007$ ); that is, men with lower free testosterone levels had higher BDI scores, which is indicative of increased depressive symptoms.<sup>41</sup> This finding has not been replicated.

Table 3. Summary of Studies Evaluating the Effects of Exogenous Androgens on Depression in Eugonadal and Hypogonadal Men

Study	Design	N <sup>a</sup>	Diagnosis	Treatment Regimen	Results
<b>Eugonadal men</b>					
Wilson et al <sup>51</sup>	CS	5	Unipolar depression	Oral methyltestosterone (15 mg) and imipramine (75–150 mg) daily	Four patients showed a rapid paranoid response; HAM-D at baseline (range, 25–31) improved by EOT (range, 0–20)
Itil et al <sup>52</sup>	CS	17	Depression	Oral MST (50–200 mg) daily for 3 wk	Significant improvements in mood and anxiety; 5 of 6 patients taking a higher dosage (mean = 138 mg) were responders; 3 of 11 patients taking a lower dosage (mean = 83 mg) were responders
Vogel et al <sup>53</sup>	CS	13	Chronic unipolar depression	Oral MST (150–400 mg) daily for 7 wk	Baseline HAM-D (23.1 ± 8.9) improved by wk 7 (10.0 ± 7.5); final level of recovery positively associated with MST dose
Itil et al <sup>54</sup>	RCT	42	DSM-III MDD	Oral MST (300–450 mg) or PBO for 6 wk	CGI-rated improvement in MST (mean = 1.4) and PBO (mean = 1.3) groups; no between-group differences
Vogel et al <sup>55</sup>	RCT	26	DSM-III MDD	PBO for wk 1 and 2; MST (150–550 mg) or amitriptyline (75–300 mg) daily for 12 wk	MST (mean difference from PBO = –7.5) and amitriptyline (–8.4) groups had significant improvements in HAM-D (p < .05); no between-group differences
<b>Hypogonadal men</b>					
Rabkin et al <sup>56</sup>	RCT	70	HIV positive with CD4 < 400 cells/mm <sup>3</sup> ; T levels < 500 ng/dL; low libido; ≥ 1 depressive symptom	IM T cypionate (200–400 mg) biweekly for 6 wk	CGI-rated improvement in depression: T 74% (28/38); PBO 19% (6/32; $\chi^2 = 20.9$ , p < .001)
Seidman and Rabkin <sup>57</sup>	CS	5	SSRI-resistant MDD; T levels 200–350 ng/dL	IM T enanthate (400 mg) biweekly for 8 wk	HAM-D improved from 19.2 ± 4.4 to 4.0 ± 2.3 by wk 8; mean % maximum score on Q-LES-Q improved from 45% to 68%
Wang et al <sup>27</sup>	RCT	227; 195	T levels ≤ 300 ng/dL	T gel 50 or 100 mg/d; T patch 5 mg/d for 3 mo; T gel 50, 75, or 100 mg/d for 3 mo	Transdermal T (gel or patch) associated with improved positive mood and decreased negative mood after reaching T threshold in low normal range
Seidman et al <sup>46</sup>	RCT	29	DSM-IV MDD; T levels ≤ 350 ng/dL	IM T enanthate (200 mg) or PBO weekly for 6 wk	Reductions in HAM-D from baseline EOT in T (10.1) and PBO (10.5) groups; increases in Q-LES-Q in T (6.7 ± 12.3) and PBO (3.8 ± 11.9); no between-group differences
McNicholas et al <sup>28</sup>	RCT	208	T levels ≤ 10.4 nmol/L	T gel 50 or 100 mg/d; T patch 2.5 mg/d for 3 mo	Both doses of T gel associated with significantly improved positive and negative mood from baseline; T patch did not improve mood
Pope et al <sup>47</sup>	RCT	22	AD-resistant MDD; T levels 100–350 ng/dL	10 g of 1% dose T gel (100 mg) or PBO daily for 7 days	Significant improvement in mean HAM-D and CGI-severity scores among T vs PBO patients

<sup>a</sup>Evaluable patients.

Abbreviations: AD = antidepressant, CGI = Clinical Global Impressions scale, CS = case series, DSM = Diagnostic and Statistical Manual of Mental Disorders, EOT = end of treatment, HAM-D = Hamilton Rating Scale for Depression, HIV = human immunodeficiency virus, IM = intramuscular, MDD = major depressive disorder, MST = mesterolone, PBO = placebo, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, RCT = randomized controlled trial, SSRI = selective serotonin reuptake inhibitor, T = testosterone.

**Clinical studies.** In young men, symptomatic hypogonadism develops when the total testosterone level falls below a certain threshold, assumed to be between 200 and 300 ng/dL by clinical consensus.<sup>1</sup> Different threshold values may have to be determined in healthy aging men, which take into account age-related HPG changes (e.g., changes in end organ responsivity to androgens). Neuroendocrine studies of HPG-axis functioning among men with MDD have been cross-sectional, i.e., mean testosterone levels in a group of depressed men are compared with a group of nondepressed control subjects, and longitu-

dinal, in which testosterone levels during acute depressive illness are compared with hormone levels after remission. Findings from such studies have been inconsistent. Comparable numbers of studies have demonstrated lower levels of testosterone in depressed men as have studies showing no difference in plasma testosterone levels between depressed subjects and normal controls (although importantly, no studies have demonstrated *higher* testosterone levels in the depressed state).<sup>1,11</sup> The inconsistent results may be due to a number of factors, including small sample sizes, different diagnostic assessments of depression, and

heterogeneity in depressive symptoms in different study samples. There is also likely to be considerable diurnal, seasonal, situational, and age-related variability in testosterone secretion from study to study.<sup>1</sup>

Some clinical data suggest that the normative age-related decline in testosterone level, persisting over years, may lead to a chronic, low-grade, depressive illness such as dysthymia. In a sample of elderly depressed men who presented to our geriatric depression clinic,<sup>42</sup> we found that the median total testosterone level in 32 men with dysthymia (295 ng/dL; range, 180 to 520 ng/dL) was significantly lower than that of 13 age-matched men with MDD (425 ng/dL; range, 248 to 657 ng/dL) or 175 age-matched "non-depressed" men from the MMAS sample (423 ng/dL; range, 9 to 1021 ng/dL). Notably, 56% of these elderly dysthymic men had testosterone levels in the hypogonadal range ( $\leq 300$  ng/dL).<sup>42</sup> These data suggest that dysthymia (and not MDD) may be the depressive illness linked to hypogonadism.

### Effects of Androgen Therapy on Mood

In most clinical trials in which exogenous testosterone was administered to nondepressed eugonadal men, significant effects on mood were not detected. For example, Tricker et al.<sup>43</sup> randomized 43 eugonadal men, aged 19 to 40 years, to double-blind treatment with either testosterone or placebo injections weekly for 10 weeks. They found no change in self- or observer-reported measures of hostility, anger, or mood during testosterone treatment. Janowsky et al.<sup>44</sup> randomized 56 elderly men to receive testosterone or placebo patches for 3 months; there were no differences between testosterone and placebo groups in self-reported measures of mood.

Reports from the older psychiatric literature (1935–1960) on the "antidepressant" effects of testosterone suggested that a substantial number of "depressed" men responded immediately and dramatically to hormone replacement therapy and subsequently relapsed when treatment was discontinued.<sup>45</sup> However, standardized, syndromal, psychiatric diagnoses were not used in these studies, and baseline testosterone levels were not assessed. Moreover, the lack of a control group limits interpretation of the results. Few studies have systematically assessed the efficacy of exogenous testosterone for MDD using modern psychiatric diagnostic criteria or accepted clinical trial methodology.

In the past 2 decades, there have been at least 10 published studies of androgen treatment for men with depression in which investigators used criteria for MDD from the *Diagnostic and Statistical Manual of Mental Disorders* and systematically followed depressive symptoms (Table 3). For example, in a double-blind, randomized clinical trial of testosterone replacement versus placebo in 30 men with MDD and hypogonadism, we found that testosterone replacement was indistinguishable from placebo in anti-

depressant efficacy: 38% responded to testosterone and 41% responded to placebo.<sup>46</sup> However, a more recent study of testosterone replacement as an augmentation to antidepressant partial response suggests that this strategy may be more promising.<sup>47</sup> Overall, although initial anecdotal reports have been favorable, systematic trials of testosterone replacement for depression have provided inconsistent support for its efficacy.

## CONCLUSIONS

Normal sexual function in men involves a complex interplay of psychological, neurologic, vascular, and endocrine factors. With regard to erectile function in particular, studies have suggested that, for the majority of middle-aged and elderly men with erectile dysfunction, the primary etiology is vascular.<sup>48–50</sup> Given this etiology and the evidence reviewed here, it appears that even though the prevalence of erectile dysfunction parallels the age-related decline in HPG-axis functioning, hypogonadism is not typically the primary cause of erectile dysfunction.<sup>32</sup> In addition, androgen treatment does not improve erectile dysfunction in eugonadal men, although it appears to be effective for erectile dysfunction associated with hypogonadism. Finally, a similar limited relationship seems to exist between androgens and depression.

Nonetheless, delineation of the role of the HPG axis in the psychiatric problems of aging men may be of substantial public health importance. The sequelae of age-related gonadal hypofunction in women (i.e., menopause) are well characterized and substantial: a growing body of evidence implicates reduced circulating estrogen in the pathophysiology of mood disorders, neurodegenerative disorders, and osteoporosis. Such knowledge, and the relative ease of hormone replacement, has led to productive therapeutics research. There is no parallel characterization of the psychophysiology of age-related male hypogonadism, despite potential implications for the treatment of psychiatric and sexual problems in this population. Future research should focus on the possible central nervous system effects of mild age-related HPG-axis hypofunctioning, with an emphasis on mild mood problems (e.g., dysthymia), mild cognitive impairment, and sexual dysfunction.

*Drug names:* amitriptyline (Elavil and others), imipramine (Tofranil and others), mesterolone (Proviron), methyltestosterone (Testred, Virilon, and others).

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