REVIEW ARTICLE
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Androgens and the Aging Male

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ABSTRACT *~ In contrast to women, men do not experience a sudden cessation of gonadal function comparable to menopause. However, there is a progressive reduction in male hypothalamic-pituitary-gonadal (HPG) axis function: testosterone levels decline through both central (pituitary) and peripheral (testicular) mechanisms, and there is a loss of the circadian rhythm of testosterone secretion. The progressive decline in testosterone levels has been demonstrated in both cross-sectional and longitudinal studies, and overall at least 25% of men over age 70 meet laboratory criteria for hypogonadism (ie, testosterone deficiency). Such age-associated HPG hypofunctioning, which has been termed "andropause," is thought to be responsible for a variety of symptoms experienced by elderly men, including weakness, fatigue, reduced muscle and bone mass, impaired hematopoiesis, sexual dysfunction (including erectile dysfunction and loss of libido), and depression. Although, it has been difficult to establish correlations between these symptoms and plasma testosterone levels, there is some evidence that testosterone replacement leads to symptom relief, particularly with respect to muscle strength, bone mineral density, and erectile dysfunction. There is little evidence of a link between the HPG axis hypofunctioning and depressive illness, and exogenous androgens have not been consistently shown to have antidepressant activity. This article reviews the relationship between androgens, depression, and sexual function in aging men.* Psychopharmacology Bulletin. *2007;40(4):205-218.*

INTRODUCTION

It has long been recognized that androgens exert potent pro-sexual effects, particularly in men. In the now classic studies performed by Berthold in the mid-19th century, he demonstrated that implantation of testes into the abdominal cavity of castrated roosters restored the sexual behaviors which had disappeared following castration. He postulated that a blood-borne substance, acting on the brain, must be responsible.[1] Modern endocrinological investigations have confirmed the role of gonadal steroids, particularly androgens, in the coordination of sexual behavior with physiologic events in the body related to fertility. Over the past century, androgens have been frequently used empirically to enhance sexual functioning.[2,3] The role of the age-related HPG axis hypofunctioning in the development of central nervous system (CNS) sequelae such as depression remains largely unexplored.

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Androgen Physiology

The gonads—testes in males and ovaries in females—and adrenals secrete several "male" sex hormones called androgens, all of which are steroid hormones (ie, derived from cholesterol and containing a basic skeleton of four fused carbon rings). Testosterone is the most potent and abundant androgen. Gonadotropin-releasing hormone (GnRH) from the hypothalamus promotes anterior pituitary release of luteinizing hormone (LH) and follicle stimulating hormone (FSH). In males, LH stimulates the interstitial cells of Leydig in the testes to synthesize and secrete testosterone; approximately 7 mg of testosterone are secreted daily. Secretion occurs in pulsatile bursts, about six per day, with a morning peak and an early evening trough, and is regulated through a negative feedback on the hypothalamus and pituitary.[4]

In the circulation, approximately 98% of testosterone molecules are protein-bound. Of this, about one third are weakly bound to albumin, and the remainder are tightly bound to sex hormone-binding globulin (SHBG). SHBG, produced primarily in the liver, consists of different protein subunits and one androgen-binding site. Fluctuations in SHBG levels affect the bioavailability of testosterone. In target cells, testosterone is converted into two active metabolites: dihydrotestosterone (DHT) and estradiol (E2). There is tissue variability in the concentration of the cytoplasmic enzymes required for this conversion (5-α-reductase and aromatase), and differential tissue sensitivity to each of these metabolites. Both testosterone and DHT bind to the androgen receptor (AR); estradiol binds to one of the estrogen receptors.[5] The steroid-receptor complex binds to specific sequences of genomic DNA, which thereby influences messenger RNA production and modulates synthesis of a wide array of enzymatic, structural, and receptor proteins.[4] Testosterone also influences cellular activity in a nongenomic manner through activation of membrane receptors, second messengers, and the membrane itself. Such nongenomic actions appear to be especially important in the CNS.[6]

Androgen actions

During the male embryonal stage, testosterone is responsible for the growth of the penis and scrotum, development of the prostate and seminal vesicles, descent of the testes, and suppression of the development of female genitalia.[4,5] The testosterone surge during puberty causes the genitalia to enlarge about eight-fold, promotes the development and maintenance of secondary sexual characteristics, and supports anabolic activity.

Androgen-sensitive physiological effects occur at multiple levels, including metabolic processes, peripheral tissues (eg, the penis and clitoris), the spinal cord, and the brain.[1] Testosterone affects hair distribution

(including baldness), stimulates prostatic secretion and growth, masculinizes the larynx and the skin, increases red blood cell production and hemoglobin synthesis, and promotes protein anabolism which leads to muscular development, bone growth, calcium retention, and an increase in basal metabolic rate.[4,5]

The sexual effects of include perinatal "organizing" effects and postpubertal "activating" effects. It has been established in many mammalian species that testosterone, acting during a brief developmentally critical period, permanently alters brain structure and function.[1,4,5] Such "organizing" effects lead to behavioral predispositions in the setting of later reexposure to testosterone (ie, testosterone-sensitive neural networks are "wired"). This has been demonstrated most clearly in rodents. For example, perinatal androgen exposure of female rats leads to masculinized sexual, aggressive, and exploratory behavior postpubertally (particularly when activated by testosterone), and loss of the female pattern of gonadotropin secretion. In humans, prenatal exposure of female fetuses to excessive androgens (as a consequence of congenital adrenal hyperplasia) is associated with the development of male-like play behavior during childhood, male-like sexual imagery and preferences in adulthood, and more aggressive behavior compared to female relatives.[7]

Age-Related HPG-Axis Changes

In 1991, Gray et al.[8] 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 studies and included the evaluation of sample characteristics (ie, selection, health status, medication usage) and design characteristics (ie, 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" 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 levels were obtained from the subgroups. Most subgroups were comprised of samples drawn in the morning and assessed using radioimmunoassay. The overall weighted mean testosterone level was 479 ± 1.2 ng/dl; however, levels varied considerably depending on the sample and methodological characteristics examined. Likewise, general linear modeling revealed a significant relation between testosterone level and age ($R2 = 0.29$; $P < .0001$) and 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. Finally, in a multiple regression analysis, the best predictors of both testosterone level (ie, higher) and the slope of the age-related decline (ie, steeper) were good general health and morning serum sampling.

Similar results have been reported from a cross-sectional study 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 "super-healthy" group compared with their age-matched counterparts in less healthy groups.[9]

Finally, in two large longitudinal studies that assessed testosterone levels in middleaged men over a period of 8–10 years, both demonstrated that the within-subject decline was even steeper than the cross-sectional declines (ie, 1% to 3% decline per year).[10,11] Overall, these findings confirm that testosterone level declines with age. The clinical significance of this decline remains an area of great controversy, particularly with regard to potential psychiatric sequelae of hypogonadism, such as depression.

Andropause

Proponents of the view that andropause as a condition exists assert that symptoms of testosterone deficiency are similar to those of the aging process itself: decreased musculoskeletal mass, increased adipose deposition, decreased hematopoiesis, decreased facial hair growth, as well as decreased libido, energy, mood, and memory.[12,13] They remind us that testosterone replacement consistently reverses these sequelae in younger hypogonadal men (ie, ages 20-60): body weight, fat-free muscle mass, muscle size and strength increase; continued bone loss is prevented; sexual function and secondary sex characteristics (eg, facial hair) are restored and maintained; and hematocrit increases.[14,15] Therefore, they contend, application of a testosterone replacement strategy for older men with low or low-normal androgen levels is capable of reversing the aging effects on bones and muscle mass, as well as enhancing mood, energy, cognition, and libido.[16] Yet, it has been difficult to correlate hormone levels with such age-related phenomena.[13,17] Moreover, there are only limited controlled data on the effects of testosterone replacement in elderly men,[18,19] and none that address psychiatric symptoms in this age group. Specific studies in aging men are particularly important, because age-related testosterone deficiency is generally more modest than the profound hypogonadism seen in the testosterone replacement trials with younger men.

DHEA

DHEA, its metabolite DHEA sulfate (DHEA[S]), and androstenedione are the major androgenic steroids secreted by the adrenal cortex.

Although not potent androgens themselves, they are converted in target organs to testosterone and DHT. This is likely of significant androgenic consequence in females.[20] DHEA(S) is also produced *in situ* in brain tissue, and hence is termed a "neurosteroid."[21]

Plasma and cerebrospinal fluid DHEA(S) levels decline with age: at age 70, DHEA(S) levels are about 20% of those at age 20.[20] In an 8-year, population-based longitudinal study, DHEA-S levels declined 5.2% per year in middleaged men.[10] Many, but not all, studies have reported lowered levels of DHEA(S) or lowered ratios of DHEA(S)-to-cortisol in patients with depression, chronic fatigue syndrome, postpartum depression, and anxiety.[20] Similarly, in many population-based studies of the elderly, DHEA(S) level has been found to positively correlate with cognitive and general functional abilities, and have negative associations with mortality. Some investigators have, therefore, proposed DHEA(S) as a marker of "successful aging."[20,22] There is speculation that DHEA(S) "buffers" the deleterious effects of excessive glucocorticoid exposure. For example, it has been shown to prevent or reduce hippocampal neurotoxicity induced by the glutamate agonist NMDA, corticosterone, and oxidative stressors. Overall, accumulating descriptive and epidemiological data suggest a relationship between DHEA(S) levels and functional abilities, memory, mood, and sense of well-being, though there are many inconsistencies in the literature.

Treatment studies to date—typically involving short treatments with DHEA—demonstrate that this treatment is generally well-tolerated and not associated with significant changes in physical examination, hepatic, thyroid, hematologic, and/or prostatic function. Relatively common side-effects include acne, oily skin, nasal congestion, and headache. Less commonly reported side-effects include insomnia, over-activation (including disinhibition, aggression, and mania), hirsutism, increased body odor, itching, irregular menstrual cycles and voice deepening.[20]

ANDROGENS AND MALE SEXUAL FUNCTION, MOOD AND AGE

Neuropsychiatric Effects of Testosterone

Testosterone's influence occurs at multiple levels: metabolic processes, peripheral (particularly genital) tissues, the spinal cord, and the brain.[6] Non-specific metabolic effects (eg, increased hematocrit, anabolism) and/or stimulatory effects on genital tissue could indirectly influence neuropsychiatric functioning (eg, via increased general arousal). Specific CNS activation occurs via binding of testosterone or DHT to androgen receptors, estradiol to estrogen receptors, and through membrane-associated actions.[23]

Sexual Function

Experimental evidence has demonstrated that androgens directly influence sexual behavior in mammals, including non-human primates. These direct effects appear to be more influenced by social factors in primates. For example, in a multi-male group of rhesus macaques (*Macaca mulatta*), castration leads to an immediate reduction in sexual behavior; in a single male/multiple female group, post-castration sexual behavior declines after 1 month; and in a male-female pair, reduced sexual activity does not occur until 2 months after testosterone suppression.[24] In human males, direct behavioral effects of androgens are less apparent, and likely to be even more influenced by social factors.

In all male mammals studied, there is a dramatic reduction in sexual activity following the removal of testosterone by either surgical ablation of the testes or through seasonal regression.[25] In most male mammals, castration is followed first by loss of ejaculation, then intromission, and finally mounting; androgen replacement restores these sexual behaviors in reverse order.

Although among humans the role of testosterone in the maintenance of male sexual function is more complex, a large body of evidence supports a strong influence. For example, increasing plasma level of androgens at puberty is correlated with the onset of nocturnal emission, masturbation, dating, and infatuation. Males with an early onset of androgen secretion (ie, precocious puberty) often develop in parallel with an early interest in sexuality and erotic fantasies.[26] Postpubertal onset of hypogonadism is characterized by a loss of libido and lack of vigor, and a loss of sleep-associated and spontaneous erections.[27] Testosterone replacement in hypogonadal men leads to a dramatic increase in sexual desire, sexual activity, and frequency of erections.[28] Finally, suppression of testosterone secretion in eugonadal men leads to reduced sexual desire and activity, and a decrease in spontaneous and fantasy-driven erections, though no decrease in erectile response to erotic film (ie, externally-driven erections).[29,30] Notably, testosterone levels in eugonadal men do not generally correlate with sexual desire or performance, though studies have been inconsistent. The clinical consensus has been that among men there is a "low testosterone threshold" (which may vary from person to person) below which some aspects of sexual function are impaired, particularly internally-driven erections and arousal.

Depression

The psychiatric symptoms of hypogonadism overlap with symptoms of depression, and include low libido, fatigue, loss of confidence, and irritability.[31] Initial interest in this relationship has focused on whether men with major depressive disorder (MDD) have HPG abnormalities.

However, most studies that have assessed this relationship have been methodologically flawed. Specific limitations include the following: (1) endocrinological studies of hypogonadal men have not included methodologically rigorous neuropsychiatric assessments; and (2) the few psychiatric studies in which HPG axis functioning was assessed in men with MDD have generally not used rigorous endocrinological methods, and have not focused on older men or on milder depressive syndromes. Overall, in most epidemiological and clinical studies that have focused on the HPG axis in men, there is limited evidence that men with MDD—at any age—have significant HPG dysfunction, or that low testosterone level gives rise to depression.[32]

Epidemiological Studies. There have been three large epidemiological studies in which the associations between the measures of male HPG axis function and depressive symptoms were examined. The Veterans' Experience Study was comprised of a representative sample of Vietnam-era veterans (mean age, 38 years).[33] Subjects were administered a structured interview for depression (ie, Diagnostic Interview Schedule [DIS]) and asked to provide morning blood samples for a testosterone assay. Overall, testosterone level was only weakly and negatively associated with depression ($r = -02$). However, in a later reanalysis of these data, Booth et al.[33] showed that the relation between testosterone level and MDD was nonlinear: below 600 ng/dl, men with lower testosterone levels were more likely to be depressed, and 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) involved a community-based sample of men aged 40 to 70 years ($N = 1,709$).[34] Participants completed a self-report depression inventory, the Center for Epidemiologic Studies Depression Scale (CES-D), and provided a morning blood sample for hormone measurement. In a multiple logistic regression analysis, serum testosterone levels were not associated with CES-D–diagnosed depression (OR 0.90; 95% CI 0.75–1.09). However, in further MMAS analyses[35] an AR genetic polymorphism was induded. The AR gene has a polymorphic cytosine-adenine-guanine (CAG) repeat sequence encoding a variable-length glutamine chain in the N-terminal transactivationdomain of the AR protein. The length of the polymorphic CAG repeat inversely correlates with the transactivation function of the AR, and inverse relations have been described between the number of CAG triplets in the AR gene and the risk of prostate cancer, younger age at diagnosis, and poor response to endocrine therapy. It was found that in the MMAS cohort there was a significant interaction between AR CAG repeats, testosterone level, and CES-D,

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 (ie, CES-D ≥ 16), in a model using all three variables, AR isotype and testosterone together predicted depression.[35] Thus, this AR trait marker may define a vulnerable group of men in whom depression is expressed when testosterone levels fall below a particular threshold.

Finally, in the Rancho Bernardo Study,[36] 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 ± 0.11, P ± .007). That is, men with lower free testosterone levels had higher BDI scores, which is indicative of increased depressive symptoms. This finding has not been replicated.

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. Neuroendocrine studies of HPG axis functioning among men with MDD have been cross-sectional (ie, mean testosterone levels in a group of depressed men are compared with a group of non-depressed control subjects) and longitudinal (ie, 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 men with depression as have those showing no difference in plasma testosterone levels between depressed subjects versus controls (although importantly, none have demonstrated higher testosterone levels in the depressed state).[37] 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.

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, we found that the median total testosterone level in 32 men with dysthymia (295 ng/dl; range, 180–520 ng/dl) was significantly lower than that of 13 age-matched men with MDD (425 ng/dl; range, 248–657 ng/dl) or 175 age-matched, "non-depressed" men from the MMAS sample (423 ng/dl; range,

9–1021 ng/dl).[38] Notably, 56% of these elderly dysthymic men had testosterone levels in the hypogonadal range (ie, ≤300 ng/dl).[38] These data suggest that dysthymia (and not MDD) may be the depressive illness linked to hypogonadism.

EXOGEONOUS ANDROGEN ADMINISTRATION

Sexual Dysfunction

There are a few well-controlled studies of testosterone administration to eugonadal men with sexual dysfunction.[39-41] In general, they have demonstrated that administration of physiologic doses of testosterone is: (1) no more effective than placebo for erectile dysfunction; (2) leads to a modest increase in sexual interest; and (3) does not lead to a change on self-report measures of mood. For example, Schiavi and colleagues[39] enrolled 18 eugonadal men (age range 46–67 years) who presented with the chief complaint of erectile dysfunction in a double-blind, placebo-controlled, cross-over study and administered testosterone 200 mg or placebo every 2 weeks for a total of 6 weeks. They found that, compared to placebo phase, during the testosterone phase: (1) ejaculatory frequency doubled and other measures of sexual arousal increased (however, these finding were not statistically significant); (2) erectile function and sexual satisfaction were unaffected; and (3) mood, assessed by self-report instruments, was unaffected.[39] Most subjects could not correctly identify the phase in which they received testosterone, and felt it was not helpful. Notably, the authors were unable to demonstrate that this schedule of testosterone administration led to an increase in circulating levels of testosterone 2 weeks after each intramuscular injection, suggesting that this dose may have been too low to over-ride the compensatory feedback mechanisms operating in eugonadal men.

O'Carroll and Bancroft[41] administered testosterone to men with erectile dysfunction (n = 10) and hypoactive sexual desire (n = 10). There was no demonstrable effect of testosterone on erectile function, and a clinically significant effect on desire was found in only three patients in the low-desire group. Carani et al.[42] administered testosterone to 14 men with sexual dysfunction and demonstrated it to be helpful only for those who were mildly hypogonadal. Finally, Anderson et al.[28] randomized 31 eugonadal men, in a single-blind manner, to receive testosterone 200 mg by intramuscular injections for 8 weeks, or placebo weekly for 4 weeks followed by testosterone 200 mg IM weekly for 4 weeks. A significant effect of testosterone was demonstrated on the psychosexual stimulation test (SES 2), which measures the extent to which an individual seeks sexual stimuli. There was no effect on measures of sexual behavior, including intercourse frequency, erectile function, or masturbation, and no apparent effect on mood.

TABLE 1

SUMMARY OF STUDIES EVALUATING THE EFFECTS OF EXOGENOUS ANDROGENS ON DEPRESSION IN EUGONADAL AND HYPOGONADAL MEN

	DESIGN DESIGN	N*	DIAGNOSIS	TREATMENT REGIMEN	RESULTS
Eugonadal Men					
Wilson et al.[48]	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.[49]	CS	17	Depression	Oral MST (50–200 mg) daily for 3 weeks	Significant improvements in mood and anxiety; 5 of 6 patients taking a higher dose (mean 138 mg) were responders; 3 of 11 patients taking a lower dosage (mean 83 mg) were responders
Vogel et al.[50]	CS	13	Chronic unipolar depression	Oral MST (150–400 mg; daily for 7 weeks)	Baseline Ham-D (23.1 ± 8.9) improved by week 7 (10.0 ± 7.5); final level of recovery positively associated with MST dose
Itil et al.[51]	RCT	42	DSM-III MDD	Oral MST (300–450 mg) or PBO for 6 weeks	CGI-rated improvement in MST (mean, 1.4) and PBO (mean, 1.3) groups; no between-group differences
Vogel et al.[52]	RCT	26	DSM-III MDD	PBO for weeks 1 and 2; MST (150–550 mg) or amitriptyline (75–300 mg) daily for 12 weeks	MST (mean difference from PBO, −7.5) and amitriptyline (−8.4) groups had significant improvements in HAM-D ($P < .05$); no between-group differences
Hypogonadal Men					
Rabkin et al.[53]	RCT	70	HIV positive with CD4 < 400 cells/mm^3; T levels < 500 ng/dl; low libido; 1 depressive symptoms	IM T cypionate (200–400 mg) biweekly for 6 weeks or PBO	CGI-rated improvement in depression: T 74% (28/38); PBO 19% (6/32; chi square = 20.9, P<.001)
Seidman and Rabkin[54]	CS	5	SSRI-resistant MDD; T levels 200–350 ng/dl	IM T enanthate (400 mg) biweekly for 8 weeks	HAM-D improved from 19.2 ± 4.4 to 4.0 ± 2.3 by week 8; mean % maximum score on Q-LES-Q improved from 45% to 68%
Wang et al.[55]	RCT	227; 195	T levels < 300 ng/dl	T gel 50 or 100 mg/day; T patch 5 mg/day for 3 months; T gel 50, 75, or 100 mg/day for 3 months	Transdermal T (gel or patch) associated with improved positive mood and decreased negative mood after reaching a T threshold in the low-normal range

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TABLE 1 (continued)

SUMMARY OF STUDIES EVALUATING THE EFFECTS OF EXOGENOUS ANDROGENS ON DEPRESSION IN EUGONADAL AND HYPOGONADAL MEN

	DESIGN	N*	DIAGNOSIS	TREATMENT REGIMEN	RESULTS
Seidman et al.[46]	RCT	29	DSM-IV MDD; T level < 350 ng/dl	IM T enanthate (200 mg) or PBO weekly for 6 weeks	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.[56]	RCT	208	T levels < 10.4 nmol/L	T gel 50 or 100 mg/ daily; T patch 2.5 mg/day for 3 months	Both doses of T gel associated with significantly improved positive and negative mood from baseline; T patch was not
Pope et al.[47]	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

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Overall, the data suggest that in eugonadal men, exogenous androgen treatment has no effect on erectile dysfunction but may help hypoactive desire. In hypogonadal men, androgen replacement clearly improves desire and some aspects of erectile functioning. It is not known whether mild, age-related HPG hypofunctioning is associated with any sexual dysfunction, and if it is, whether androgen replacement is effective.

Depression

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.[43] 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.[43] Matsumoto[44] administered 100 mg T, 300 mg T, and palcebo weekly for 6 months to 20 young eugonadal men, and Janowsky and colleagues[45] randomized 56 elderly men to receive testosterone or placebo patches for 3 months. In both studies, 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.[37] 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.

In the past two decades there have been at least ten 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 (see Table). Most studies used oral androgen mesterolone (a derivative of DHT which lacks testosterone's non-DHT actions [ie, testosterone-specific and estrogenic activity]), and three used DHEA. In a double-blind, randomized, clinical trial of testosterone replacement versus placebo in 30 men with MDD and hypogonadism, our group demonstrated that testosterone replacement was indistinguishable from placebo in antidepressant efficacy: 38% responded to testosterone, and 41% responded to placebo.[46] However, a more recent study of testosterone replacement as an augmentation therapy to patients with partial response to antidepressants suggests that this strategy may be more promising,[47] though our unpublished findings do not support these findings. Overall, although initial anecdotal reports have been favorable, systematic trials of androgen replacement for depression have provided inconsistent support for its efficacy.

CONCLUSION

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 (ie, menopause) are well characterized and substantial. Yet, 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 CNS effects of mild age-related HPG-axis hypofunctioning with an emphasis on mild mood problems (eg, dysthymia), mild cognitive impairment, and sexual dysfunction. ✤

REFERENCES

1. Gonadal and adrenal steroids and the brain: Implications for depression. In: McEwen BS, Halbreich U (eds), *Hormones and Depression.* New York: Raven Press; 1998:239-253.
2. Sternbach H. Age-associated testosterone decline in men: clinical issues for psychiatry. *Am J Psychiatry* 1998;155:1310-1318.
3. Rubinow DR, Schmidt PJ. Androgens, brain, and behavior. *Am J Psychiatry.* 1996;153:974-984.
4. Laycock JF, Wise PH. *Male reproductive endocrinology.* 3rd ed. New York: Oxford University Press; 1996.
5. Bagatell CJ, Bremner WJ. Androgens in men: uses and abuses. *N Engl J Med.* 1996;334:707-714.
6. Schmidt PJ, Rubinow DR. Neuroregulatory role of gonadal steroids in humans. *Psychopharmacol Bull.* 1997;33:219-220.

7. Berenbaum SA, Duck SC, Bryk K. Behavioral effects of prenatal versus postnatal androgen excess in children with 21-hydroxylase-deficient congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 2000;85:727-733.
8. Gray A, Berlin JA, McKinlay JB, Longcope C. 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.
9. Schatzl G, Madersbacher S, Temml C, et al. Serum androgen levels in men: impact of health status and age. *Urology.* 2003;61:629-633.
10. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab.* 2002;87:589-598.
11. Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab.* 2002;87:5001-5007.
12. Haren MT, Morley JE, Chapman IM, O'Loughlin PD, Wittert GA. Defining 'relative' androgen deficiency in aging men: how should testosterone be measured and what are the relationships between androgen levels and physical, sexual and emotional health? *Climacteric.* 2002;5:15-25.
13. Morales A, Heaton JP, Carson CC. Andropause: a misnomer for a true clinical entity. *J Urol.* 2000;163:705-712.
14. Burris AS, Banks SM, Carter CS, Davidson JM, Sherins RJ. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. *J Androl.* 1992;13:297-304.
15. Snyder PJ, Peachey H, Berlin JA, et al. Effects of testosterone replacement in hypogonadal men. *J Clin Endocrinol Metab.* 2000;85:2670-2677.
16. Morley JE. Testosterone treatment in older men: effects on the prostate. *Endocr Pract.* 2000;6:218-221.
17. McKinlay JB, Longcope C, Gray A. The questionable physiologic and epidemiologic basis for a male climacteric syndrome: preliminary results from the Massachusetts Male Aging Study. *Maturitas.* 1989;11:103-115.
18. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab.* 1999;84:1966-1972.
19. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab.* 1999;84:2647-2653.
20. Wolkowitz OM, Brizendine L, Reus VI. The role of dehydroepiandrosterone (DHEA) in psychiatry. *Psychiatric Annals.* 2000;30:123-128.
21. Rupprecht R. The neuropsychopharmacological potential of neuroactive steroids. *J Psychiatr Res.* 1997;31:314-315.
22. Ravaglia G, Forti P, Maioli F, et al. Determinants of functional status in healthy Italian nonagenarians and centenarians: a comprehensive functional assessment by the instruments of geriatric practice. *J Am Geriatr Soc.* 1997;45:1196-1202.
23. Guo Z, Benten WP, Krucken J, Wunderlich F. Nongenomic testosterone calcium signaling: genotropic actions in androgen receptor-free macrophages. *J Biol Chem.* 2002;277:29600-29607.
24. Wallen K, Eisler JA, Tannenbaum PL, Nagell KM, Mann DR. Antide (Nal-Lys GnRH antagonist) suppression of pituitary-testicular function and sexual behavior in group-living rhesus monkeys. *Physiol Behav.* 1991;50:429-435.
25. Hormonal determinants of erectile function. In: Davidson JM, Rosen RC, Leiblum SR, eds. *Erectile disorders: Assessment and treatment.* New York: Guilford Press; 1992:72-95.
26. Feder HH. Hormones and sexual behavior. *Ann Rev Psychol.* 1984;35:165-200.
27. Plymate S. Hypogonadism. Endocrinology and metabolism. *Clin North Am*. 1994;23:749-772.
28. 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.
29. Bagatell CJ, Heiman JR, Rivier JE, Bremner WJ. Effects of endogenous testosterone and estradiol on sexual behavior in normal young men. *J Clin Endocrinol Metab.* 1994;78:711-716.
30. Rosler A, Witzum E. Treatment of men with paraphilia with a long-acting analogue of gonadotropin-releasing hormone. *N Engl J Med.* 1998;338:416-422.
31. Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. *J Clin Endocrinol Metab.* 2000;85:2839-2853.
32. Seidman SN. The neuroendocrine system in late life. In: Roose SP, Sackeim HA, eds. *Late Life Depression.* New York: Oxford University Press; 2003.
33. Booth A, Johnson DR, Granger DA. Testosterone and men's depression: the role of social behavior. *J Health Soc Behav.* 1999;40:130-140.

34. Araujo AB, Durante R, Feldman HA, Goldstein I, McKinlay JB. The relationship between depressive symptoms and male erectile dysfunction: Cross sectional results from the Massachusetts Male Aging Study. *Psychosom Med.* 1998;60:458-465.
35. Seidman SN, Araujo AB, Roose SP, McKinlay JB. Testosterone level, androgen receptor polymorphism, and depressive symptoms in middle-aged men. *Biol Psychiatry.* 2001;50:371-376.
36. Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. *J Clin Endocrinol Metab.* 1999;84:573-577.
37. Seidman SN, Walsh BT. Testosterone and depression in aging men. *Am J Geriatr Psychiatry.* 1999;7: 18-33.
38. Seidman SN, Araujo AB, Roose SP, et al. Low testosterone levels in elderly men with dysthymic disorder. *Am J Psychiatry.* 2002;159:456-459.
39. Schiavi RC, White D, Mandeli J, Levine AC. Effect of testosterone administration on sexual behavior and mood in men with erectile dysfunction. *Arch Sex Behav.* 1997;26:231-241.
40. Benkert O, Witt W, Adam W, Leitz A. Effects of testosterone undecanoate on sexual potency and the hypothalamic-pituitary-gonadal axis of impotent males. *Arch Sex Behav*. 1979;8:471-479.
41. O'Carroll R, Bancroft J. Testosterone therapy for low sexual interest and erectile dysfunction in men: a controlled study. *Br J Psychiatry.* 1984;145:146-151.
42. Carani C, Zini D, Baldini A, et al. Effect of androgen treatment in impotent men with normal and low levels of free testosterone. *Arch Sex Behav.* 1990;19:223-234.
43. Tricker R, Casaburi R, Storer TW. The effects of supraphysiological doses of testosterone on angry behavior in healthy eugonadal men-a clinical research center study. *J Clin Endocrinol Metab.* 1996;81: 3754-3758.
44. Matsumoto AM. Effects of chronic testosterone administration in normal men: safety and efficacy of high dosage testosterone and parallel dose- dependent suppression of luteinizing hormone, follicle-stimulating hormone, and sperm production. *J Clin Endocrinol Metab.* 1990;70:282-287.
45. Janowsky JS, Oviatt SK, Orwoll ES. Testosterone influences spatial cognition in older men. *Behav Neurosci.* 1994;108:325-332.
46. Seidman SN, Spatz E, Rizzo C, Roose SP. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. *J Clin Psychiatry.* 2001;62: 406-412.
47. Pope HGJ, Cohane GH, Kanayama G, Siegel AJ, Hudson JI. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry.* 2003;160:105-111.
48. Wilson IC, Prange AJ, Jr., Lara PP. Methyltestosterone with imipramine in men: conversion of depression to paranoid reaction. *Am J Psychiatry.* 1974;131(1):21-24.
49. Itil TM, Herrmann WM, Blasucci D, Freedman A. Male hormones in the treatment of depression: Effects of mesterolone. *Prog Neuropsychopharmacol.* 1978;2:457-467.
50. Vogel W, Klaiber EL, Broverman DM. Roles of the gonadal steroid hormones in psychiatric depression in men and women. *Prog Neuro-Psychopharmacol.* 1978;2:487-503.
51. Itil TM, Michael ST, Shapiro DM, Itil KZ. The effects of mesterolone, a male sex hormone in depressed patients (a double blind controlled study). *Methods Find Exp Clin Pharmacol.* 1984;6(6):331-337.
52. 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(1):6-8.
53. Rabkin JG, Wagner G, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Arch Gen Psychiatry.* 2000;57:141-147.
54. Seidman SN, Rabkin JG. Testosterone replacement therapy for hypogonadal men with SSRI-refractory depression. *J Affect Disord.* 1998;48(2-3):157-161.
55. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. *J Clin Endocrinol Metab.* 2000;85(8):2839-2853.
56. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. *BJU Int.* 2003;91(1):69-74.