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Testosterone and behavior

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> Although it is unlikely that wholesale replacement will result in 80 year olds forming gangs to roam the streets and beat up other seniors, it is possible that testosterone will enhance lesser degrees of aggressive behaviors.
>
> J.E. Morley, 2000 [1]

From ancient times testosterone has been considered to modulate behavior. Aretaeus, the Cappadocian, suggested that testosterone makes men "spirited and strong to act" and Galen believed that castration "slows down their whole vitality." Despite these early anecdotes, there is surprisingly little literature examining the effects of testosterone on behavior. As far as aggression is concerned both low and high testosterone levels seem to be associated with this behavior [2]. Much of this literature is confounded by the fact that the environment and a lifetime of learning experience greatly modify the response to any given hormone level.

Testosterone and behavior in older women

In women testosterone levels decline markedly between the ages of 20 and 40 years of age [3]. The levels of testosterone by 40 are about half of those of a younger woman. Although total testosterone levels do not decline during the menopause transition, the lack of estrogen results in a fall in sex hormone–binding globulin and an increase in free testosterone. Testosterone levels then increase slowly over the rest of the lifespan [4]. When a menopausal woman receives estrogen there is an increase in sex hormone-binding globulin resulting in a decline in free testosterone. Ovariectomy results in a 50% decline in testosterone [5].

Libido declines in some but not all women at the time of menopause [6,7]. The cause of this decline is multifactorial and is not predominantly caused by the fall

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in testosterone. In older women the level of free testosterone has been positively correlated with sexual desire [8].

Since 1977 when a study by Studd et al [9] suggested that a combination of estradiol and testosterone pellets had beneficial effects on sexuality in postmenopausal women, a number of studies have shown an improvement in libido with testosterone administration in postmenopausal women. The addition of testosterone implants to estradiol implants produced greater sexual activity, satisfaction, and orgasmic frequency than estradiol alone [10]. Testosterone injections improved sexual desires, fantasy, and arousal to a greater extent than estrogen in oophorectomized women [11]. Esterified estrogens with methyltestosterone (Estratest, Solvay Pharmaceuticals, Inc.) improve sexual function [12,13].

Shifren et al [14] showed that a 300-mg testosterone patch increased sexual activity and pleasure-orgasm. All women were oophorectomized, were receiving estrogen, and ranged from 31 to 56 years of age. A lower dose (150 mg) failed to produce any significant effects, but did increase sexual fantasies by 8% compared with 14% at the higher dose. Masturbation increased with both doses. The 300 mg per day patch resulted in supraphysiologic doses of total testosterone and dihydrotestosterone.

Testosterone improved the Psychological General Well-Being Index and decreased dysphoria [14]. Older women had a better psychologic response than younger women. In the study by Dobs et al [13], there was an improvement in psychologic well-being and quality of life. Two other studies in women have suggested that testosterone enhanced mood but did not distinguish whether this was truly an effect of testosterone or, in part, caused by concomitant estrogen administration [15,16].

Loss of muscle mass and frailty are major problems in older women [17–20]. In postmenopausal women testosterone improves muscle mass [21]. It is possible that some of the psychologic effects are secondary to improvements in physical functioning and well-being. Tibolone is a unique drug that demonstrates estrogenic, prostagenic, and androgenic effects. Tibolone enhances sexual function [22,23]. It tends to enhance mood, have some effects on memory, and improve quality of life [24–26].

Dehydroepiandrosterone (DHEA) is an adrenal androgen. DHEA levels decline dramatically with aging [27]. DHEA has been shown to increase libido especially in older women [28].

Overall, the effects of androgen replacement in older women have been poorly studied. Although they have been shown to have some intriguing effects on libido and behavior, further studies are necessary before their use can be recommended. There are no studies on long-term toxicity.

Testosterone and behavior in older men

It is now well established that testosterone levels fall over the lifetime in men [29–31]. The behavioral effects of this fall, however, are poorly established [32].

Eight studies have suggested that there is a behavioral syndrome associated with the fall in testosterone [33–40]. The features of this syndrome include decreased libido, fatigue, irritability, dysphoria, sleep disturbances, low dominance, memory problems, and headaches (Table 1). Treatment with testosterone seems to improve many of these symptoms in some, but not all men [37,39]. Two studies found that screening tests for behavioral symptoms of the andropause needed to exclude major depression if the screening test was to be effective [37,41]. In addition, stress has been shown to reduce testosterone levels [42–44]. The role of testosterone in producing a behavioral syndrome in middle-aged and older men remains controversial.

Table 1
Behavioral effects of the andropause

Study no	1	2	3	4
Author	Werner [33]	Greenblatt et al [34]	Heineman et al [35]	Wu et al [36]
Source	JAMA	J Am Geriatr Soc	Aging Male	Chang-Keng I Hsueh Tsa Chih
Year	1946	1979	1999	2000
Behavioral effects	Decreased libido[a] Nervousness Irritability Fatigue[a] Depression[a] Memory problems Sleep disturbances[a]	Decreased libido[a] Fatigue[a] Depression[a] Headaches	Decreased libido[a] Anxiety Nervousness Tiredness[a] Sleep problems[a] Decreased general well-being Irritability Depressive mood[a] Feeling burnt-out Feeling past ones peak	Decreased libido[a] Lack of energy[a] Falling asleep after dinner[a] Memory impairment[a] Sad or grumpy[a] Decreased work performance

Study no	5	6	7	8
Author	Morley et al [37]	Smith et al [38]	Li et al [39]	Delhez et al [40]
Source	Metabolism	Clin Endocrinol	Aging Male	Psychoneuro-endocrinology
Year	2000	2000	2002	2003
Behavioral factors	Decreased libido[a] Lack of energy[a] Decreased enjoyment of life Sad or grumpy[a] Decreased work performance Falling asleep after dinner[a]	Low dominance Headaches Sleepiness[a]	Decreased libido[a] Amnesia Distractibility Panic Irritability Loss of interest	Dysphoria[a]

[a] Factors that appear on four or more lists (ie, decreased libido, sleep problems, and dysphoric mood).

Testosterone and dysphoria in men

Many men receiving testosterone have an enhanced sense of well-being. Women have nearly twice the prevalence of depression compared with men. In 1948, Altschule and Tillotson [45] suggested that testosterone could be used to treat depression. These findings had suggested a role for testosterone deficiency in mood disorders.

A number of epidemiologic studies have suggested that low testosterone levels are associated with depression or dysphoria. Barrett-Connor et al [46] studied 856 men aged 50 to 89 years of age. They found that bioavailable testosterone was related to scores on the Beck Depression Inventory. This finding remained after factoring out age, weight change, and physical activity. The 25 men with true depression had testosterone levels that were 17% lower than the rest of the subjects studied. Bioavailable estradiol was not associated with dysphoria.

Seidman et al [47] using subjects from the Massachusetts Male Aging Study found that persons with a dysthymic disorder had median total testosterone levels (295 ng/dL) lower than those with major depression (425 ng/dL) and with no depression (423 ng/dL). Unfortunately, despite having the ability to calculate a free testosterone value, the authors only used a total testosterone value, the authors only used a total testosterone level. In view of the known problems with total testosterone as a measurement of hypogonadism in older persons [48] this limits the value of this report. Schweiger et al [49] performed frequent testosterone sampling over 24 hours in a group of depressed (N = 15) and normal (N = 24) men. Twenty-four mean testosterone levels were lower in the depressed group and luteinizing hormone pulse frequency was also depressed, suggesting depression may result in secondary hypogonadism. This could be caused by the suppressive effects of corticotrophin-releasing factor on the hypothalamic–pituitary–gonadal axis. Other studies have also found lower testosterone levels in men with depression independent of age [50,51]. Delhez et al [40] using a calculated free testosterone index found that depressive symptoms on the Carroll Rating Scale were more common among hypogonadal subjects. Anxiety and quality of life were not different in eugonadal and hypogonadal subjects. In another study, being sad or grumpy was associated with lower testosterone levels [37].

Booth et al [52] investigated the role of testosterone in modulating social behavior. Men with testosterone levels below normal levels had more dysphoria as did those with above average testosterone levels. This suggests that the relationship of testosterone to dysphoria is parabolic. Those men with higher testosterone levels, however, no longer showed a testosterone relationship to dysphoria when antisocial and risk-taking behavior and protective factors, such as marriage and regular employment, were factored into the analysis.

A number of open label studies have suggested that testosterone may be useful in the treatment of depression. In 1977, Reiter [53] believed that most depressed men responded to androgens and that relapses occurred often when treatment was stopped. Itil et al [54] showed that mesterolone improved mood in men with depressive symptoms. Vogel et al [55] confirmed this finding. Seidman and

Rabkin [56] treated five men whose mood had failed to improve with selective serotonin reuptake inhibitors. Testosterone augmentation was associated with rapid improvement in depressive symptoms. Testosterone treatment improves mood in dysphoric men who are HIV seropositive [57,58]. On the other hand, Sih et al [59] found no improvement in dysphoria symptoms, using the Geriatric Depression Scale, in nondepressed men in a placebo-controlled testosterone replacement study.

Seidman et al [60] entered 30 men with *Diagnostic and Statistical Manual-IV* major depressive disorder and a testosterone level below 350 ng/dL into a placebo-controlled trial. They received either 200 mg of testosterone enanthate or sesame seed oil weekly for 6 weeks. The average age of the patients was 52 years. Hamilton-D scores decreased to the same extent in both groups. The response rate, defined as a 50% or more reduction in the Hamilton-D score, was 38.5% in those receiving testosterone and 41.2% in those receiving placebo.

Wolkowitz et al [61,62] have reported two studies in which DHEA was used to treat a mixed group of men and women with major depressive order. In these studies, DHEA seemed to improve mood. In a double-blind, randomized, placebo-controlled trial DHEA improved mood in 12 men with midlife-onset dysthymia [63].

It seems that testosterone decreases in many men with depression. The role of low testosterone levels in day-to-day mood fluctuations is not clear. Testosterone does not seem to be effective in reducing the symptoms in major depression or classical dysthymic symptoms. Anecdotal studies in older men and a study in younger men [64] suggest that testosterone may enhance positive thoughts and inhibit negative thoughts. A single small study failed, however, to show an improvement in Psychological General Well-Being and Health Related Quality of Life in men over 65 years of age [65]. Large placebo-controlled trials using appropriate psychologic scales are necessary to determine whether or not testosterone truly enhances the feeling of general well-being.

Cognitive problems in men

Androgens are important for the development of brain structure and function in rodents. The ability of testosterone to enhance memory in rodents depends both on its ability to be aromatized to estrogen and its conversion by 5α-reductase to dihydrotestosterone [66]. The SAMP8 mouse is a rodent model of Alzheimer's disease that develops early memory deficits, and overproduces amyloid precursor protein [67,68]. These memory deficits can be reversed by antibodies to β-amyloid or an antisense to its messenger RNA [69–71]. SAMP8 mice have low testosterone levels by 12 months of age [72]. Testosterone replacement reverses the memory deficit in these animals and reduces the amyloid precursor protein levels in the limbic system. Testosterone reduces the production of amyloid precursor protein in tissue cultures [73]. Testosterone prevents phosphorylation of tau protein [74] and reversed age-related increase in glial fibrillary acidic protein [75]. Testoster-

one decreases circulating β-amyloid in humans [76]. Low testosterone levels are associated with the future development of Alzheimer's disease.

Epidemiologic studies have suggested a relationship of testosterone to cognitive function. Morley et al [77] found that bioavailable testosterone was related to memory problems. It was a better predictor of memory decline than other hormones. Another study suggested that the age-related decline in explicit memory was less likely in men with higher estradiol levels [78]. The Rancho Bernado studies in 547 men aged 58 to 89 years found that higher levels of bioavailable testosterone correlated with better scores on the Blessed Information Memory Concentration Test and the Buschke Selective Reminding Test [79]. There was a u-shaped relationship to spelling "world" backwards and bioavailable testosterone. Overall, this study supported the concept that an optimal testosterone level exists for cognition, with levels that are either too high or too low being disruptive. In younger men a curvilinear relationship of testosterone to spatial, but not verbal, cognitive tasks has been found [80].

Janowsky et al [81] studied 56 men aged 60 to 75 years who either received 15 mg testosterone scrotal patches or placebo patches. Testosterone treatment improved spatial cognition as measured by the Block Design subtest of the Wechsler Adult Intelligence Scale–Revised. There was no effect of testosterone on verbal memory or visual memory. There was no effect on fine motor speed. There was also no change in the Profile of Mood States. In a second study the same authors demonstrated an improvement in working memory using intramuscular testosterone [82]. In this study, they used the Subject Ordered Pointing Test.

Cherrier et al [83] in a double-blind study using intramuscular testosterone found an improvement in spatial memory and ability and verbal memory. Wolf et al [84] reported that a single injection of testosterone blocked the practice effect in verbal fluency, but was without effect on spatial or verbal memory. Sih et al [59] used a battery of cognitive tests over a period of a year. They found no change in motor speed, verbal or auditory memory, or in animal naming.

Almeida [85] compared 27 healthy older adults receiving testosterone patches with 29 control subjects receiving placebo. Testosterone improved spatial cognition as measured by the block design test. There were no effects on other tests or cognitive functioning.

In a single case Almeida et al [86] followed an 80-year-old man with Alzheimer's disease who received androgen blockade for adenocarcinoma of the prostate. As his testosterone level declined he showed marked deterioration on the Mini-Mental Status Examination and on the Cambridge Examination for Mental Disorders in the Elderly. There was no change in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire.

Overall the available data support an effect of testosterone on spatial memory. Possible effects also exist on working memory and verbal memory. It is important to recognize that these effects are relatively small. It also seems that there is an optimal level of testosterone to produce cognition enhancement, with higher and lower levels being less efficacious. Low testosterone levels may allow the development of Alzheimer's disease.

Sexuality and testosterone in older men

Healthy older men have a decline in sexual activity and interest and desire in sex [37,87]. There is a decrease in masturbatory behavior [88]. Men who remained sexually active over 80 years of age reported that most indulged in caressing and touching without intercourse [89].

Davidson et al [90] showed that free testosterone and elevated luteinizing hormone levels correlated with a decline in sexual activity, libido, and potency. Schiavi et al [91] reported that bioavailable testosterone correlates with frequency of sexual thoughts, frequency of desire for sex, easiness in becoming aroused, degree of coital erection, and frequency of sleep erections. Morley et al [37] found a correlation between bioavailable testosterone and libido. Libido was lower not only in hypogonadal men but also in those with intermediate bioavailable testosterone levels. Davidson et al [92] studying young persons found that testosterone was responsible for improving sexual thoughts, libido, and activity in hypogonadal younger men.

A number of studies have shown that testosterone improves libido in older men [37,93–95]. Morales et al [96] reported that libido improved in approximately two thirds of patients. Erectile function improves, but to a lesser extent [96,97].

Testosterone increases nitric oxide synthase activity [98]. Sildenafil, the phosphodiesterase-5 inhibitor, enhances erectile function in older men [99]. Addition of testosterone to sildenafil improves the quality of the erection.

Summary

In older men and women testosterone clearly improves libido and perhaps sexual activity. A number of authors have tried to describe a set of behavioral symptoms associated with the andropause. In older women testosterone seems to decrease dysphoria. In men the effects of testosterone on mood are less clear. In older men testosterone enhances spatial memory and possibly verbal and working memory. Table 2 summarizes the putative behavioral effects of testosterone.

Table 2
Putative behavioral effects of low testosterone in older women and men

	Men	Women
Sexuality	Decreased libido	Decreased libido
	Decreased sexual thoughts	Decreased sexual thoughts
Cognitive function	Poor spatial memory	Unknown
	Poor verbal memory	
	Poor working memory	
Mood	Possibly dysphoria	Poor psychologic well-being
	Decreased positive thoughts	Dysphoria
Nonspecific	Fatigue	Unknown
	Sleep disturbances	
	Irritability	

There is a clear need for better designed large-scale behavioral studies to determine the effects of testosterone in older men and women.

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