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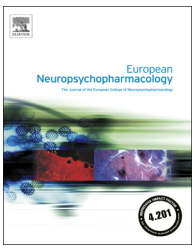

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The use of dehydroepiandrosterone in the treatment of hypoactive sexual desire disorder: A report of gender differences

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Abstract
Data regarding the efficacy of dehydroepiandrosterone (DHEA) in the treatment of hypoactive sexual desire disorder (HSDD) are scarce and inconsistent. We aimed to determine possible gender differences in the efficacy of DHEA as a treatment for HDSS. Postmenopausal women (n=27), and men (n=21) with HSDD, were randomized to receive either DHEA 100 mg daily or placebo for 6 weeks in a controlled, double blind study. Primary outcome measures were sexual function questionnaires. Hormone serum levels of DHEAS, total and bioavailable testosterone, estradiol, and urine levels of DHEA and androsterone were also measured. Participants on active treatment showed a significant increase in circulating serum levels of DHEAS, while bioavailable testosterone levels increased in women only. In women only, significant interaction effects were observed for sexual arousal ($p<0.05$), satisfaction ($p<0.05$), and cognition (trend; p=0.06). For arousal, a significant improvement was observed for the DHEA treated group at 6 weeks (p=0.001). Significant correlations were observed between bioavailable T and sexual cognitions, arousal and orgasm, while DHEAS was correlated with satisfaction. In the men, significant correlations were observed between testosterone and arousal (r=.45), sexual drive (r=.50) and orgasm (r=.55). In women with HSDD, DHEA treatment had a significant beneficial effect on arousal, whereas no efficacy was demonstrated in men, indicating a possible gender difference. This improvement seems to be mediated via DHEA's metabolism to testosterone. Our positive results suggest that the neurosteroid DHEA may be effective as a treatment for women with HSDD if administered at a dose of at least 100 mg per day.

1. Introduction

Hypoactive sexual desire disorder (HSDD) is the most common female sexual dysfunction and a subject of much

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debate (Brotto et al., 2010; Brotto, 2010). According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM—IV; APA, 2000) criteria, the diagnosis of HSDD requires the existence of personal distress or interpersonal difficulties associated with low sexual fantasies and desire for sexual activity, not due to medical or substance-use related conditions. HSDD is also frequently associated with problems in arousal and orgasm (Warnock, 2002).

The prevalence of HSDD is higher in women than in men (Laumann et al., 1999). Using the DSM—IV criteria HSDD, prevalence in women vary by age and menopausal status and have been reported in the range of 6–16% (Dennerstein et al., 2006; Shifren et al., 2008). Using a different model which defines HSDD without the obligatory 'distress' factor, the prevalence for HSDD is even higher (Basson et al., 2003). The prevalence of low desire in men aged 16–59 years ranges from 14% to 17% with an increased prevalence at older ages (DeRogatis et al., 2012).

Gonadal steroids, acting as neuroactive steroids, are a necessary factor, but not the only component in the maintenance of satisfying libido (Buvat et al., 2010) and are of importance in maintaining the equilibrium between excitatory and inhibitory factors that control sexual functioning (Clayton, 2010). Women require a minimum level of testosterone and estradiol to maximize their sexual response (Davis et al., 2005). In women, estrogens play an essential role both in the arousal process, and in modulating the dopaminergic system involved in drive, motivation, and the pursuit of pleasure (Clayton et al., 1999). Androgens play a critical role in activating and maintaining libido in both men and women (Rubinow and Schmidt, 1996). In women this is usually apparent (albeit not uniformly) after oophorectomy and adrenalectomy (Waxenberg et al., 1960). In men, plasma testosterone (T) levels above a threshold are necessary for normal sexual function and desire (Buvat et al., 2010), and hypoandrogenic states are clearly associated with low libido (Bloch et al., 2006; Schmidt et al., 2004). The administration of testosterone to women with HSDD after oophorectomy is clearly beneficial (Shifren et al., 2000; Simon et al. 2005), as well as testosterone administration in hypogonadal men (Wang et al., 2000).

For postmenopausal women with acquired (secondary) HSDD, the administration of androgens such as testosterone patches (Simon et al., 2005) or a combination of estrogen and methyltestosterone have been reported to be moderately beneficial in improving sexual functioning (Davis et al., 2005; Shifren et al., 2006). Hypogonadal men with HSDD are often treated with testosterone with moderately good results but to a lesser extent when low-normal testosterone level are present (Buvat et al., 2010). The main limitations in testosterone treatment in both men and women are a multitude of side effects, contraindications and uncertainty regarding long-term adverse effects. For these reasons an effective and safe treatment option for HSDD is unavailable and is very much needed.

Dehydroepiandrosterone (DHEA) and its conjugate DHEAS are prohormones produced in the adrenal gland, which is mostly converted to androstenedione and then into androsterone (A) and testosterone (T) which in turn is partially metabolized into estradiol. Peripherally, DHEA appears to act primarily through its metabolites. DHEA is also a neurosteroid, produced de novo in the brain (Strous et al., 2006). Davis et al. (2005) found that no single androgen was predictive of female HSDD; however, for premenopausal women, low scores of sexual responsiveness, arousal and desire were associated with a low DHEAS level. Also, significant differences between women with low libido and controls in total T, free T and DHEA-S levels were found, and these were negatively correlated with sexual function scores for desire and arousal, suggesting that women with low libido have lower androgen levels compared to age-matched normal control groups (Turna et al., 2005).

The efficacy of DHEA supplementation for HSDD in healthy premenopausal and postmenopausal euadrenal women is still mostly unknown. A number of studies showed a beneficiary effect (Arlt et al., 1999; Bloch et al., 1999; Johannsson et al., 2002; Munarriz et al., 2002; Rabkin et al., 2000), but many of these have major design limitations. Studies in which non-hypogonadal subjects who are formally diagnosed with HSDD using DSM—IV criteria are scarce. Two studies using relatively high DHEA doses showed improvement in sexual function parameters (Hackbert and Heiman 2002; Schmidt et al., 2005). Two recent studies employing validated measures of sexual function, larger sample sizes and a longer treatment duration did not demonstrate a positive effect in sexual function for DHEA treatment (Kritz-Silverstein et al., 2008; Panjari et al., 2009). However, only in one of these studies (Panjari et al., 2009) was women actually diagnosed with HSDD, and in both studies a relatively low 50 mg daily dose of DHEA was used.

In hypogonadal men, low sexual desire improved with testosterone treatment, and this improvement correlated with change in CSF measures of androsterone levels, thus further emphasizing the role of neurosteroids in the modulation of sexual function (Bloch et al., 1999). A treatment study in which DHEA was administered for midlife-onset depressed patients concluded that DHEA treatment was associated with an improvement in sexual function, including libido in both sexes (Schmidt et al., 2005). However, studies directly assessing the effect of DHEA on HSDD in men are scarce. One clinical trial in 140 healthy elderly men found no effect of 50 mg DHEA per day for 12 months on sexual function (Baulieu et al., 2000).

We propose to conduct a double blind, placebo controlled, short-term treatment study, using a relatively high dose of DHEA (100 mg daily) for the treatment of formally diagnosed men and women suffering from HSDD.

2. Experimental procedures

2.1. Study overview and eligibility criteria

The study was a single-center (Tel Aviv Sourasky Medical Center, Israel), 6-week, randomized, double-blind trial of DHEA treatment for subjects diagnosed with HSDD. Patients were recruited by media advertisements. A power analysis was performed apriorily, based on data derived from Schmidt et al. (2005). Using an alpha=0.05, power of 0.80, the calculated sample size needed for significant difference between the groups was a total of 50 subjects.

Patient inclusion criteria were: age 30–65 for men and 45–65 for women; all women were postmenopausal (at least 1 year of amenorrhea); meet DSM-IV HSDD criteria by the Structured Clinical Interview for DSM-IV Axis I Disorders (Shalev et al., 1994). Exclusion