DHEA therapy for women: effect on sexual function and wellbeing

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DHEA is increasingly available commercially as a supplement aimed at improving libido and wellbeing in postmenopausal women. However, there is scant evidence to support the use of DHEA for this purpose, and safety data for DHEA therapy are lacking. Dehydroepiandrosterone (DHEA) and its sulphate DHEAS are the most abundant circulating sex steroid hormones in women, providing a large precursor reservoir for the intracellular production of androgens and oestrogens in non-reproductive tissues. Levels of DHEA and DHEAS decline with age. It has been proposed that restoring the circulating levels of these steroids to those found in young people may have anti-ageing effects and improve wellbeing and sexual function. However, this is not supported by the published literature. We have reviewed the physiology of DHEA and DHEAS in women and the published literature pertaining to the use of DHEA therapy for libido and wellbeing in postmenopausal women. The literature was searched using Medline (Ovid) and Pub-Med for original studies. Overall, the interpretation of data from randomised controlled trials conducted in well women is limited by inadequate sample size and short treatment durations with inconsistent results for the outcomes of libido and wellbeing. Studies of DHEA in women with adrenal insufficiency, although indicating potential improvements in mood and libido, are also limited by their short treatment phase durations. In addition, safety data for DHEA therapy are lacking. The potential value of DHEA therapy for women still requires exploration in adequately powered well-designed randomised placebo-controlled trials. The studies of DHEA therapy in women with adrenal insufficiency suggest that this group is the most likely to derive health benefits from DHEA supplementation.

Key words: androgen therapy/DHEA/DHEAS/sexual function

Introduction

Dehydroepiandrosterone (DHEA) and its sulphate ester (DHEAS), are the most abundant circulating sex steroid hormones in women. The ovaries and adrenal glands produce DHEA, whereas DHEAS synthesis occurs in the zona reticularis of the adrenal cortex (Labrie, 1991, 2003). Circulating DHEA and DHEAS provide a large precursor reservoir for the intracellular production of androgens and estrogens in non-reproductive tissues (Labrie, 1991). Whether DHEA exerts direct effects on cellular function remains contentious. Serum levels of both DHEA and DHEAS decline with age (Davison et al., 2005) resulting in widespread speculation that the age-related decline in these C19 steroids results in loss of well being, deterioration in cognition and lowered libido (Baulieu et al., 2000). Whether DHEA exerts direct effects on cellular function remains contentious. Serum levels of both DHEA and DHEAS decline with age (Davison et al., 2005) resulting in widespread speculation that the age-related decline in these C19 steroids results in loss of well being, deterioration in cognition and lowered libido (Baulieu et al., 2000). Observational studies have shown that circulating DHEAS levels below the 10th centile are associated with increased likelihood of low sexual function in both premenopausal and post-menopausal women (Davis et al., 2005) and an association between low circulating DHEAS and low wellbeing has been reported in premenopausal women. It has been proposed that restoration of serum DHEA to the levels found in young people may have anti-aging effects (Baulieu et al., 2000). However, whether the decline in DHEA and DHEAS with advancing age results in a deficiency state that merits treatment or has a favourable physiological role in ageing and should not be altered still attracts considerable debate. A number of epidemiological studies, observational studies and randomized controlled trials concerning DHEA have been published but the results are inconsistent.

In the light of conflicting research data and differing beliefs regarding the use of DHEA therapy, we have reviewed the physiology of DHEA and DHEAS in women and the published literature pertaining to the use of DHEA therapy for libido and
wellbeing in post-menopausal women. To ensure a comprehensive review, the existing literature was searched using MEDLINE (Ovid) (1966 to the present) and Pub-Med (1966 to the present) for original studies. Search terms used included DHEA, DHEAS, dehydroepiandrosterone, dehydroepiandrosterone sulphate, in combination with the terms randomized trial, androgen replacement, adrenal insufficiency, menopause, libido and wellbeing. The analysis provided is purely descriptive as the published studies do not provide adequate data for inclusion in a meta-analysis.

**Physiology**

**DHEA and DHEAS production**

In target tissues such as the brain, bone, breast and adipose, DHEAS is converted by the sulphotransfer enzyme to DHEA, which may then be further metabolized to androstenediol, androstenedione (A), estrone (E1), testosterone (T), dihydrotestosterone (DHT) and 17β-estradiol (E2) (Labrie et al., 1997a, 2001). This process has been termed intracrinology (Labrie et al., 1988) and defined as ‘the synthesis of active steroids in peripheral target tissues where the action is exerted in the same cells in which synthesis takes place without release in the extracellular space and general circulation’. The transformation of DHEA and DHEAS into androgens and estrogens in the peripheral tissues depends on the level of expression of the steroidogenic and metabolizing enzymes present in the tissues. To date, 30 human genes have been found to code for enzymes of steroidogenesis (Labrie, 2004). This allows for tissue-specific expression and local control of steroid production according to local needs and allows for local regulation of steroid action independently of circulating levels of these steroids. This mechanism serves to eliminate the exposure of other tissues to androgens or estrogens, thus minimizing unwanted side effects (Labrie, 2004; Labrie et al., 1998, 2003).

It has been estimated that, in women, 75% of estrogens are produced by intracrine activity in the peripheral tissues before menopause and close to 100% after (Labrie et al., 1988; Labrie, 1991). In addition, it has been estimated that women produce approximately 71% of the total androgens synthesized in men, mostly DHT and testosterone produced from DHEA and DHEAS in the peripheral tissues (Labrie, 2003). The major androgens found in women, in decreasing order of their serum concentration, are DHEAS, DHEA, androstenedione, testosterone and DHT.

About 5% of DHEA synthesis occurs in the ovaries, whereas DHEAS is almost exclusively a product of the adrenal cortex. DHEA is the key precursor of onward synthesis of androgens and estrogens. The biosynthesis of DHEA and DHEAS in the adrenals and ovaries from cholesterol involves two cytochrome P450 enzymes, P450sc (cholesterol side chain cleavage) and P450 c17 (17α-hydroxylase/17,20-lyase). The cleavage of a side chain from cholesterol to form pregnenolone is catalysed by P450sc; and then P450 c17 converts pregnenolone to DHEA by two actions, 17-hydroxylation (17α-hydroxylase) and 17–20 bond cleavage (17,20-lyase). The enzyme DHEA-sulphotransferase, found in high levels in adrenal glands but not ovaries, converts DHEA to DHEAS. The further metabolism of DHEA to androstenedione requires another key enzyme 3β-hydroxysteroid dehydrogenase (3β-HSD) (Auchus, 2004; Payne and Hales, 2004); androstenedione is converted to testosterone by 17β-HSD and further to DHT by 5α-reductase. There is subsequent aromatization to estrone and estradiol (Labrie et al., 1997a, 2003). The active steroids are further metabolized mostly to inactive, conjugated, reduced steroids for excretion.

Daily production rates are approximately 6–8 mg/day and 3.5–20 mg/day for DHEA and DHEAS, respectively, and both circulate in micromolar concentrations (Burger, 2002). In contrast, the production of testosterone in premenopausal women is approximately 0.1–0.4 mg/day and total testosterone circulates in nanomolar concentrations (Burger, 2002). The circulating concentration of DHEAS is 250 times greater than DHEA as it has a much slower metabolic clearance rate of 13 l/day compared with 2000 l/day for DHEA. In addition, DHEA has a longer half-life of 10–20 h compared with 1–3 h for DHEA. Clearance rates are also influenced by the strong affinity of DHEAS for albumin (Kroboth et al., 1999). As a result of the low metabolic clearance rate, the concentration of DHEAS remains approximately the same level 24 h a day (Baulieu, 1996, Baulieu et al., 2000). Sex hormone binding globulin (SHBG) only weakly binds DHEA but not DHEAS (Dunn et al., 1981), thus circulating DHEA is highly metabolically available.

In normal circumstances, DHEA secretion is synchronous with cortisol and stimulated by adrenocorticotropic hormone (ACTH) (Kroboth et al., 1999). DHEAS synthesis is also stimulated by ACTH; however, due to the low metabolic clearance rate of DHEAS, the serum concentration of DHEAS remains at the same level (Baulieu, 1996). Adrenal androgens and cortisol production are not always linked. Circulating adrenal androgen levels have been observed to be normal or suppressed in acute stress, severe systemic illness, anorexia nervosa and Cushing’s syndrome which are otherwise characterized by elevated cortisol levels. This may be due to diminished or enhanced activity of 17, 20-lyase. Increased adrenal androgen production may also be seen in association with hyperprolactinaemia, although the majority of patients with this disorder have normal androgen levels (Vermeulen and Ando, 1978). Excess adrenal androgen levels is prevalent in approximately 40–65% of women with polycystic ovary syndrome (PCOS) (Lobo, 1984; Kumar et al., 2005).

**Independent effects of DHEA**

There is still considerable uncertainty as to whether DHEA has significant physiological actions independent of its conversion to other estrogenic and androgenic steroids. In competition binding studies, Chen et al. (2005) recently demonstrated that DHEA exhibits affinity to the androgen receptor (AR) and the estrogen receptors (ERs) with preference for ERβ over ERα. In this system, DHEA exhibited weak AR antagonist actions but transcriptional activation of ERβ, such that the authors concluded that the latter might represent a physiologically meaningful interaction.

Previous researchers have reported the identification of two DHEA receptors in vascular endothelium (Liu and Dillon, 2002, 2004) and murine T cells (Meikle et al., 1992). Zapata et al. (2005) have reported DHEA inhibited the proliferation of human umbilical vein endothelial cells, where as 17 β-estradiol exhibited...
a stimulatory effect. In contrast, Williams et al. (2004) reported that DHEA increased endothelial cell proliferation, using similar concentrations of DHEA, which was not altered by ER or AR blockade. A recent review concluded that, although there are strong data to support a plasma membrane receptor for DHEA, this receptor has not yet been isolated (Widstrom and Dillon, 2004). Definitive understanding of the role of DHEA is dependent on the isolation of a receptor. This undoubtedly remains a controversial area.

**Changes in DHEA and DHEAS with age**

In humans, the secretion of DHEA and DHEAS by the adrenals increases at the age of 6–8 years as a consequence of the maturation of the zona reticularis of the adrenal cortex with the resultant initiation of adrenarche (Havelock et al., 2004). Maximal values of circulating DHEAS are reached between the age of 20 and 30 years. Thereafter, serum DHEAS and DHEA steadily decline (Labrie et al., 1997b; Zumoff et al., 1980; Davison et al., 2005) (Figure 1). By the age of 70 years, serum DHEAS levels are approximately 20–23% of their peak values (Labrie, et al., 1998; Labrie, 2003; Davison et al., 2005). In parallel with this reduction during ageing, Labrie et al. (2001) have suggested that there is a concurrent reduction in the formation of androgens and estrogens in the peripheral target tissues. Conversely in vivo studies have demonstrated an increase in aromatase gene expression in adipose tissue in women with increasing age which implies an increased capacity of adipose to produce oestrogens (Bulun and Simpson, 1994; Misso et al., 2005). However, the decline in the production of the adrenal pre-androgens with age may contribute to the decline in total and free testosterone production (Haning et al., 1993; Davison et al., 2005). The decrease in DHEA and DHEAS in women appears to be unrelated to menopause status (Burger et al., 2000; Davison et al., 2005). The mechanism for this physiological decline is unknown.

**Findings from randomized controlled clinical trials**

We identified 26 published studies of the effects of DHEA supplementation on libido and wellbeing in women, 16 in ‘well’ women and 10 in women with adrenal insufficiency. Together, the studies involved premenopausal women, perimenopausal women, recently post-menopausal women and late post-menopausal women (>60 years). Nine of the 16 trials in well women were randomized double-blind placebo-controlled trials, 10 randomized placebo-controlled trials in women with adrenal insufficiency were identified; however, only 5 measured sexual function and mood and are included in this review (Figure 2).

![Figure 1. Dehydroepiandrosterone sulphate (DHEAS) versus age. Reproduced from Davison et al. (2005).](image-url)
Studies of the effects of DHEA in otherwise well women

Effects on sexual function

Seven trials have investigated the use of DHEA for the treatment of low sexual function in otherwise healthy women (Table I), although four of these also included men and three included perimenopausal women. A positive effect on female sexual function was reported in only three studies, each of which had major methodological limitations.

A small, double-blind randomized controlled trial (RCT) showed that the women given a single dose of 300 mg DHEA displayed increased subjective mental and physical response to an erotic video versus those given a single dose of placebo (Hackbert and Heiman, 2002). Both therapy and placebo increased vaginal pulse amplitude and vaginal blood volume with no difference between the two groups.

Another double blind RCT of a 50 mg oral DHEA daily dose versus placebo (Baulieu et al., 2000) reported DHEA therapy increased libido in women aged over 70. Sexual function was not evaluated using a validated instrument, and the visual analogue scale used to measure libido was understood by only 25% of the sample. A double-blind placebo-controlled crossover trial in which women with midlife onset depression were treated with 90 mg DHEA for 3 weeks then, 450 mg DHEA for 3 weeks versus 6 weeks of placebo (Schmidt et al., 2005) reported that libido improved in the active treatment group. This was assessed using the Derogatis Interview for Sexual Functioning, which consists of five subscales measuring levels of sexual fantasy, arousal, activity, quality of orgasm and sexual drive and quality of sexual relationship. The primary endpoint for this study was the effect on depression not libido and the doses administered were supraphysiological.

The remaining trials showed no positive effect of DHEA therapy on sexual function/libido (Mortola and Yen, 1990; Morales et al., 1994; Wolf et al., 1997; Barnhart et al., 1999; Meston and Heiman, 2002). Mortola and Yen (1990) reported no change in the self-reported sex drive of six post-menopausal women treated, in an double-blind crossover study, with a massive dose of 1600 mg oral DHEA for 28 days. Morales et al. (1994) in a double-blind placebo-controlled crossover design gave 2 premenopausal and 15 post-menopausal women 50 mg oral DHEA for 3 months (Morales et al., 1994). No change in libido as measured by a visual analogue scale was found. Eight of the menopausal women were already using estrogen therapy which may have had confounding effects. Barnhart et al. (1999) used 50 mg oral DHEA daily for 3 months in a placebo-controlled parallel group trial but only one question on the Hamilton Depression Rating Scale (HDRS) was used to measure libido.

All of the above-mentioned trials reported increased levels of serum DHEA/DHEAS, after oral therapy with DHEA preparations, restoring concentrations to the so-called 'young levels'. The existing trials are characterized by small sample size and likely inadequate study power, short therapeutic periods, differing DHEA doses, heterogeneous study populations and measurement of sexual function by non-validated instruments. Consequently, no conclusions can be made regarding the effects of DHEA therapy on female sexual function.

Effects on mood and wellbeing

Six studies have evaluated the effects of DHEA on mood and wellbeing, although not all employed validated questionnaires (Table II). Five of these trials reported a positive effect of DHEA on mood and wellbeing.

In a double-blind, placebo-controlled crossover trial, 50 mg DHEA administered daily for 3 months to premenopausal and post-menopausal women resulted in improved sense of wellbeing.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Time</th>
<th>n</th>
<th>Dose (mg)</th>
<th>Female participants</th>
<th>Changes in hormones reported</th>
<th>Sexual thoughts and behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortola and Yen (1990)</td>
<td>RCT double-blind placebo crossover</td>
<td>28 days</td>
<td>6 F</td>
<td>1600</td>
<td>Post-menopausal 46–61 years</td>
<td>↑ DHEAS, DHEA, A, testosterone, DHT, E1, E2 ↓ SHBG</td>
<td>No change in self-reported sex drive(^a)</td>
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<tr>
<td>Morales et al. (1994)</td>
<td>RCT double-blind placebo crossover</td>
<td>3 months</td>
<td>17 F, 13 M</td>
<td>50</td>
<td>2 premenopausal 15 years (8 ET post-hysterectomy) 40–70 years</td>
<td>↑ DHEAS, DHEA, A, testosterone, DHT No change E1, E2 ↓ SHBG</td>
<td>No change in libido: VAS</td>
</tr>
<tr>
<td>Wolf et al. (1997)</td>
<td>RCT double-blind placebo crossover</td>
<td>2 weeks</td>
<td>15 F, 25 M</td>
<td>50</td>
<td>Post-menopausal 69.1 ± 1.7 years (4 HT)</td>
<td>↑ DHEA, DHEAS, A, testosterone</td>
<td>No change in libido(^a)</td>
</tr>
<tr>
<td>Baurhurt et al. (1999)</td>
<td>RCT double-blind placebo parallel group</td>
<td>3 months</td>
<td>66 F</td>
<td>50</td>
<td>Symptomatic Perimenopausal 45–55 years</td>
<td>↑ DHEA, DHEAS, total testosterone</td>
<td>No difference between groups: HDRS</td>
</tr>
<tr>
<td>Baulieu et al. (2000)</td>
<td>RCT double-blind placebo parallel group Multicentre</td>
<td>12 months</td>
<td>140 F, 140 M</td>
<td>50</td>
<td>Post-menopausal ageing &gt;60 years</td>
<td>↑ DHEAS (6 m &gt; 12 m), testosterone, E2, ADG</td>
<td>↑ Libido in &gt; 70 years VAS</td>
</tr>
<tr>
<td>Hackbert and Heiman (2002)</td>
<td>RCT double-blind placebo crossover</td>
<td>2 session within 1 week</td>
<td>16 F</td>
<td>300</td>
<td>Post-menopausal 51–68 years</td>
<td>↑ DHEAS</td>
<td>FES, DSFI, OFQ and self-report ↑ Subjective mental and physical response to erotic video ↑ VPA and VBV in both groups</td>
</tr>
<tr>
<td>Schmidt et al. (2005)</td>
<td>RCT double-blind placebo crossover</td>
<td>1–2 weeks washout</td>
<td>23 F, 23 M</td>
<td>90 (3 weeks), 450 (3 weeks)</td>
<td>5 peri, 6 post, 12 premenopausal midlife depression 40–65 years</td>
<td>↑ DHEA, DHEAS, free testosterone, A ↓ SHBG</td>
<td>Improved libido: DISF HDRS, BDI, CDS</td>
</tr>
</tbody>
</table>

F, female; M, male; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; A, Androstenedione; DHT, dihydrotestosterone; E1, estrone; E2, estradiol; SHBG, sex hormone binding globulin; HDRS, Hamilton Depression Rating Scale; DISF, Derogatis Interview for Sexual Functioning; VAS, visual analogue scale; VPA, vaginal pulse amplitude; VBV, vaginal blood volume; OFQ, Orgasmic functioning Questionnaire; FES, Film Evaluation Scale; SDS, sexual distress scale; FSFI, female sexual function inventory; BDI, Beck Depression Inventory; CDS, Cornell Dysthymia Scale. \(^a\)No validated instrument.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Time</th>
<th>n</th>
<th>Dose (mg)</th>
<th>Participants</th>
<th>Changes in hormones reported</th>
<th>Mood/wellbeing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales et al.</td>
<td>RCT double blind placebo crossover Washout time not stated</td>
<td>3 months</td>
<td>17 F 13 M</td>
<td>50</td>
<td>2 premenopausal, 15 post-menopausal (8 ET post-hysterectomy) 40–70 years</td>
<td>↑ DHEAS, DHEA, A, testosterone, DHT</td>
<td>Improved wellbeing (sleep quality, relaxation, energy, ability to handle stress): 82% self-reported*</td>
</tr>
<tr>
<td>Wolf et al.</td>
<td>RCT double blind Placebo crossover 2 weeks washout</td>
<td>2 weeks 15 F 25 M</td>
<td>50</td>
<td>Post-menopausal 69.1 ± 1.7 years (4 HT)</td>
<td>↑ DHEA, DHEAS, A, testosterone</td>
<td>Trend ↑ quality of life, mood, wakefulness</td>
<td></td>
</tr>
<tr>
<td>Barnhart et al.</td>
<td>RCT double-blind placebo parallel group</td>
<td>3 months 66 F</td>
<td>50</td>
<td>Symptomatic perimenopausal 45–55 years</td>
<td>↑ DHEA, DHEAS, total testosterone</td>
<td>No difference between groups: HDRS, HRQOL, DSR, profile of mood scale, SKB QOL</td>
<td></td>
</tr>
<tr>
<td>Bloch et al.</td>
<td>RCT double-blind placebo crossover 1 week washout</td>
<td>6 weeks</td>
<td>3 F 12 M</td>
<td>90 (3 weeks) 450 (3 weeks)</td>
<td>Post-menopausal 45–63 years</td>
<td>↑ DHEA, DHEAS, total testosterone, free testosterone</td>
<td></td>
</tr>
<tr>
<td>Wolkowitz et al.</td>
<td>RCT double-blind placebo parallel group</td>
<td>6 weeks 10 F 12 M</td>
<td>30, 60, 90 (2 weeks)</td>
<td>33–53 years women depression (menopausal status not described)</td>
<td>↓ Total estrogens, E2</td>
<td>BDI, HDRS, CDS: improved depression scores</td>
<td></td>
</tr>
<tr>
<td>Schmidt et al.</td>
<td>RCT double blind placebo cross over 1-2 week washout</td>
<td>6 weeks</td>
<td>23 F 23 M</td>
<td>90 (3 weeks) 450 (3 weeks)</td>
<td>↑ DHEA, DHEAS, free testosterone, A</td>
<td>Change in HDRS: antidepressant effect</td>
<td></td>
</tr>
</tbody>
</table>

DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; A Androstenedione; DHT, dihydrotestosterone; E1, estrone; E2, estradiol; SHBG, sex hormone binding globulin; HRQOL, health-related quality of life; BDI, Beck Depression Inventory; HDRS, Hamilton Depression Rating Scale; CDS, Cornell Dysthymia Scale; DSR, daily symptom rating; SKB QOL, Smith Kline Beecham quality of life.

*No validated instrument.
in 82% of the sample (Morales et al., 1994). This was manifest as improved sleep quality, greater relaxation, increased energy and improved ability to handle stress, although these factors were self-reported rather than measured with a validated instrument. Wolf et al. (1997) in a 2-week double-blind placebo-controlled crossover trial of 50 mg oral DHEA daily in post-menopausal women reported a trend towards improved quality of life and mood. Another trial of similar design but 6 weeks duration in post-menopausal women reported improvement in mood as measured by several validated depression questionnaires, Beck Depression Inventory, HDRS, and Cornell Dysthymia Scale (Bloch et al., 1999). However, they did not find a relationship between onset of mood disorder and serum DHEA levels. In a double-blind parallel group placebo-controlled trial, depressed women and men were given increasing doses of DHEA 30, 60 and 90 mg biweekly for 6 weeks versus placebo for 6 weeks. A greater antidepressant effect was reported in the DHEA group (Wolkowitz et al., 1999).

More recently, a double-blind placebo-controlled crossover trial examined the use of DHEA for the management of midlife onset major and minor depression (Schmidt et al., 2005). The trial involved both men and women in various stages of menopause. Oral dosage was 90 mg daily for 3 weeks, then 450 mg daily for 3 weeks versus a group on placebo for 6 weeks. The DHEA dose was a significantly higher dosage than that used in other trials. Although improvements in mood were seen for participants treated with DHEA, the high doses administered albeit for only 6 weeks preclude the recommendation of DHEA at this dose for the treatment of depression based on safety.

Barnhart et al. (1999) in a double-blind placebo-controlled trial of 50 mg DHEA in perimenopausal women found that both treatment and placebo groups significantly improved in wellbeing from baseline at 3 months and that there was no difference between the two groups (Barnhart et al., 1999). The authors attribute this finding to the ‘Hawthorne effect’ or because the women were under additional surveillance by participating in a clinical trial.

In summary, short treatment duration, high DHEA dosage and small subject numbers with probable lack of power limited trials evaluating wellbeing. Thus, the value of using DHEA to improve mood or quality of life remains unclear.

Studies of the effects of DHEA in women with adrenal insufficiency

Adrenal insufficiency is characterized by abnormally low, sometimes unmeasurable serum concentrations of DHEA and DHEAS. Adrenal insufficiency is associated with impaired quality of life, low libido and lack of wellbeing (Arlt and Alloio, 2003a; Lovas et al., 2003; Arlt, 2004). It is thought that this group of women would be the most likely to derive benefit from DHEA replacement therapy.

There are five studies in women with adrenal insufficiency that assessed sexual function or mood: three in women with primary adrenal insufficiency (Addison’s disease), one in women with secondary adrenal insufficiency (pituitary gland failure) and one in women with pan-hypopituitarism (adrenocortical and gonadal insufficiency) (Table III).

Arlt et al. (1999) studied 24 women with primary (14) and secondary (10) adrenal insufficiency. The women were randomized to treatment with either 50 mg oral DHEA daily for 4 months or placebo in a double-blind crossover trial. During the time of active treatment, there were significant increases in serum levels of DHEA, DHEAS, androstenedione, testosterone and DHT. SHBG decreased and estrogens were not changed. Improvements in sexual function (thoughts, interest and satisfaction measured by a visual analogue scale) and mood were associated with the change in androgen levels. Symptoms of depression, anxiety and their physical correlates, such as exhaustion, were significantly improved after 4 months of treatment with DHEA.

In contrast, Hunt et al. (2000) found no effect of the same dose of DHEA on sexual function, cognition, body composition or bone mineral density. There was, however, improved wellbeing, self-esteem and mood and a decrease in fatigue. Lovas et al. (2003) in a parallel group trial of 25 mg oral DHEA daily versus placebo also found no impact of treatment on sexual function or wellbeing. However, this study has been since criticized for being under-powered for a parallel group trial as there were only 39 women in total (Arlt and Alloio, 2003b).

Johammson et al. (2002) studied women who were androgen-deficient from hypopituitarism in a double-blind placebo-controlled trial for 6 months followed by 6-month open-label phase. Increased sexual interest and activity were only reported during the open-label phase and there was no significant change in quality of life in either phase of the trial. Their partners also assessed the effect of DHEA on the quality of life of the women after the 6-month blinded treatment and they reported an overall improvement.

In a double-blind crossover study, patients with secondary adrenal insufficiency were given 50 mg DHEA for 16 weeks in addition to substitution with recombinant human GH (van Thiel et al., 2005). The 15 women in the trial were all post-menopausal and not on estrogen replacement therapy. Five validated questionnaires were used to assess improvements in sexual function and quality of life. There was no substantial improvement associated with DHEA therapy on either parameter.

Taken together, the studies of DHEA therapy in women with adrenal insufficiency would suggest that this group may derive health benefits from DHEA supplementation. In particular, impaired mood and reduced libido may respond to DHEA replacement.

Discussion

The idea of compensating for the ravages of ageing with oral DHEA therapy has been percolating for some time. In 1985, the US Food and Drug Administration (FDA) removed DHEA from the over-the-counter market, as there was no support for the health claims that were made for this product. However, because of the US Dietary Supplement Health and Education Act of 1994, DHEA once more became readily available over-the-counter. This act allows certain substances to be sold without FDA approval as long as they are sold as dietary supplements and the product labelling includes no drug intent. DHEA is considered by the FDA as a nutritional supplement and is now available as such in the USA, despite not being a component of any food. This also that suggests that there is little control over the contents of DHEA supplements or of the manufacturing procedures of the companies that make the supplements. In the past, discrepancies between label claims and actual DHEA
Table III. DHEA therapy in women with adrenal insufficiency

<table>
<thead>
<tr>
<th>Author</th>
<th>Study</th>
<th>Time</th>
<th>n</th>
<th>Dose/day (mg)</th>
<th>Age</th>
<th>Changes in hormones reported</th>
<th>Sexual thoughts and behaviour</th>
<th>Mood/wellbeing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arlt et al.</td>
<td>RCT double blind placebo</td>
<td>4 months</td>
<td>24 F</td>
<td>50</td>
<td>23–59 years with adrenal</td>
<td>↑ DHEA, DHEAS, A, testosterone, DHT no change E2, E1 ↓ SHGB</td>
<td>4 VAS</td>
<td>90-ISC, MMQ, VZL, HADS ↑ Wellbeing</td>
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<tr>
<td>et al. (1999)</td>
<td>crossover 1 month washout</td>
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<td>insufficiency (14 primary</td>
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<td>and 10 secondary)</td>
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<td>25–69 years with Addison’s</td>
<td>↑ DHEAS, A, testosterone</td>
<td>GRISS (interest, arousal, frequency of intercourse, lubrication): no</td>
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<td></td>
<td></td>
<td>disease</td>
<td></td>
<td>change</td>
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<tr>
<td>Hunt et al.</td>
<td>RCT double blind placebo</td>
<td>3 months</td>
<td>24 F</td>
<td>50</td>
<td>25–69 years with Addison’s</td>
<td>↑ DHEAS, A, testosterone</td>
<td>GRISS (interest, arousal, frequency of intercourse, lubrication): no</td>
<td>GHQ-30 Profile of mood Questionnaire Cognitive tests ↑ Wellbeing</td>
</tr>
<tr>
<td>(2000)</td>
<td>crossover 1 month washout</td>
<td></td>
<td>15 M</td>
<td></td>
<td>disease</td>
<td></td>
<td>change</td>
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<tr>
<td>Johannsson et</td>
<td>RCT double blind placebo</td>
<td>12 months</td>
<td>38 F</td>
<td>10 or 15 mg twice daily</td>
<td>25-60 with hypopituitarism, severe androgen deficiency</td>
<td>↑ DHEAS, A, testosterone, no change SHGB</td>
<td>Self report changes in interest and activity ↑ Sexual interest/ activity during open phase only</td>
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<tr>
<td>et al. (2002)</td>
<td>parallel group then 6 months</td>
<td></td>
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<tr>
<td>Lovas et al.</td>
<td>RCT double blind parallel</td>
<td>9 months</td>
<td>39 F</td>
<td>25</td>
<td>18–70 y with adrenal failure</td>
<td>↑ DHEAS, A, testosterone</td>
<td>McCoy sex Scale Q</td>
<td>SF-36, Fatigue Q No effect general health or vitality</td>
</tr>
<tr>
<td>(2003)</td>
<td>group</td>
<td></td>
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<tr>
<td>van Thiel et al.</td>
<td>RCT double-blind placebo</td>
<td>16 weeks</td>
<td>15 F</td>
<td>50</td>
<td>61.5 ± 1.7 years Post-Menopausal with secondary adrenal insufficiency on rhGH</td>
<td>↑ DHEA, DHEAS A, E1, E2</td>
<td>SFQ: no change</td>
<td>HADS SF-36, MFI-20 QOL-GHD No change</td>
</tr>
<tr>
<td>(2005)</td>
<td>crossover 8 weeks washout</td>
<td></td>
<td>16 M</td>
<td></td>
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DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; A, Androstenedione; DHT, dihydrotestosterone; E1, estrone; E2, estradiol; SHBG, sex hormone binding globulin; VAS, visual analogue scale; HADS, hospital anxiety and depression scale; PGWB, psychological general wellbeing index; GHQ-30, 30-item General Health Questionnaire; 90-ISC, 90-item symptom checklist VSL, von Zerssen Symptom List; MMQ, Multidimensional Mood Questionnaire; SF-36, Short form-36; MFI-20, Multidimensional Fatigue Inventory-20; QOL-GHD, Quality of Life assessment of GHD in adults; GHQ, general Health Questionnaire; HSCL, Hopkins Symptoms Checklist; PGWB, Psychological General Wellbeing Index; GRISS, Golombok Rust Inventory of Sexual Satisfaction; SFQ, The Eleven Questions on Sexual Function Questionnaire; rhGH, recombinant human GH.
content of supplements have been reported (Parasrampuria et al., 1998); however, this may not be the case now.

To articulate the role of DHEA therapy, to whom and why it should be given requires data from quality clinical trials. The relationship between the decline in circulating DHEA and ageing is clear. If the physiological decrease in circulating DHEA is responsible for some age-associated difficulties, such as lack of libido, then restoring levels may circumvent this. Findings regarding improvements in sexuality and wellbeing in otherwise healthy women, from this review of the literature, are inconsistent. Factors contributing to the inconsistent findings include low study power, short treatment duration, differing doses of DHEA administered, variations in the instruments used to measure sexual function and wellbeing and use of non-validated instruments. Women with adrenal insufficiency are a special case and some of the trials indeed report a positive result in this group.

Although not the primary subject of this review, there is a striking paucity of formal documentation of the safety of DHEA therapy, with the little data available resulting from extremely small patient numbers. Potential risks of DHEA therapy include direct adverse metabolic effects and effects of the estrogenic and androgenic actions of DHEA metabolites. The side effects acne and hirsutism have been described as being seen relatively frequently in studies employing high-dose DHEA (van Vollenhoven, 2002). Few studies have used objective measures of acne and hirsutism. Oral DHEA treatment may result in changes in lipid profile with small reductions in HDL cholesterol and apolipoprotein A1 versus placebo at low doses (25 mg/day) (Casson et al., 1998; Dean, 2000). Again, there is a lack of data for higher doses and longer durations of therapy. There is insufficient documentation of the use of DHEA regarding effects on the breast and uterus. Labrie et al. (2003) have investigated the effects of DHEA on mammary tissue extensively in vitro and rodent models. They have consistently reported an inhibitory effect of DHEA on mammary carcinoma development. However, this warrants further investigation in women. Concerns pertaining to the psychiatric effects of DHEA therapy have been raised and severe psychiatric symptoms have been reported in a subset of users in the community (Dean, 2000).

The widely held belief that female androgen insufficiency, which may explain the so-called disorders, such as female sexual dysfunction, is defined by low serum androgen levels is unsubstantiated. Our recent study identified self-reported low sexual function as being associated with a greater probability of having low DHEAS (Davis et al., 2005). However, it did not follow that women with low serum DHEAS all reported low libido. The results failed to demonstrate that serum levels of testosterone or DHEAS were predictive of low sexual function. Our data taken in conjunction with known intracrine physiology show that sex steroids do play a part in female sexuality but no serum androgen level defines female androgen insufficiency. Although these data do not provide absolute support for the use of DHEA therapy to improve sexual function for post-menopausal women, only a large well-designed prospective clinical trial may substantiate its utility.

In summary, it may be expedient to conclude that there is limited value in giving DHEA to healthy women. However, the potential of DHEA therapy given at a dose, which re-establishes levels found in the serum of normal young women to improve aspects of quality of life in premenopausal or post-menopausal women, needs further exploration. This is particularly significant in light of the commercial availability of DHEA over-the-counter.

Acknowledgement

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Zumboff B, Rosenfeld RS and Strain GW (1980) Sex differences in the 24 hour mean plasma concentrations of dehydroisoandrosterone (DHA) and dehydroisoandrosterone sulfate (DHAS) and the DHA to DHAS ratio in normal adults. J Clin Endocrinol Metab 51,330–334.

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