Assessing the Effects of Dehydroepiandrosterone (DHEA) Replacement on the Mood and Well-Being of Hypoadrenal Women

A Thesis Submitted to Mayo Graduate School

By

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Abbreviations Used in This Dissertation

ACTH – Adrenocorticotrophic Hormone

AD – Alzheimer's disease

ApoE4 – Apolipoprotein E epsilon 4

AVLT – Auditory Visual Learning Test

BA – Bilateral Adrenalectomy

BDI – Beck Depression Inventory

BMI – Body Mass Index

C – Cross-over design

CBC – Complete Blood Count

CD – Cushing's Disease

COWAT – Controlled Word Association Test

CS – Cushing's Syndrome

CSF – Cerebro-Spinal Fluid

CSFQ – Changes in Sexual Functioning Questionnaire

DEXA – Dual Energy X-Ray Absorptiometry

DHEA – Dehydroepiandrosterone

DHEAS – Dehydroepiandrosterone Sulfate

DHEA(S) – Both Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate

ECG – Electrocardiogram

GABA – Gamma Amino Butyric Acid

GCRC – General Clinical Research Center

GH – Growth Hormone

HPA – Hypothalamic – Pituitary – Adrenal

HSQ – Health Status Questionnaire

IGF – Insulin Like Growth Factor

IGF BP – Insulin Like Growth Factor Bonding Protein

Kg – Kilogram

MID – Multi Infarct Dementia

MFQ – Memory Functioning Questionnaire

N/A – Not applicable

NMDA – *N*-Methyl-d-Aspartate

O – Observational

OL – Open label

P – Placebo controlled

QOL – Quality Of Life

R – Randomized trial

REM – Rapid Eye Movement

T_3 – Triiodothyronine

T_4 – Thyroxine

TMT – Trail Making Test

TSH – Thyroid Stimulating Hormone

Abstract

Background:

Dehydroepiandrosterone (DHEA) and its sulfated ester (DHEAS) are produced in abundance by healthy adrenal glands. Their physiological significance other than as sex hormone precursors has yet to be determined. In hypoadrenal subjects little or no DHEA is produced. Several studies have previously been done assessing the effects of DHEA on mood and well-being. These have had conflicting results.

Methods:

We conducted a single centre randomized double blind, cross over study of 33 hypoadrenal women aged between 20 and 80 years. These subjects were given a single 50 mg dose of DHEA per day for 3 months or identically encapsulated placebo. They underwent a series of well-validated psychological assessments to determine any changes in several parameters of psychological well-being. These were the Auditory Verbal Learning Test (AVLT), Controlled Word Association Test (COWAT), Trail Making Test (TMT), Memory Functioning Questionnaire (MFQ), Changes in Sexual Functioning Questionnaire (CSFQ), Health Status Questionnaire (HSQ), and the Beck Depression Inventory (BDI).

Results:

Complete data was available for 26 subjects. General health perception improved in the 14 women given DHEA in the second phase of the study (median

with interquartile range) (-0.506, (-1.42, 0.11) vs –0.135, (-0.82, 0.3), baseline score vs DHEA score, p = 0.002). There was a significant decline in arousal scores in the second phase of treatment in the 12 women given DHEA during the first phase (9.00, (7.3, 10.0) vs 8.00, (6.3, 9.8), p = 0.016). There was also a significant improvement in total AVLT score after the DHEA phase (52.00, (45.3, 59.3) vs 57.00, (50.8, 62.0), p = 0.03). There were no significant differences between the DHEA and placebo in any of the other measured psychological parameters.

Discussion:

This study shows that 50 mg of DHEA given for 3 months results in improvements in general health perception and learning efficiency. There was a decline in arousal scores during the second phase of the study when DHEA was given during the first phase. DHEA does not affect memory retrieval or any other aspects of psychological well being in Caucasian hypoadrenal women. Thus DHEA replacement may need to be considered for this patient population. Our study is in agreement with other work that showed some effect on general well being, sexual function and memory. The results from this study suggest there may be a role for DHEA replacement in hypoadrenal women.

Background and Introduction

Dehydroepiandrosterone (DHEA) and its sulfated ester (DHEAS) [together known as DHEA(S)] have become increasingly fashionable over the past few years with more and more evidence emerging as to their possible roles in normal human physiology. Recent data has shown DHEA(S) levels to be highly correlated to longevity in non-human primates [1], and headline phrases such as 'mother of all hormones', 'superhormone', 'fountain of youth' and 'a therapy to restore body, pep of youth' [2] have brought these hormones to the attention of the lay public. A search on the internet search engine Google (www.google.com) in the last week of August 2003, revealed over 400,000 websites mentioning DHEA.

Low or absent levels of DHEA(S) are found in healthy elderly individuals and hypoadrenal subjects. Long-term trials of DHEA replacement in these groups of people are currently in progress in the UK and in the USA, however these studies are not due to report for some time. With the availability of DHEA over the counter in the USA and on the internet worldwide, we perceived a need for a properly conducted study to help clarify of some of the claims made about this hormone on muscle function in those people in whom DHEA levels are low.

The Early Anatomical History of the Adrenal Gland

The adrenal glands were initially unrecognized by early anatomists. A portion of Vesalius' (1514 - 1564) Book Five of De Corporis Humani Fabrica, published in 1543 concerns the urogenital system [3]. Within it there are four excellent illustrations of the kidney however, none shows another structure at the upper pole of either organ (Figure 1). Thus Vesalius, who became the father of human anatomy by demonstrating that the anatomic concepts of Galen (129 - 199) were derived from the dissection of animals, also seems to have overlooked the adrenal glands. So did the numerous anatomists who sought to confirm Vesalius' findings or to deny them, insisting that Galen was infallible.

It was not until 1564, over 20 years after publication of the Fabrica, that Bartolomeo Eustachius (1520 - 1574) first described the 'glandulae quae renibus incumbentes' [4]. The importance of the adrenal gland was then once again neglected until the father and son anatomists Caspar Bartholin (1585 - 1629) and Thomas Bartholin (1616 - 1680) turned their attention to the gland. Bartholin the younger described the gland as having no duct but containing a large cavity filled with a dark fluid. Although he confessed ignorance of the gland's true function, he speculated that the dark fluid in the cavity was bile - like liquid excrement derived mainly from blood that had passed through the spleen. The fluid accumulated until pressure forced it through the kidney producing the dark urine that often heralds the onset of disease. He named the glands 'capsulae atrabiliaria', a name that, among others, was in use until well into the 19th century. The modern name, the 'suprarenal gland,' is attributed to Riolan the Younger (1580 - 1657).

Q,Q *His characteribus ſiniſtræ lateris membrana notatur, quæ illi correſpondet, quam nuper* O, O *indicarunt.*

R,S *Vteri ceruicis anterior pars, inter* R *&* S *ea adhuc obducta tunica, quam peritonæi partes illi offerũt, quæ ipſi uaſa exporrigunt, deducuntq́, ac illum peritonæo adnectunt. Cæterùm inter uallum inter* R *&* S *conſiſtens, uteri ceruicis amplitudinem quodammodo ſignificat. Rugæ uerò hic conſpicuæ, illæ ſunt quas uteri ceruix in ſe collapſa, neq; aliàs diſtenta, inter ſecandum commonſtrat.*

T *Veſica, cuius poſterior facies hic potiſsimum ſpectatur. ita enim in figuræ huius delineatione oculum direximus, ac ſi in corpore proſtrato, poſteriorem ueſicæ ſedem quæ uterum ſpectat, potiſsimum cernere uoluiſſemus. Si enim præſens muliebre corpus ita uti id quod modò ſubſequetur, erectum arbitrareris, etiam ſecus atq; res ſe habet, uteri fundum multo elatius ipſa ueſica delineatum eſſe tibi perſuaderes.*

V *Vmbilici eſt portio, à peritonæo inter ſecãdum liberata, & unà cum uaſis fœtui peculiaribus hic deorſum reflexa.*

X *Portio uenæ ab umbilico iecur petentis.*

Y *Meatus à ueſicæ fundi elatiſsima ſede ad umbilicum pertinens, ac fœtus urinam inter ſecundum & intimum ipſius inuolucrum deducens.*

Z, et & *Duæ arteriæ ab umbilico huc ſecundùm ueſicæ latera prorepentes, atq; hac ſede magnæ arteriæ ramis pubis oſſium foramina potiſsimum adeuntibus inſertæ, ſeu continuæ.*

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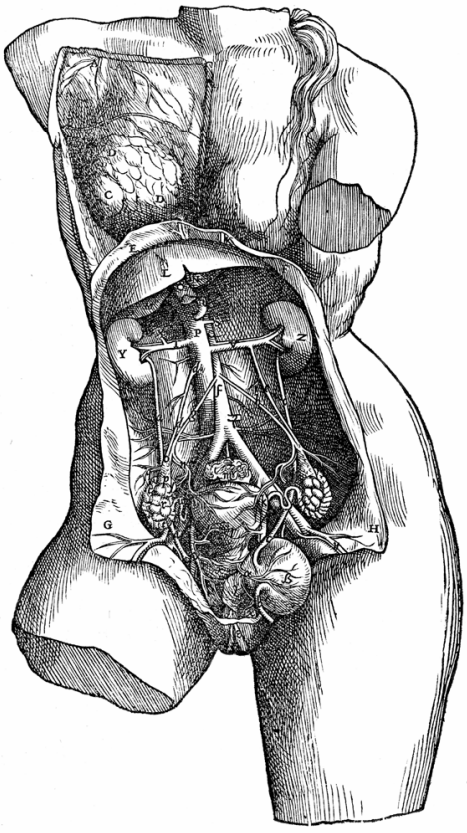


VIGE.

Figure 1 Illustration of the Female Abdomen

From reference 3 – note the absence of identifiable adrenal glands.

It was in 1855 that Thomas Addison (1795 - 1860) first made the connection between the clinical syndrome that consisted of hyperpigmentation and wasting with insufficiency of the adrenal gland. In 1855 Addison wrote a paper entitled 'On the Constitutional and Local Effects of Disease of the Suprarenal Capsules'. In his classic description, Addison described 10 cases characterized by "anaemia . . . feebleness of the heart action . . . a peculiar change of colour in the skin occurring in connection with a diseased condition of the 'suprarenal capsules'" [5]. The same paper also described pernicious anemia, and it has been recognized as perhaps the only paper that describes two diseases, both named for the author [6].

The importance of the glands for normal physiological functioning was established unequivocally by Brown-Sequard (1817 - 1894), who proved that the glands were essential for life and that bilateral adrenalectomy was invariably quickly fatal [7].

It was in 1901 that Takamini first isolated adrenaline [8]. By 1929 investigators had discovered the gland was divided into two parts – the medulla that produced the vasoactive catacholamines, and the cortex that was responsible for the production of hormones that regulated sugar, salt and water balance [9].

It was not until the middle of the 20th Century and the Nobel Prize winning work of Kendall, Sarett and Reichstein that led to the discovery and synthesis of cortisone which provided the life saving glucocorticoid replacement therapy for hypoadrenal individuals [10].

Addison's Disease

Addison's disease, or chronic primary adrenal insufficiency is a relatively rare condition with a prevalence of 93 to 140 per million and an incidence of 4.7 to 6.2 per million in white populations [11]. Women are more commonly affected than men with a ratio of 1:1.5 - 3.5. The peak age of onset is in the 4th decade of life. Addison's disease results from progressive destruction of the adrenals, and must involve more than 90% of the glands before adrenal insufficiency appears. There are three broad categories of causes for non - iatrogenic hypoadrenalism. These are a) adrenal dysgenesis, b) adrenal destruction, and c) impaired steroidogenesis. These are more fully discussed elsewhere [11,12]. The most common cause is probably idiopathic autoimmune destruction, with TB being possibly the most common worldwide cause of primary adrenal insufficiency. Other causes include adrenoleukodystrophy [13], bilateral hemorrhage [14], tumor metastases [15], HIV [16], cytomegalovirus (usually with HIV infection in the form of CMV necrotizing adrenalitis) [17], other infections due to the presence of HIV include *Cryptococcus neoformans, Toxoplasma gondii*, or Kaposi sarcoma [18], adrenomyeloneuropathy [13] or, very rarely, sarcoidosis [19]. Addison's disease is characterized by both glucocorticoid and mineralocorticoid deficiency, which require lifelong oral replacement therapy. Secondary adrenal insufficiency is most often caused by withdrawal of iatrogenic long-term glucocorticoid replacement, or by lesions within the hypothalamus or pituitary gland. In these conditions, while glucocorticoid function may be lost, mineralocorticoid function is preserved. This is because the trophic effects of ACTH are important in the maintenance of zona reticularis and zona fasciculata. Once ACTH drive is lost,

either by pituitary suppression by administration of exogenous steroids, or by primary or secondary hypopituitarism, the zona reticularis and zona fasciculata involute, leading to secondary adrenal insufficiency with preservation of mineralocorticoid function.

There are very few current estimates for the rate of death due to undiagnosed hypoadrenalism or for mortality rates in subjects with confirmed Addison's disease. When TB was more prevalent, the death rate was approximately 1.4 deaths per 1,000,000 cases per year.

At present the current replacement regime for people who are hypoadrenal consists of glucocorticoid and mineralocorticoid replacement. Hydrocortisone is the mainstay of glucocorticoid replacement therapy with alternative drugs being prednisolone, prednisone or, less commonly, dexamethasone. The dose of hydrocortisone for most adults depending on their size is a total of 20 mg to 30 mg per day. To simulate the normal diurnal adrenal rhythm the dose is divided throughout the day with most being given in the morning. Since this replacement dosage of hydrocortisone does not replace the mineralocorticoid component of the adrenal hormones, mineralocorticoid supplementation is usually needed. This is usually by oral administration of 0.05 mg to 0.1 mg of fludrocortisone per day. These replacement regimes restore life expectancy to that seen in subjects with normal adrenal function. However, despite normal biochemical values, overall quality of life in subjects with Addison's disease has been shown to be reduced [20-22].

Dehydroepiandrosterone and Dehydroepiandrosterone Sulfate

Biochemistry and Physiology of DHEA

Dehydroepiandrosterone (DHEA) [3β-hydroxy-5-androsten-17-one] and its sulfated ester (DHEAS) are two of the major C_{19} steroids secreted by the (innermost) zona reticularis region of the adrenals. Secretion is partly under the influence of adrenocorticotrophic hormone (ACTH) [23,24], but because levels change during different phases of life without corresponding changes in circulating ACTH levels, this suggests that other factors determine DHEA release [25].

DHEA was first described in 1934 [26] and isolated 20 years later [27]. It was in 1960 that Baulieu showed that DHEAS was the most common form of the hormone found in the circulation [28].

As with all C_{19} steroids, these hormones are products of cholesterol metabolism and are derived from the action of the side chain cleavage enzyme product of the CYP11A1 gene (cytochrome P450scc) on the inner membrane of the highly active mitochondria found in the adrenal cortex [29]. DHEA and DHEAS are the most abundant circulating steroid hormones in humans. Their role remains to be fully elucidated. DHEAS can be readily converted to unconjugated DHEA by ubiquitous tissue steroid sulfatases, and thus probably serves as a reservoir for DHEA. DHEA is a weak, 17-ketosteroid group androgen precursor. Figure 2 shows a simplified illustration of the steroid synthesis pathway.

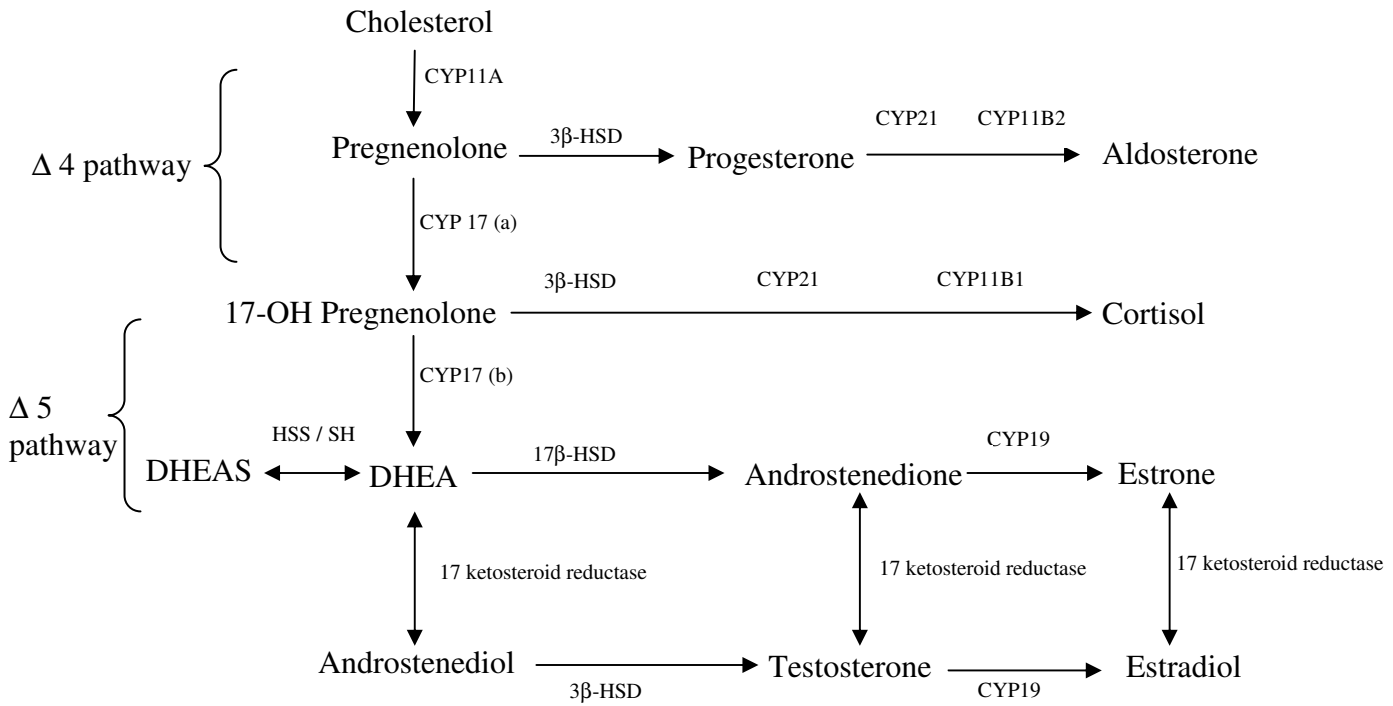


Figure 2 Simplified Steroid Synthesis Pathway

CYP 11A: 20, 22 Hydroxylase, 20, 22- desmolase; CYP11B1: 11β hydroxylase; CYP11B2: 11β hydroxylase, 18 – hydroxylase and 18 – oxidase; CYP17 (a): 17α Hydroxylase (catalyzed by $P450_{c17}$); CYP17 (b): 17, 20 Lyase (catalyzed by $P450_{c17}$); CYP19: Aromatase; CYP21: 21 Hydroxylase; 3β-HSD: 3β-Hydroxysteroid dehydrogenase; 17β-HSD: 17β-Hydroxysteroid dehydrogenase; HSS: 3β Hydroxysteroid sulfotransferase, SH: sulfohydrolayse.

It can be seen that DHEA, testosterone and estrogens are derived from the precursor 17-hydroxypregnenolone by the action of 17, 20 lyase, a reaction that is catalysed by cytochrome $P450_{c17}$. Thus, DHEA and DHEAS are adrenal precursor sex steroids. DHEA is the active form and DHEAS is enzymatically converted to DHEA in peripheral tissues in an intracrine fashion [30]. While both DHEA and DHEAS are bound to albumin in the plasma, DHEAS is bound more firmly, and unlike DHEA, DHEAS is not bound to sex hormone binding globulin, but is free in the circulation. In addition, because of the relative lack of protein binding, DHEA is rapidly cleared from the circulation - at approximately 2 litres per day - and has a half-life of 1 to 3 hours. For certain periods during life, due to it's short circulating half life, DHEA also has a circadian rhythm more closely related to that of the secretion of adrenocorticotrophic hormone than DHEAS [24,31]. DHEAS is cleared at only 13 ml/day and subsequently has a half-life of 10 to 20 hours, thus levels do not vary greatly in the plasma [32]. These differences in clearance rates result in plasma DHEAS concentrations 250 to 500 times greater than DHEA [33].

DHEA is handled differently in men and women, such that the half-life in women is 11.7 hours, and in men 7.2 hours after the first dose, and then after 2 weeks of oral administration, this changes to 8.6 and 6.0 respectively. The numbers for DHEAS are 27.1 and 25 hours for day 1 in men and women, and 23.8 and 20.8 respectively by day 15 [34].

The effects of DHEA(S) are thought to be mediated through a specific G protein coupled plasma membrane receptor [35], and through a nuclear DHEA specific receptor binding complex [36]. In much of the published literature DHEA and DHEAS

are referred to as 'weak androgens', however there is no evidence that they bind to the androgen receptor. Thus, DHEA and DHEAS have little or no intrinsic androgenic activity. However, they are converted into androstenedione and then further into potent androgens and estrogens in the liver and other target organs [37]. These transformations are dependant on the tissue activity of steroidogenic and metabolising enzymes such as 3β-hydroxysteroid dehydrogenase/Δ^5-Δ^4-isomerase, 17β-hydroxysteroid dehydrogenase, 5α-reductase, and aromatase [38].

As can be seen from Figure 3, DHEAS levels vary profoundly throughout life in both sexes. Due to the immaturity of the 11β hydroxylase enzyme in utero, the Δ 4 pathway within the adrenal gland remains inactive, thus driving the cholesterol metabolites towards the Δ 5 pathway, resulting in high DHEA levels. As the 11β hydroxylase enzyme matures after birth, the zona glomerulosa become more active, reducing the activity of the Δ 5 pathway, thus lowering DHEA levels. Levels of DHEA then start to rise at 'adrenarche', i.e. between 8 to 10 years of age, reaching a peak by the middle or end of the second decade of life. Levels then decline by 10% per decade plateauing after the age of 80 [39,40]. Although there are a number of theories why this decline occurs, the reason currently remains unknown [41]. It has been proposed that one of the potential causes of this reduction of DHEA(S) levels is due to the reduction in enzyme activity of 17, 20 lyase that converts 17-hydroxypregnenolone to DHEA resulting in low levels of DHEA and testosterone [41-43]. This is manifested in the elderly by a reduced level in circulating DHEA(S) levels and by a blunted response to ACTH stimulation, with a normal cortisol response [44].

However, the picture becomes more unclear because in conditions where there is chronic ACTH stimulation, DHEA(S) levels may remain normal or decrease [45].

It has been suggested that circulating plasma DHEA(S) levels are a marker for longevity [1]. Further evidence for this comes from looking at ethnic differences in DHEA(S) levels which suggests that life expectancy may be higher in those populations in whom DHEA(S) levels are highest [46].

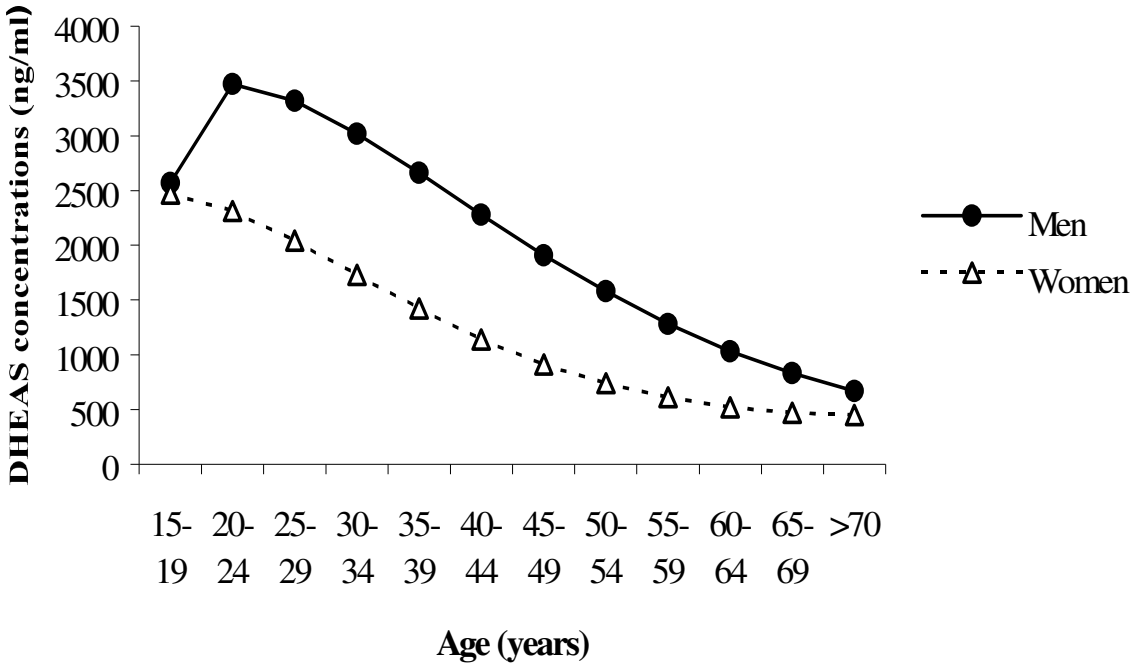


Figure 3 Changes in Levels of Circulating DHEAS With Aging.

From reference 39

The direct mechanism of action of DHEA, if any, remains unknown. The effects of DHEA are due to the actions of the sex hormones into which it is converted. While recent studies have found specific receptors to help explain some of the actions of DHEA, the mechanisms of other actions of this hormone remain

elusive. Examples of these receptors include skeletal muscle binding sites [47]. These receptors may be of therapeutic value in the treatment of disorders associated with low DHEA levels, such as myotonic dystrophy [47]. Other receptors include those thought to be responsible for some of the protective cardiovascular effects of DHEA.

The potentially beneficial cardiovascular effects are mediated through a variety of possible mechanisms. One is thought to be a specific G protein coupled plasma membrane receptor leading to an increase in endothelial nitric oxide synthase [35]. Other recent animal work has suggested that there are unique mechanisms within vascular epithelial cells that account for the DHEA induced restoration of nitric oxide levels by enhancing and stabilizing endothelial nitric oxide synthase expression. This appears to be by direct effects on the genome, but also by non-transcriptional mechanisms [48]. Another DHEA specific receptor-binding complex has also been found in murine and human T cells. In this model, DHEA binding to this receptor complex led to an increase in interleukin 2 production leading to the claim that DHEA 'improves immune function' [36,49]. However, the mechanism of action of DHEA on this receptor has yet to be described.

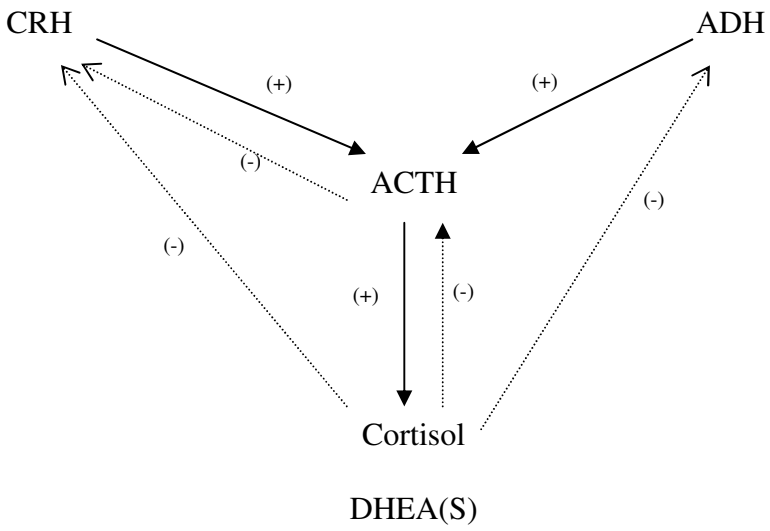


Figure 4 The Hypothalamic – Pituitary – Adrenal (HPA) Axis.

The solid arrows with black arrowheads represent stimulation (+), the dotted arrows with open arrowheads represent inhibition (-). Corticotrophin releasing hormone (CRH) from the hypothalamus, and antidiuretic hormone (ADH) from the posterior pituitary stimulate adrenocorticotrophic hormone (ACTH) release from the anterior pituitary, which in turn stimulated the adrenals to produce both cortisol and DHEA(S). However, only cortisol feeds back to inhibit ACTH, CRH and ADH. Adapted from reference 45.

The decline in circulating DHEA levels parallel many age-related changes such as sarcopenia and osteopenia. In men, studies with castrated subjects show that approximately 30% to 50% of circulating androgens are derived from DHEA. The remaining androgens come from the testes as testosterone. Both DHEA and

testosterone are then converted to the active androgen dihydrotestosterone, in the peripheral tissues [50]. In postmenopausal women however, there is conflict over the origin of most circulating androgens. Some authors state that these androgens are derived from DHEA, with less than 50% coming from the ovaries [51,52], while others state that the ovaries remain an important source of testosterone [53,54].

Whatever the origin of these androgens, women with adrenal insufficiency suffer from chronic DHEA(S) deficiency, because routine replacement therapy with glucocorticoids and mineralocorticoids fails to restore the androgens derived from the adrenal precursors. Replacement of adrenal precursor derived androgens in subjects with adrenal insufficiency should ideally restore DHEA(S) concentrations to levels equivalent to those before the onset of the condition. There has been a great deal of previous work to determine the optimal replacement dose in both elderly [55] and hypoadrenal [56] subjects to restore DHEA(S) levels to that seen in young adults. This has been shown to be 50 mg per day, which is sufficient to increase DHEA(S) levels into the normal range of age matched young adults [57,58].

Most previous studies have been carried out looking at changes in physiological parameters in DHEA(S) deficient individuals, both normal elderly and adrenalectomized / hypoadrenal subjects. Many of these authors have also looked at different measures of general well being, libido and mood [20,21,57,59]. This study provided an opportunity to confirm these findings with the use of validated standardized instruments [60-62].

Clearly there are differences to be expected between the normal physiological process of aging, and the pathological state of adrenal insufficiency. In hypoadrenal

individuals there is little or no circulating DHEA, the elderly however, while having substantially lower levels than healthy individuals in their second or third decade, have levels that may be several fold greater than the hypoadrenal individual. These differences mean that relating and inferring results from one group to another is more difficult, however, the premise of much of the current clinical research in both aging and hypoadrenal subjects is that the two are interchangeable. This link between the elderly and hypoadrenal subjects is compounded by the findings of studies such as those looking at different measures of general well being, libido and mood that have found similar results in both groups of subjects [20,21,57,59]. Despite this, there are clearly differences in the between the way a hypoadrenal subject may present clinically.

Many of the disorders of aging such as reduced immunocompetence, obesity, diabetes and cancers have been attributed to changes in DHEA(S) levels on the basis of animal studies [30,63] and epidemiological data [64-67]. Further animal studies have shown potential cardiovascular benefits including a reduction in cholesterol accumulation within the large vessels [68,69] and inhibition of platelet aggregation [70]. There is conflicting evidence from human studies to show whether circulating androgen levels are associated with changes in cardiovascular mortality [65,71]. Some work has been done looking at the effect of DHEA supplementation in autoimmune conditions with some success [72]. In addition to these findings, a relative or absolute lack of DHEA(S) has been associated with effects on muscle tissue that include a decrease in muscle fiber size and number. However, data showing that these changes can be reversed in either hypoadrenal subjects or normal elderly subjects by restoring DHEA(S) levels has been conflicting to date [20,21,73,74]. Whilst one of the aims of a

study currently in progress at Mayo Clinic, Rochester is looking at the effects of DHEA(S) replacement in the well, elderly population, the trial is not due to report it's findings until the middle of 2004. In our study we aimed to study replacement in this, other group – i.e. those with adrenal insufficiency.

DHEA(S) replacement therapy may be of special importance for patients with adrenal insufficiency, because adrenal androgen precursor deficiency in these patients is frequently neglected [75]. Accordingly, it has been shown that despite an otherwise adequate glucocorticoid and mineralocorticoid replacement regime in Addison's disease or hypoadrenalism, quality of life may be inferior to that of subjects with functioning adrenal glands [22,76]. Thus, DHEA replacement in subjects with adrenal insufficiency may hold the potential to improve both their well being and their functional status [77]. Moreover, DHEA administration to these patients is well suited to gain further insight into the psychological and physiological role of DHEA, because a true deficiency is replaced.

Relatively few studies have looked specifically at the use of DHEA(S) replacement in hypoadrenal and adrenalectomized subjects. Those studies available, have shown conflicting results [20,21,59,74]. Few studies have looked at the range of parameters that we originally proposed. The innovative aspects of this study were the methods that we proposed to use. In addition to using the previously calibrated best dose of DHEA(S) – 50 mg per day, we standardized the glucocorticoid replacement regime to try and decrease any confounding effects due to the multitude of replacement regimes available [78]. This had not been done in previous studies. Riedel et al evaluated the effects of three different cortisol replacement modes on subjective

health status. These authors found that twice daily dosing was better than once daily, but that no regime normalized the health status to that seen in subjects with normal adrenal function [76]. The study involved a double blind cross over design involving 14 subjects and assessed wellbeing by the use of questionnaires. Another study, using a similar cross over design, evaluated three different glucocorticoid replacement regimes and found that none was superior to any other in terms of subjective health status [79].

The mineralocorticoid replacement regime remained unchanged unless the screening urinary or serum electrolytes or blood pressure suggest that the regime that the subject was on at the start of the study was inappropriate. There is evidence that mineralocorticoid antagonist therapy (i.e. spironolactone - there is currently no data for eplereonone) decreases DHEAS levels in both sexes [80,81]. Spironolactone therapy also increases serum cortisol, so raising the cortisol/DHEA(S) ratio [82]. However, there is no evidence that adequate mineralocorticoid replacement therapy (i.e. fludrocortisone) has a detrimental effect on memory, mood, wellbeing, and sexual function.

The dose of 50 mg of DHEA has been shown to be the appropriate dose by assessing the 24 hour urinary excretion of androstenedione glucuronide, an androgen metabolite regarded as a reliable marker of the pool of testosterone [33]. This increased to levels seen in normal young women in accordance with the report from Arlt et al [20], who noted serum levels of this metabolite in the upper normal range 24 hours after the intake of 50 mg of DHEA.

Hypothesis

Global Hypothesis

That 50 mg of once daily administered DHEA replacement for 12 weeks in hypoadrenal women is associated with beneficial changes in several parameters of cognitive function, well being and sexual health when compared to placebo.

Primary Aim

To confirm, with the use of well-validated instruments, that DHEA replacement in hypoadrenal subjects leads to an improvement in psychological and sexual function.

Primary Hypothesis

That DHEA deficiency is associated with a lower than normal psychological quality of life and that replacement of this hormone in hypoadrenal women will improve memory, mood, quality of life, sexual wellbeing and cognitive function

Methods

Subjects

The protocol was approved by the Institutional Review Board at Mayo Clinic, Rochester. The nature, purpose and possible risks involved in the study were carefully explained to each subject before their verbal and written informed consent was obtained.

The target population was hypoadrenal women. The accessible population was women recruited from the Mayo surgical and medical indices, internet support groups for people with Addison's disease (http://groups.yahoo.com/group/Addisons_Disease/, www.healinglight.com), the National Adrenal Diseases Foundation website and newsletter (www.medhelp.org/nadf), the Cushing's Disease Support and Research Foundation (http://world.std.com/~csrf) and others. The intended sample and actual sample came from these sources (23 from Mayo held records and 10 from internet sources). A summary of the recruitment process is illustrated in Figure 5.

An initial search was made of the Mayo Clinic medical and surgical indices of hypoadrenal subjects seen at Mayo Clinic, Rochester, Minnesota in the 5 years prior to the start of enrolment into the study (i.e. May 1997 to May 2002). 1175 records were evaluated. Of these, 716 (60.9%) were women. 37 (3.1%) were women who had undergone total adrenalectomies with bilateral oopherectomies. Of the 716 women evaluated, 46 (6.4%) had died, 195 (27%) had either been seen only once, had no documentation available or lived greater than 500 miles from Mayo Clinic, Rochester

(an initial recruitment consideration). A further 342 (47.7%) had exclusion criteria documented in the clinical notes.

A three-phase recruitment approach was used for the remaining 133 women. These women were initially invited by letter to take part in the study. There were 86 replies (64.7%). The non-responders were contacted again by letter 6 weeks after the first invitation. 3 replies (3.4%) were received in response to this second invitation. Of the 89 respondents, 52 expressed an interest in taking part in the study. The second phase of recruitment was that those subjects who expressed an interest in participating were contacted by telephone to have an initial exclusion criteria questionnaire. 23 of these 52 subjects (44%) had a previously undocumented exclusion criterion and were subsequently excluded from further participation. The final phase of recruitment was that the remaining 29 subjects were screened in the General Clinical Research Center at St Marys Hospital, Rochester. Of these 29 subjects, 2 subjects withdrew prior to the screening visit. 3 subjects failed the screen, 2 due to abnormal renal or liver function and one due to a positive exercise stress test. One person passed the screen, but declined to take part in the study and was not randomized.

From the initial list of 1175, 23 (1.96%) subjects were randomized into the study. Of these, 1 person withdrew after 10 weeks in the first arm of the study due to protracted diarrhea (on DHEA). The diarrhea stopped on cessation of the drug. 2 subjects finished the first arm of the study, but declined to complete the second half (both on placebo). One subject was recruited despite a protocol violation in her antidepressant medication and thus she is not included for the results of the psychometric tests. This only became clear after the subject had completed the study.

She was not replaced. One subject started taking estrogen replacement therapy during the first arm of the study. One subject was unable to speak English, and despite an interpreter being present, it was felt that the validation of the questionnaires was questionable, therefore her data was not included in the final analysis. 3 additional subjects were recruited to compensate for these omitted subjects.

It became clear that recruitment of the 30 necessary subjects would not be complete using the Mayo clinic indices. IRB approval was granted to allow an advertisement in the Minneapolis press, the National Adrenal Diseases Foundation newsletter, and also on the internet. The newspaper advertisement drew 2 responses, both of whom failed the telephone screen. The internet advertising was aimed at self help groups for subjects with adrenal insufficiency. 185 replies were received from all over the world in the subsequent 6 months. Of these, a convenience sample was used. The first subjects who passed the telephone questionnaire were invited to be screened. These subjects came from all over North America. Distance from Mayo Clinic was no longer considered a limiting factor. Of the 11 subjects invited for screening, one failed due to abnormal thyroid function tests. 1 subject started the study and then withdrew prior to the 11 week visit. 1 subject unblinded herself by measuring her blood levels of DHEA during the first arm of the study. Thus 33 women were randomized into the study.

Additional tests were done on these subjects to assess the effects of DHEA on body composition, insulin sensitivity and effects on different aspects of skeletal muscle physiology. Those results are presented elsewhere [83].

Data is therefore presented of the 26 women who completed the study. All subjects were White and Caucasian. In addition to travel costs, subjects were compensated for their participation in the study.

Figure 5 Recruitment Process

Inclusion and Exclusion Criteria

Inclusion criteria were women over 18 years old who had been hypoadrenal (from whatever cause) for greater than 24 months. Women of childbearing age in whom estrogen status had been steady for greater than 6 months were eligible, as were women on other forms of hormone replacement therapy (e.g. thyroxine) in whom the dose had remained the same for greater than 6 months.

Exclusion criteria included a BMI greater than 35 Kg/m^2, fasting blood glucose above 120 mg/dl, or a history of sex hormone dependant malignancy. Women with a history of cerebrovascular, neurological, liver or cardiovascular disease (other than hypertension), polycythemia or renal failure were excluded. Women who were pregnant or breastfeeding were excluded, in addition to postmenopausal women who had been on estrogen replacement therapy for less than six months.

Drug Usage

Standardization onto hydrocortisone 10 mg on rising, 10 mg at 4 pm and 5 mg at bedtime was attempted from at least 3 weeks prior to entry into the study. If subjects were on either a lower equivalent dose of prednisolone or a lower overall hydrocortisone dose prior to entry into the study then they were asked to stay on their current dose. For those on hydrocortisone, subjects were asked to go to at least a twice or three times a day regime. All of these changes were made with full approval of the volunteer's primary physician and/ or endocrinologist. Average total daily dose of hydrocotisone (± SD) at entry into the study was 24.90 ± 7.05 mg, divided between 1 and 3 times per day. 10 subjects had been on prednisone, average dose 4.14 ± 1.07 mg, and been changed to hydrocortisone at least 3 weeks prior to randomization.

Two subjects had previously been on commercially available DHEA. One had been on 25 mg per day and the other had been on 50 mg per day. Both subjects stopped the DHEA at least 6 months prior to starting the study.

Randomization was done by the Division of Biostatistics at Mayo Clinic.

Study Protocol

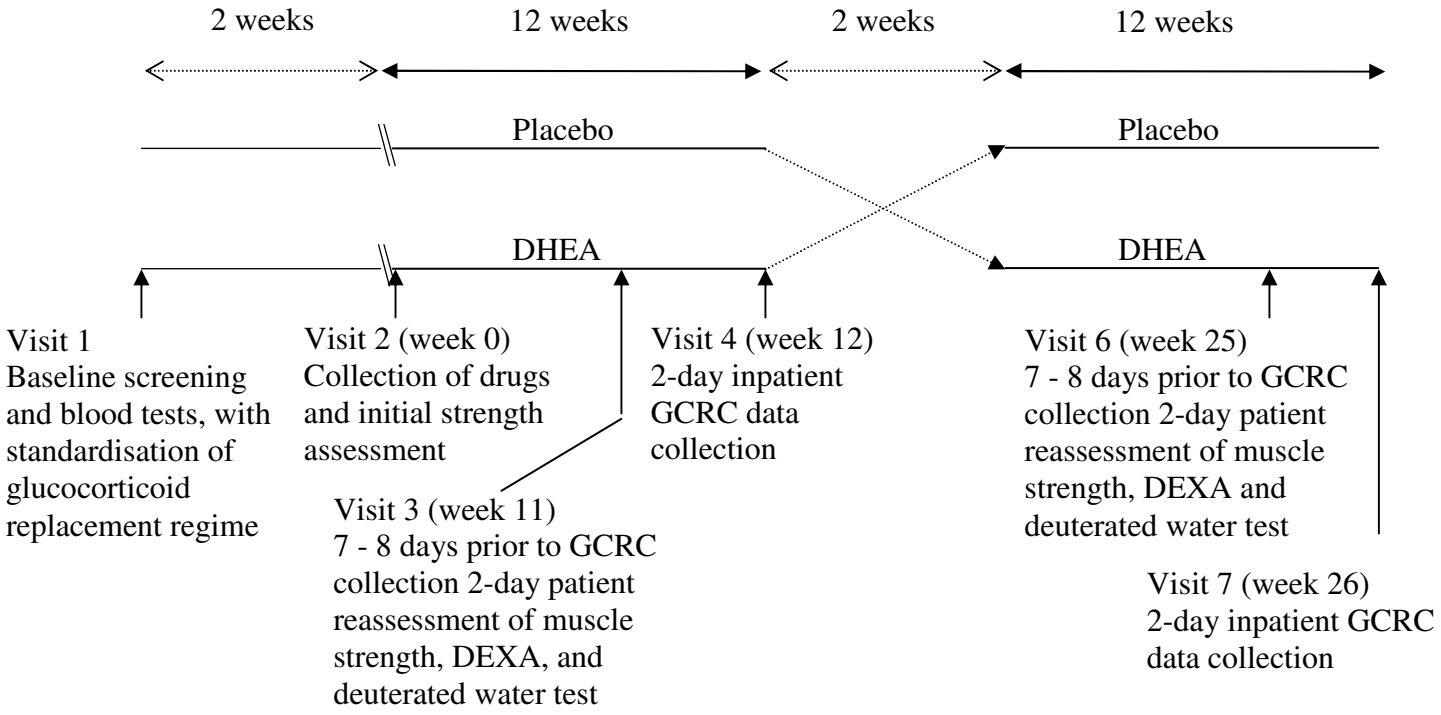


Figure 6 Overall Study Design

This was a single daily dose, randomized, placebo controlled, crossover design performed at a single centre. At the initial screening visit total body mass was measured to 0.1 Kg, and height was measured in centimetres. Body mass index was calculated from these measurements (Kg/m^2). Subjects then had a standard, submaximal treadmill exercise stress test with continuous monitoring of a 12-lead electrocardiogram to verify the absence of any previously undiagnosed cardiorespiratory abnormalities. The study schedule is shown in Figure 6.

The volunteers returned at the start of week 0 to the GCRC to have the initial set of questionnaires under the supervision of a trained psychometrist, and to collect the study drug. DHEA (Gardena, CA) was given at a dose of 50 mg per day or placebo and taken at the same time every day. Both placebo and DHEA were identically encapsulated (Clinical Encapsulation Services, Schenectady, NY). Pregnancy status was assessed in premenopausal women and during the course of the study these volunteers were advised against getting pregnant. However, no measures were taken to ensure the premenopausal subjects were in the same stage of the menstrual cycle when blood samples were drawn.

Psychological Tests - Cognition

The Auditory Verbal Learning Test (AVLT)

The AVLT is a measure of verbal learning and memory [84]. It is a widely used tool that consists of a 15 item repeated reminding test. The subjects read a list of 15 items which they are asked to recall during 5 learning trials (AVLT I to AVLT V). These are summated and the total (out of a possible of 75) is used for analysis. There is then a recall trial, asking the subjects to recite the original list 30 minutes later as a test of memory consolidation. Percent retention is then recorded [62]. Alternate forms of were used to minimize practice effects.

The Controlled Word Association Test (COWAT).

This is a measure of a person's ability to rapidly retrieve lexical information. It involves the on the spontaneous production of words that begin with a certain letter (specifically C, F and L or P, R and W) within a specific time limit. It is part of the Multilingual Aphasia battery developed by Benton and Hamsher [85]. The assessment provides useful information about brain function, with low scores being found in subjects with a variety of disorders including Parkinson's disease, Korsakoff's psychosis and Huntington's Disease [86]. The score is a sum of all of the words attained in 3 one-minute trials. Alternate forms were used to minimize practice effects.

The Trail Making Test (TMT)

This is a measure of attention and concentration involving perceptual motor speed, visual searching and sequencing, and the ability to make alternating conceptual

shifts [87]. The test consisted of two parts, A and B, and the results are expressed in terms of the time in seconds required for each part of the test. A ratio may also then be calculated for Trail B/Trail A. The normal range is dependent on age. For someone aged 56 to 62, the normal for trail A is between 27 to39 seconds and trail B, 66-75 seconds. For someone aged 64 and above, the normal ranges are 33 to 37 seconds for trail A, and 34 to 39 seconds for trail B.

Psychometric Tests - Self-Perception

The Memory Functioning Questionnaire (MFQ)

This is a widely used instrument developed to evaluate self-perception of every day memory functioning. It consists of 64 items on a seven point scale and provides four unit-weight factor score measuring frequency of forgetting, seriousness of forgetting, retrospective functioning and mnemonic usage. A higher score indicates higher levels of perceived memory functioning, i.e. fewer forgetting incidents, less frequent use of mnemonics [88].

The Changes in Sexual Functioning Questionnaire (CSFQ)

This is an instrument developed to systematically track changes in sexual function in populations who may experience specific or unusual sexual side effects of medications [89]. It is a measure of sexual desire, physiological function, and sexual satisfaction. If the subject feels uncomfortable with the semi-structured format then it

could be self-administered. There are specific questionnaires for males (36 items) and females (34 items), however the first 21 items are shared between both.

The CSFQ measure five aspects of sexual functioning – sexual desire/frequency, sexual desire/interest, sexual pleasure, arousal/excitement, and orgasm/completion. The remaining questions are about clinical history. The scores are calculated on these items, as well as two other questions, one on loss of arousal, and the other on painful orgasm.

The Beck Depression Inventory (BDI)

This is a 21 item self-report rating inventory measuring characteristic attitudes and symptoms of depression. The score can range from 0 to 63, with scores of 9 or below considered to be within the normal range. Scores of 10 to 18 indicate mild to moderate depression, with scores of 19 to 29 moderate to severe, and score of 30 or higher severe depression [90].

The Health Status Questionnaire

The 36-Item Short-Form Health Survey (SF-36) was developed to capture behavioural dysfunction caused by health problems [91,92]. The HSQ is a modification of the SF-36, adding 3 questions (total of 39) to assess better emotional or mental health. The HSQ has been demonstrated to be easy to understand by patients, takes only minutes to complete, and has excellent consistency and reliability between subgroups of patients with different chronic diseases [91]. The 39 questions are collapsed into 8 dimensions or scales of health status. The scores for each scale are

linearly ranged from 0 to 100, with higher scores for better health status. The 8 scales are general health perception (6 questions), physical functioning (10 questions), physical role limitations (the interference with work by physical health) (4 questions), emotional role limitations (interference with work by emotional problems) (3 questions), social functioning (2 questions), mental health (8 questions), bodily pain (2 questions), and energy/vitality (4 questions).

Safety Monitoring

As part of the ongoing assessment within the study, all of the blood tests were looked at by one of the principle investigators within 48 hours of the results being made available. Rules about aberrant results had been discussed a priori. These were to have been to determine if an aberrant result constituted an 'adverse event'. If an adverse event were to be noted then the subject was to be taken off the drug and given the opportunity to be followed on an 'intent to treat' basis. Subjects were to be asked to perform the questionnaires. If they were on the first arm of the study they would be offered the chance to go onto the second arm. In addition, a physician was present during exercise stress testing.

Hormonal Assays

DHEA and DHEAS were measured using a competitive RIA from Diagnostic Systems Laboratories (Webster, TX). The intra-assay coefficient of variation is 3.7% at 220 ng/ml and 1.9% at 2000 ng/ml. The assay has cross-reactivities of 41% with dehydroepiandrosterone, 7% with androsterone, 2.9% with androstenedione and < 1% with other related steroids [93].

Growth Hormone was measured by a two-site immunoenzymometric assay using the ACCESS® automated immunoassay system (Sanofi Diagnostics Pasteur, Chaska, MN). The assay precision varies from 4.7% at 2 ng/ml to 5.5% at 11 ng/ml. The lowest detectable level is 0.01 ng/ml.

Testosterone was measured with the coat-a-count RIA (DPC, Los Angeles, CA). The assay has 20% cross-reactivity with nontestosterone, 3.3% with dehydrotestosterone, and 1.7% with methyltestosterone. The inter-assay CV is 11% at 76 ng/dL, 6.4% at 264 ng/dL, and 6.0% at 672 ng/dL. The lowest measurable level is 4 ng/dL.

Sex-Hormone Binding Globulin was measured with a two-site immunoradiometric assay from Diagnostic Systems Laboratories (Webster, TX). The intra-assay CV is 5.0% at 48 nmol/L and 5.5% at 117 nmol/L. The lowest detectable level is 5 nmol/L [94].

Total IGF 1 was measured with a two-site immunoradiometric assay from Diagnostic Systems Laboratories (Webster, TX). The assay has a minimum detection

of 0.8 ng/ml and precision of 9% at 64 ng/ml and 6.2% at 157 ng/ml. No cross reactivity is noted for IGF 2, insulin, proinsulin, and growth hormone [95].

IGF BP3 was measured using an immunoradiometric assay from Diagnostic Systems Laboratories (Webster, TX). The assay has an inter-assay CV of 1.0 to 1.9%. The minimal detection dose is 2.0 ng/ml [96].

Statistical Analysis

Statistical analyses were done using Wilcoxon sign rank tests. Analysis was done to assess changes of endpoints from pre-treatment to post-treatment within each treatment as well as to compare these changes between treatments. An analysis was only performed on those subjects for whom complete data were available. All efforts were made to obtain complete data on each subject regardless of compliance level.

Power calculation was based on previous data based on the visual analogue scale for sexuality assessment used by Arlt et al [*personal communication*]. In that study, changes in components of the scales of sexual activity had standard deviations ranging from 23.8 to 29.9. Based on this, paired t-tests at the 5% level have 80% power to detect changes of 13.9 to 19.02, or 40.3 to 50.7% of baseline values with 25 subjects. Arlt et al observed within subject changes of this magnitude in subjects on DHEA treatment [20].

Carry over effect was assessed by comparing those who had DHEA first to those who had DHEA in the second phase of treatment. Assumptions were made that the two-week washout period was long enough to ensure that there was no such effect. In addition, as psychological testing was at least 14 weeks apart, that no such effect would be present given the short half life of DHEA and DHEAS in circulation.

Non-parametric tests were used for analyses due to the relatively small sample size and small number of missing data. Despite this, data is given as mean ± standard deviations. Median and interquartile ranges were not used as on further analysis, most data was normally distributed.

Interpretation of Results

We anticipated that while on the DHEA(S) replacement arm of the study that mood, memory, psychological and sexual wellbeing would be improved.

Potential Problems in Interpretation

It is possible that 12 weeks was not long enough to see these effects, however, previous studies looking at our primary hypothesis have showed results within 12 weeks.

Missing Data

Data was unable to be collected in some individuals. As demonstrated in Figure 5, of the 33 subjects randomized into the study, 1 subject withdrew from the study due to diarrhea at 10 weeks (on DHEA). 2 subjects withdrew after completing the first half of the study (both on Placebo), 1 subject unblinded herself (on DHEA) during the first half of the study and 1 subject withdrew without being able to complete the first half of the study citing pressure of work (on DHEA). 2 subjects violated the protocol by changing the drugs they were on. Thus, analysis was made only on the 26 women in whom complete data from both halves of the study is available.

Results

Baseline Demographics of Study Subjects

	Mean Baseline Value
Age in years (± SD)	51.03 (14.6)
BMI (Kg/m^2) (± SD)	26.98 (4.35)
Percentage of postmenopausal women	50 (n = 13)
Percentage of women on estrogen*	53.8 (n = 14)
Average length of time being hypoadrenal in years (± SD)	12.5 (10.1)
Percentage of subjects with Addison's Disease **	73 (n = 19)
Percentage of subjects with hypothyroidism #	50 (n = 13)

Table 1 Overall Baseline Demographic Data.

* On either oral contraception or estrogen replacement therapy. ** Other diagnoses include bilateral adrenalectomy due to Cushing's syndrome (n = 5), bilateral benign pheochromocytomas (n = 1) and congenital adrenal hyperplasia (n = 1). Cushing's syndrome cases were due to pituitary adenoma (n = 3), Carney's complex (n = 1), ectopic ACTH production from pulmonary carcinoid tumour (n = 1). # One 32 year old subject had hyperthyroidism treated by total thyroidectomy aged 16, now on thyroxine replacement therapy.

Hormonal Data

DHEA administration raised levels significantly compared to baseline levels. Also raised were levels of androstendione and testosterone. These results are shown in Table 2. Estrodiol levels in the 5 postmenopausal women not on estrogen therapy showed a strong trend to being increased on DHEA (20.17 ± 10.1 vs 0.2 ± 0.0 pg/ml, p = 0.063). Levels in premenopausal women not on estrogens were not different (61.5 ± 34.7 vs 66.72 ± 58.21 pg/ml, p = 0.844), but no attempt was made during the study to synchronize with the menstrual cycle. This is shown in Figure 7.

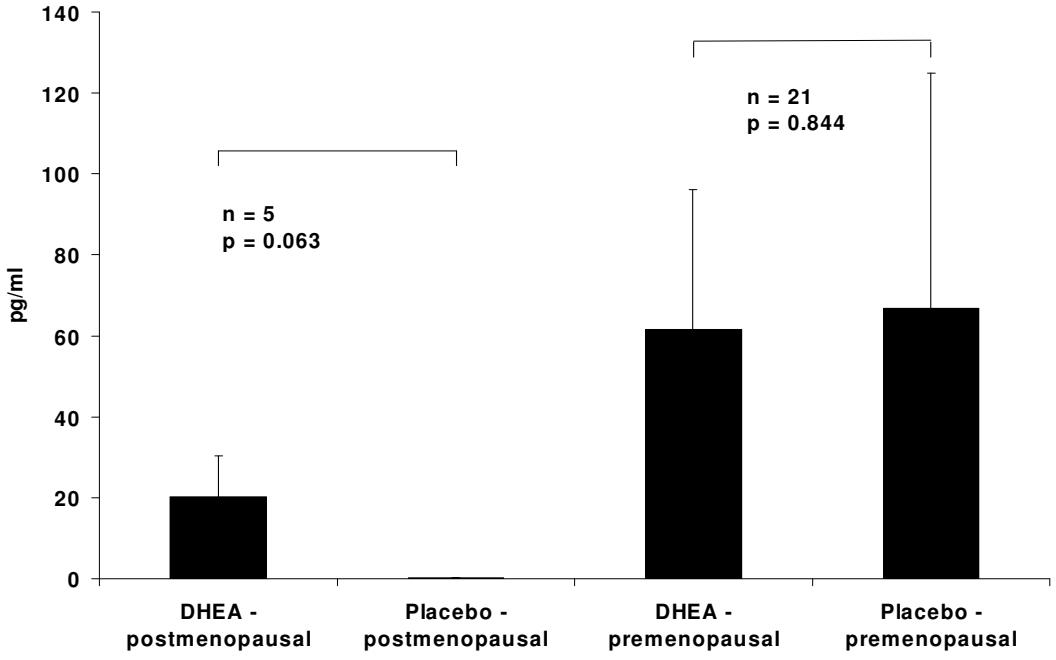


Figure 7 High Sensitivity Estrodiol Levels

	Mean Value after 12 weeks on Placebo (± SD)	**Mean Value after 12 weeks on DHEA (± SD)**	**95% Confidence Interval**	**P value**
DHEAS (µg/ml)	< 0.3 (0.0)	3.60 (1.31)	2.76, 3.88	< 0.001
Bioavailable Testosterone (%)	10.96 (4.42)	13.5 (5.54)	1.29, 3.79	< 0.001
Androstendione (ng/ml)	0.2 (0.49)	1.69 (1.62)	1.012, 1.97	< 0.001
Sex Hormone Binding Globulin (nmol/l)	58.81 (33.44)	54.0 (35.31)	45.31, 72.32	< 0.001
Cortisol (µg/dl)	27.75 (16.1)	24.48 (12.71)	-7.57, 1.03	0.088
IGF 1 (ng/ml)	225.4 (106.6)	270.6 (98.6)	11.0, 79.4	0.011
IGF BP3 (ng/ml)	4659 (1288)	4788 (1515)	-444, 701	0.873
Hemoglobin (g/dl)	13.07 (0.79)	13.22 (1.07)	-0.12, 0.43	0.303
Hematocrit (%)	37.91 (2.62)	38.57 (3.0)	-0.07, 1.38	0.079
Aspartate transaminase (U/l)	24.85 (10.36)	23.31 (8.13)	-4.39, 1.31	0.206
Alanine Transaminase (U/l)	23.58 (24.61)	21.62 (12.04)	-10.82, 6.90	0.9
Alkaline Phosphatase (U/l)	143.3 (75.3)	127.5 (53.0)	-50.3, 18.68	0.561

Table 2 Hormonal and Hematological Data

Psychological Data

Data is shown for the 26 subjects for whom all data was available. Data is shown as median and interquartile range.

Overall scores for general health perception measured by the HSQ were not different between DHEA and placebo (US population adjusted, -0.258, (-0.82, 0.3) vs -0.135, (-0.75, 0.24), p = 0.315). They also remained unchanged in the 12 women given DHEA first (-0.258, (-1.06, 0.61) vs –0.011, (-0.63, -0.01) first half vs second half respectively, p = 0.637). However in the 14 subjects given placebo first, there was a significant improvement in general health perception when on DHEA (-0.135, (-0.81, 0.3) vs –0.382, (-0.82, -0.38) first half vs second half, p = 0.039). This effect persisted when scores were adjusted for age and sex, (51.474, (40.51, 55.21) vs 49.791, (48.02, 56.37), first half vs second half, p = 0.043). General health perception scores were also significantly improved compared to baseline, for the 14 women given DHEA during the second phase of the study (-0.506, (-1.42, 0.11) vs –0.135, (-0.82, 0.3), baseline score vs DHEA score, p = 0.002). This effect persisted when scores were adjusted for age and sex (46.632, (40.66, 53.17) vs 52.468, (44.85, 54.92), baseline score vs DHEA score, p = 0.002). These changes are illustrated in Figures 26 and 27 on page 62.

For the group as a whole (n = 26) there was a non-significant trend for higher arousal scores whilst on DHEA, (9.00, (6.0, 10.0) vs 8.00, (6.75, 10.0), p = 0.063). This is illustrated in Figure 20. However, arousal was significantly lower at the end of the second phase in those 12 women who had been on DHEA in the first phase of the

study (9.00, (7.3, 10.0) vs 8.00, (6.3, 9.8), p = 0.016). This is illustrated in Figure 21 on page 57.

There was a statistically significant improvement in total AVLT score measuring learning efficiency (52.00, (45.3, 59.3) vs 57.00, (50.8, 62.0), p = 0.03). There was no change in percent AVLT retention, a test of delayed recall nor any other parameter measuring psychological or sexual health. This is illustrated in Figure 8.

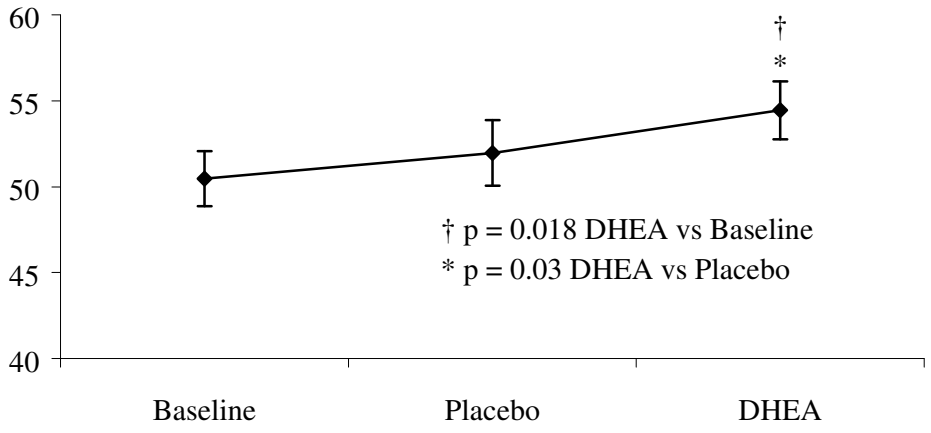


Figure 8 Auditory Verbal Learning Test - Total Score

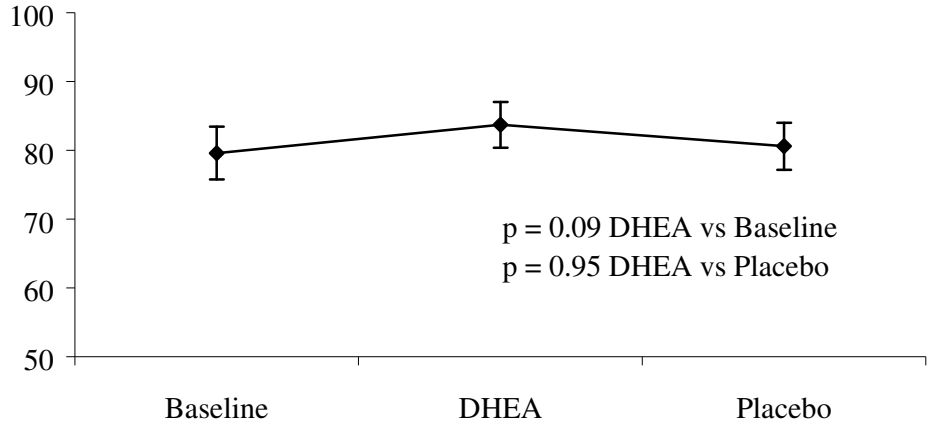


Figure 9 Percent Auditory Verbal Learning Test Retention

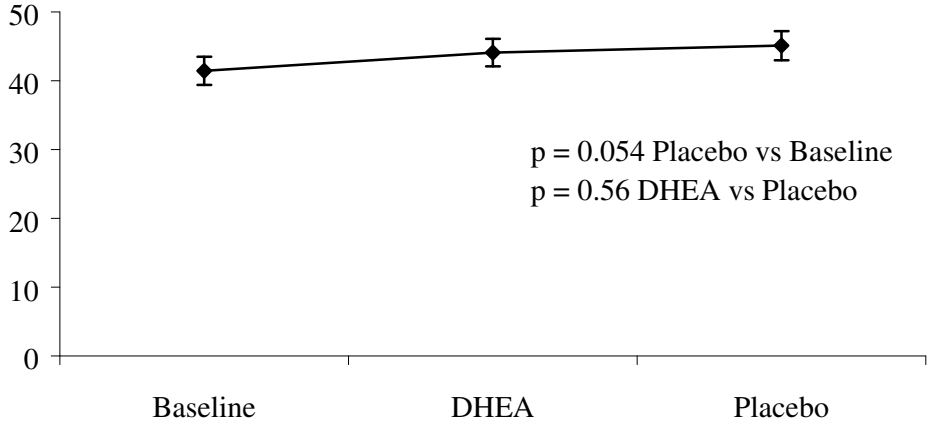


Figure 10 Controlled Oral Word Association Test

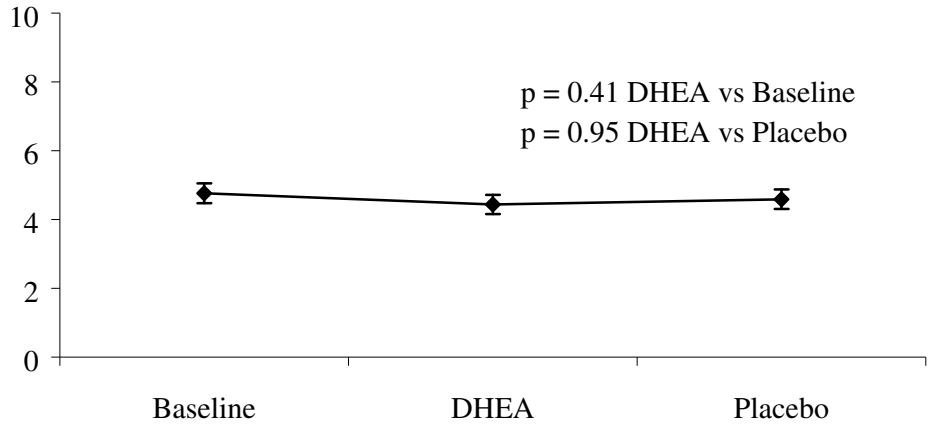


Figure 11 Memory Functioning Questionnaire - General Rating

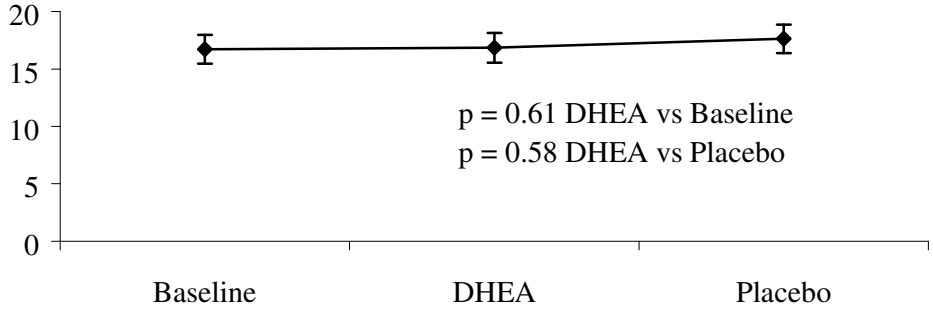


Figure 12 Memory Functioning Questionnaire - Retrospective Function

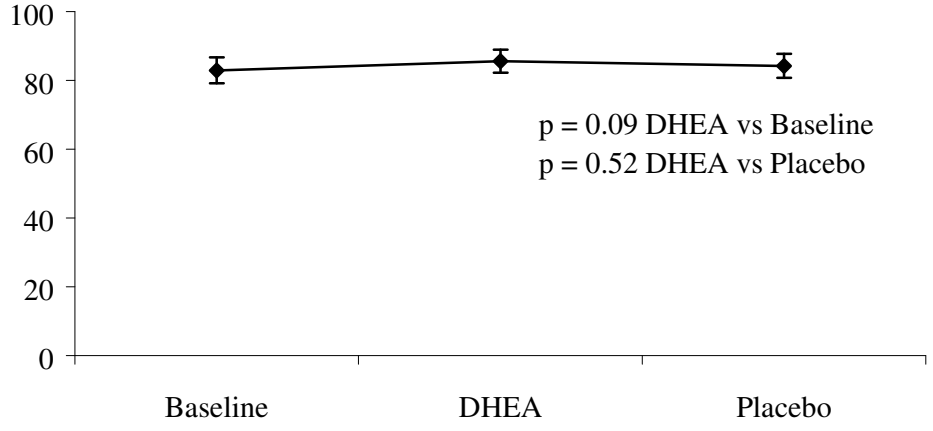


Figure 13 Memory Functioning Questionnaire - Frequency of Forgetting

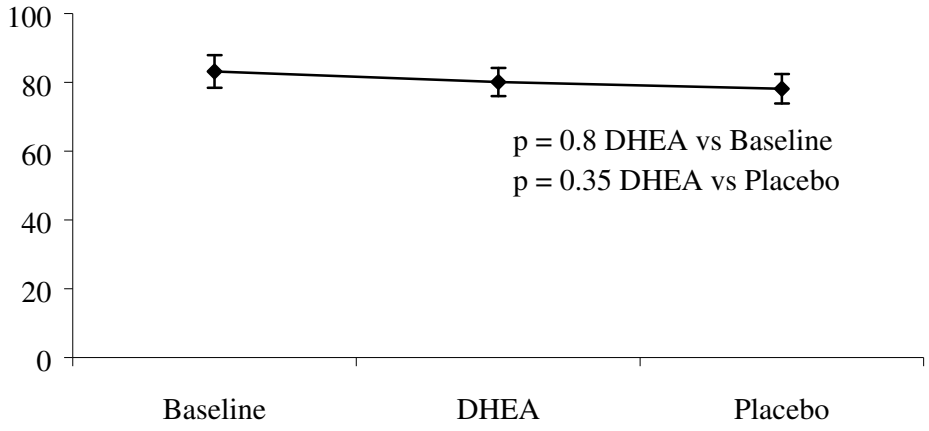


Figure 14 Memory Functioning Questionnaire – Seriousness

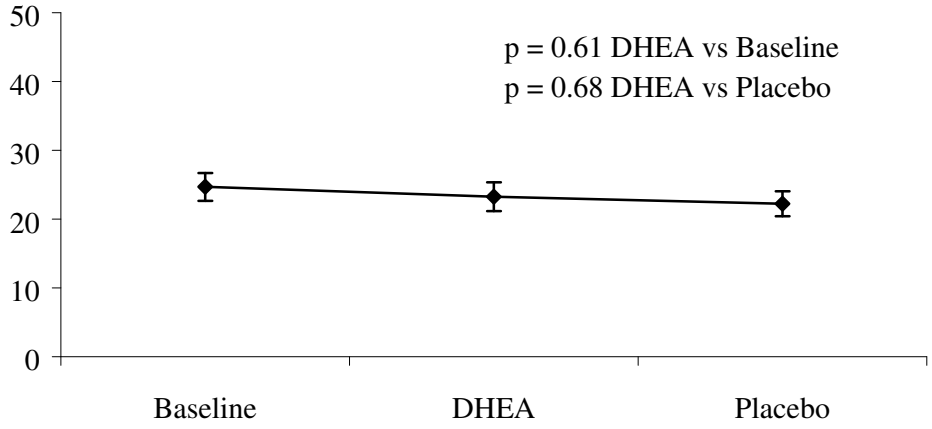


Figure 15 Memory Functioning Questionnaire - Mnemonic Use

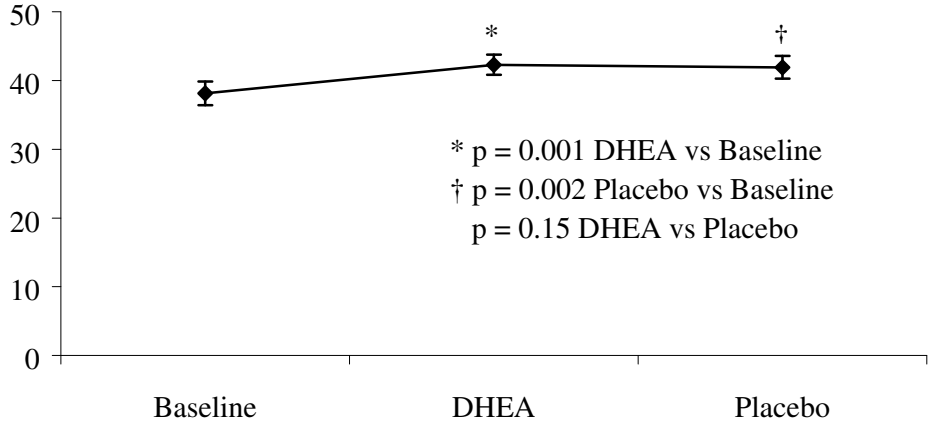


Figure 16 Changes in Sexual Functioning Questionnaire – Total

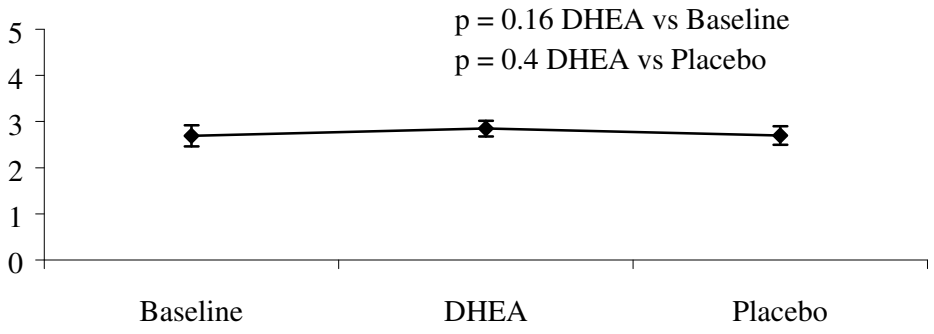


Figure 17 Changes in Sexual Functioning Questionnaire – Pleasure

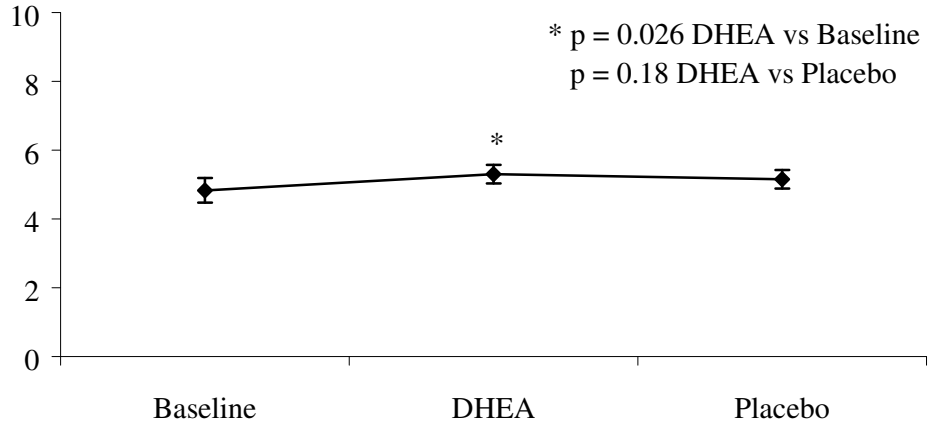


Figure 18 Changes in Sexual Functioning Questionnaire - Desire – Frequency

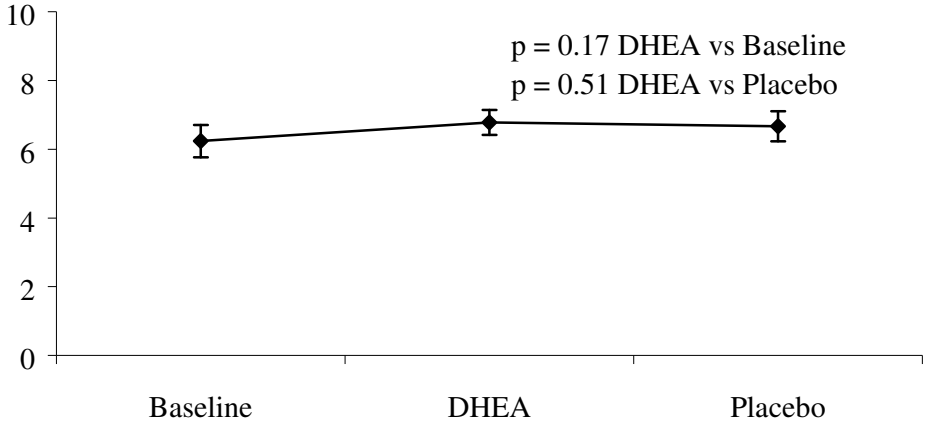


Figure 19 Changes in Sexual Functioning Questionnaire - Desire – Interest

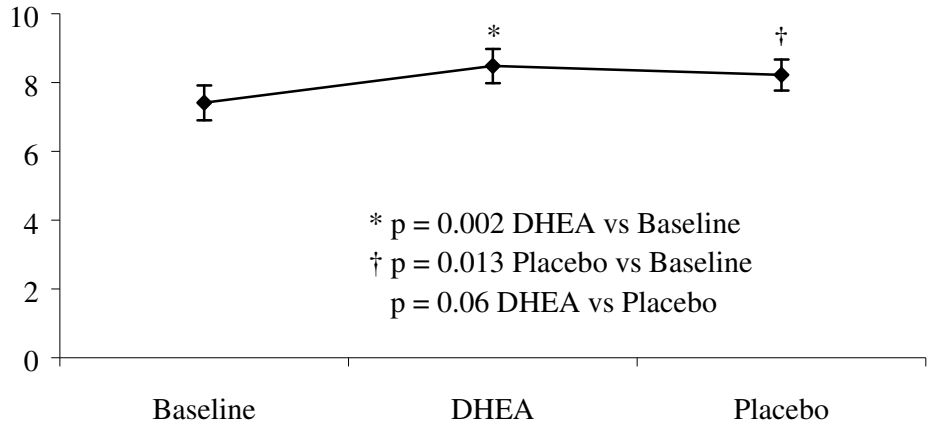


Figure 20 Changes in Sexual Functioning Questionnaire – Arousal

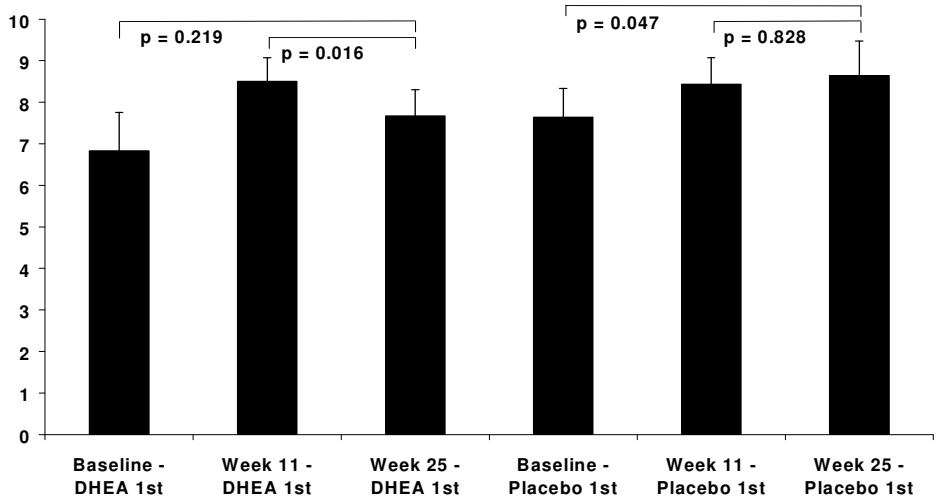


Figure 21 Carryover Effects for Arousal

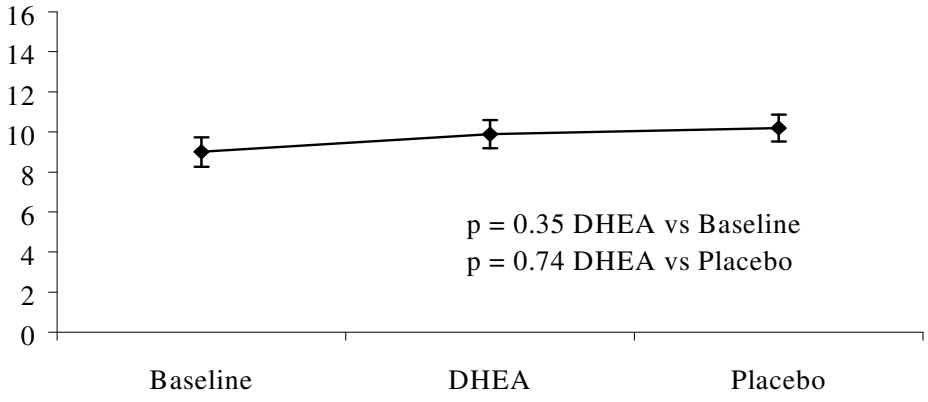


Figure 22 Changes in Sexual Functioning Questionnaire - Orgasm

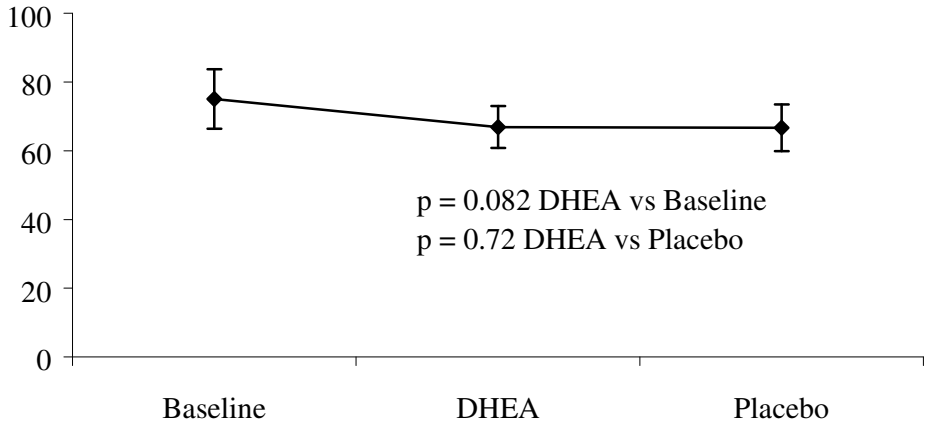


Figure 23 Trails Making Test A

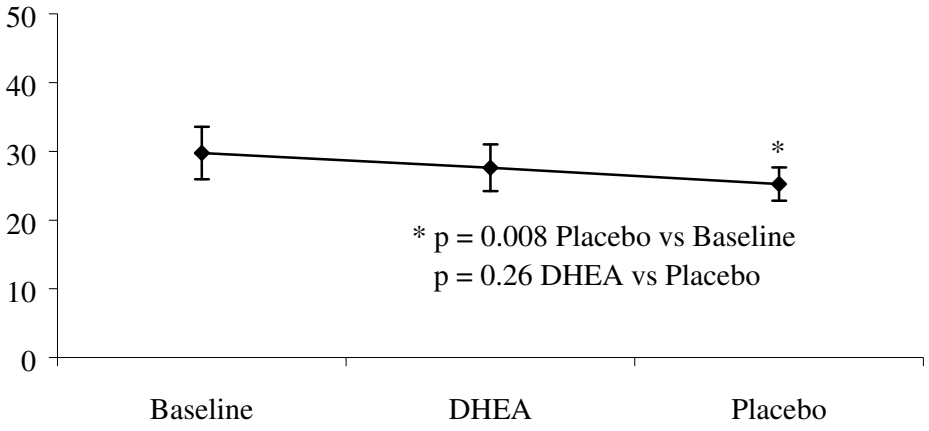


Figure 24 Trails Making Test B

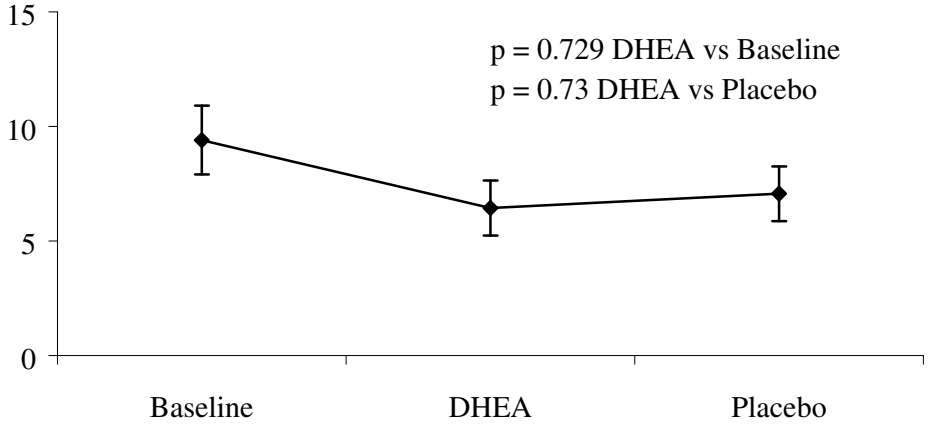


Figure 25 Beck Depression Inventory Score

	US Population Adjusted				US Population Adjusted for Age and Sex			
Median (Interquartile range)	**Baseline**	**Placebo**	**DHEA**	**P value**	**Baseline**	**Placebo**	**DHEA**	**P value**
Physical Functioning	0.021 (-0.85, 0.24)	0.021 (-0.74, 0.46)	-0.198 (-0.63, 0.46)	0.958	49.91 (45.91, 55.6)	50.99 (46.37, 56.74)	53.14 (47.06, 55.7)	0.289
Role Limitation due to Physical Health Related Problems	0.556 (-0.92, 0.56)	0.556 (-0.92, 0.56)	0.556 (-0.183, 0.56)	0.283	54.91 (38.22, 56.4)	49.82 (41.54, 57.13)	55.08 (49.73, 56.55)	0.336
Role Limitation due to Emotional Health Related Problems	0.566 (-0.95, 0.57)	0.566 (-0.7, 0.57)	0.566 (-0.43, 0.57)	0.59	55.88 (40.81, 55.92)	55.649 (45.89, 55.92)	55.649 (46.08, 55.92)	0.681

General Health Perceptions	-0.011 (-1.1, 0.24)	-0.135 (-0.75, 0.24)	-0.258 (-0.82, 0.3)	0.315	50.739 (43.29, 55.15)	49.895 (47.26, 53.17)	51.65 (44.85, 54.92)	0.329
Vitality	-0.769 (-1.61, -0.17)	-0.53 (-0.95, -0.43)	-0.53 (-1.07, 0.67)	0.341	44.415 (36.21, 49.24)	46.55 (42.31, 55.57)	45.884 (40.04, 57.45)	0.498
Mental Health	-0.158 (-1.27, 0.62)	0.064 (-0.82, 0.73)	0.508 (-0.38, 0.73)	0.245	49.758 (38.33, 55.74)	50.649 (42.69, 55.72)	55.002 (44.01, 57.54)	0.35
Bodily Pain	-0.573 (-1.02, 1.04)	0.064 (-0.57, 0.53)	0.361 (-0.68, 1.04)	0.71	49.47 (44.73, 59.09)	54.487 (46.19, 58.78)	53.894 (43.58, 59.74)	0.90
Social Functioning	0.174 (-1.22, 0.73)	-0.105 (-0.52, 0.73)	0.733 (-0.52, 0.73)	0.828	52.987 (39.58, 57.72)	51.133 (45.3, 57.61)	57.275 (45.3, 57.94)	0.774
Overall Physical Component of HSQ	50.599 (41.05, 53.68)	50.088 (44.96, 53.87)	51.879 (43.64, 55.92)	0.487	51.725 (37.59, 56.65)	52.4 (43.05, 56.33)	52.924 (42.05, 57.35)	0.612
Overall Mental Component of HSQ	50.477 (37.24, 57.21)	51.335 (43.47, 55.79)	51.756 (42.48, 57.61)	0.99	52.449 (46.61, 55.19)	53.028 (46.03, 56.58)	53.612 (49.69, 58.36)	0.391

Table 3 Breakdown of the Health Status Questionnaire Results

For the Health Status Questionnaire there are two sets of scores are derived, the z-score, which are adjusted to the US general population (left hand side of the table). When the data is normally distributed, it should have a mean of 0 and a standard deviation of 1, and a score adjusted to the US general population by age and sex (right hand side of the table). These have a mean of 50 and a standard deviation of 10. Furthermore, the overall physical component of the HSQ and the mental component are derived from the z-scores, but scaled to have a mean of 50 and a standard deviation of 10.

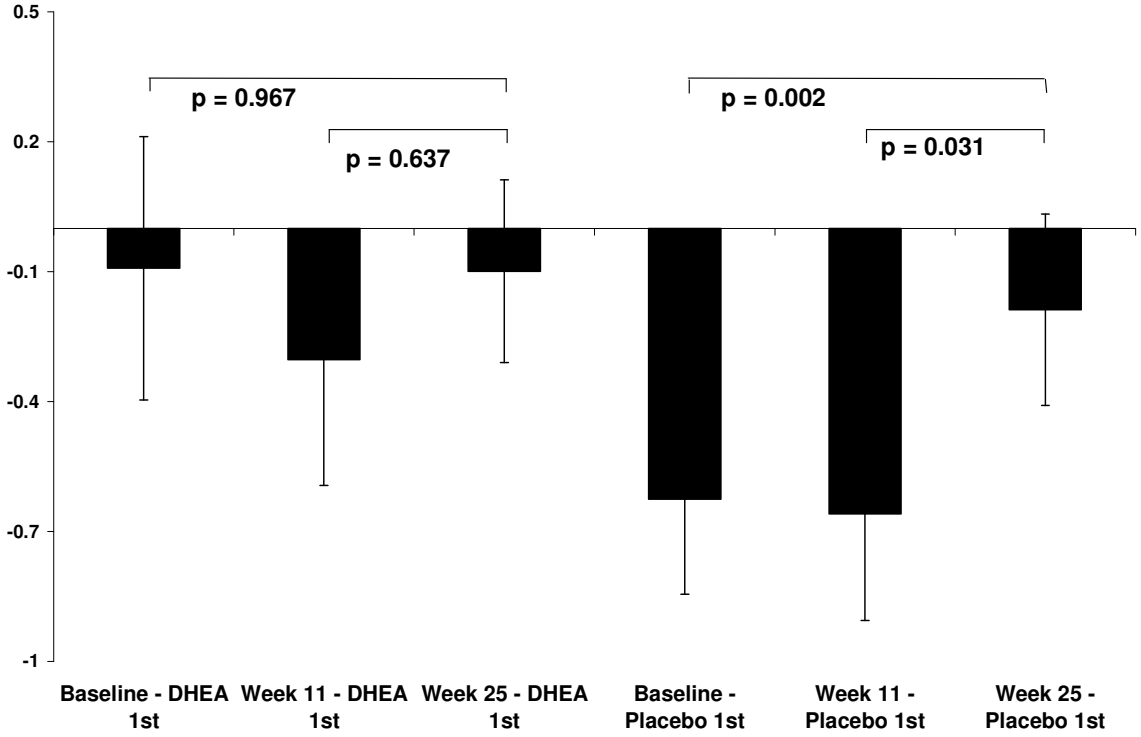


Figure 26 HSQ - General Health Perceptions US Population

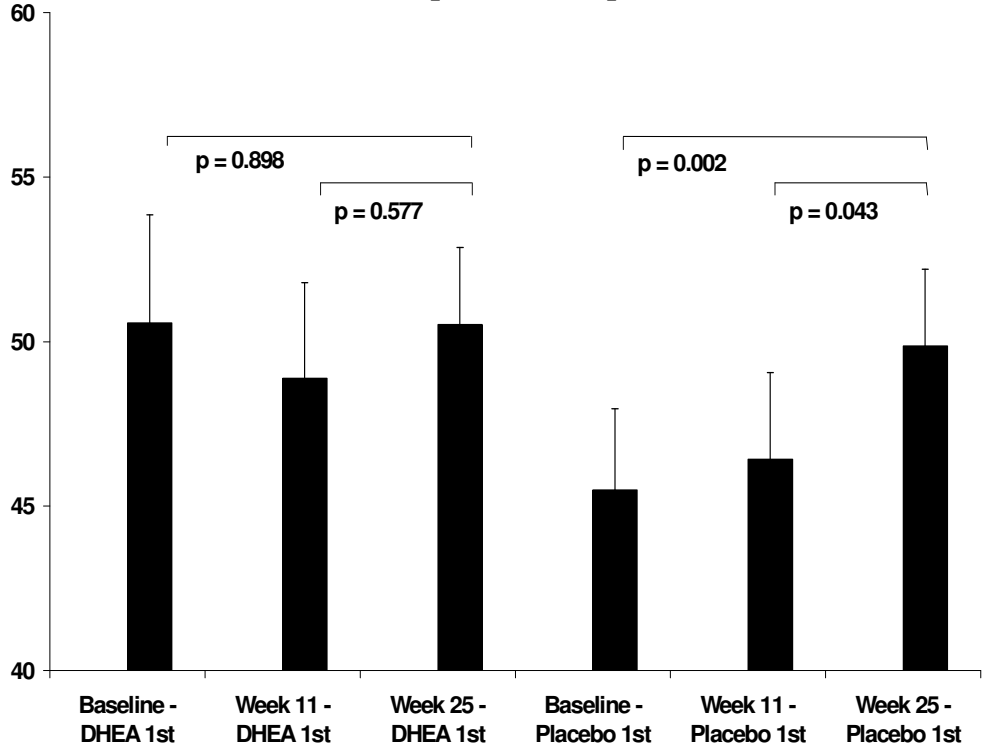


Figure 27 HSQ - General Health Perceptions Adjusted for Age and Sex

Median (Interquartile Range)	Baseline	Placebo	DHEA	P value
Risk of Major Depression	2.00 (1.0, 2.0)	2.00 (1.00, 2.00)	2.00 (1.75, 2.00)	0.453
Risk of Dysthymia	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	1.0
Risk of Major Depression Superimposed on Dysthymia	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	1.0

Table 4 HSQ Depression Ratings

Carryover Effects

Time taken for Trail Making Test A was significantly shorter during the second half for those on DHEA in the first half (24.5, (18.5, 28.5) vs 19.5, (16.5, 27.8) seconds, $p = 0.024$). This compared with no differences between the group as a whole (22.00, (18.0, 28.3) vs 22.5, (18, 28.3) seconds DHEA and placebo groups respectively, $p = 0.138$). It is probable that the finding of a carryover effect is a Type 1 error. It is unlikely to be a learning effect as the time to complete the test for those who started on placebo first were not significantly different (23.0, (19.5, 33.0) vs 20.5, (17.8, 28.5) seconds first half vs second half respectively, $p = 0.531$).

No other carryover effects were seen.

Discussion

Our study has shown that, when compared to placebo, 50 mg of once daily DHEA has significant positive effects on general health perception, arousal, and learning efficiency when given to hypoadrenal Caucasian women aged between 20 and 80 years. There are no further effects on psychological or sexual health.

Previous work has shown that hypoadrenal women who are not on DHEA have lower scores in general health perception when assessed using population standardized instruments such as the SF-36.[22] In the current study we have found that general health perception was higher in hypoadrenal women after 12 weeks DHEA. Other work has shown that DHEA replacement therapy in hypoadrenal women is associated with improved sexuality scores.[20] This is in agreement with our findings of increased sexual arousal following DHEA replacement. This is the first study to show a significant effect of DHEA replacement on learning efficiency. Collectively these findings suggest that DHEA replacement may play an important role in the in psychological function in hypoadrenal women who have very low circulating levels of DHEA.

Experimental Evidence of Biological and Clinical Effects

Mood, Wellbeing and Quality of Life

Quality of life (QOL), based on the World Health Organization definition of health, incorporates all five aspects of well being which comprise of mental, physical, emotional, spiritual and economic welfare [97]. Sex hormones are known to play an important role in mood, quality of life and wellbeing in both men and women. As

levels of these hormones decline with aging there is a parallel deterioration of mental function and DHEA(S) replacement is thought to be of potential benefit.

Neuroactive neurosteroids are allosteric modulators of neurotransmitter receptor activities [98]. DHEA(S) as neuroactive neurosteroids have become a greater issue with the discovery that these hormones are produced in the brain independently, and not under the influences of the factors that control adrenal DHEA(S) secretion [99]. While it is known that pregnenolone and its sulfated ester are the precursors for DHEA(S), how it is produced in neural tissue remains under investigation [31]. Studies of rat brains have shown that there is differential expression of the 3ß-hydroxysteroid-dehydrogenase Δ^5- Δ^4 isomerase enzyme system at different times during brain development [100]. The role of DHEA(S) in the brain also remains to be fully understood, but recent work has proposed that it is important in the guiding of thalamic fibres to their cortical targets in the embryonic brain by the regulation of motility and growth of cortico-thalamic projections [101].

There is biological plausibility for the psychotropic effects of DHEA because there is some in vitro and animal data that shows that DHEA(S) is a neurosteriod which acts as a non-competitive antagonist on the receptor of the major inhibitory neurotransmitter, γ - amino butyric acid (GABA) [102] by inhibiting the chloride ion transport currents in a dose dependant way. Another study showed that, in rats, levels of hypothalamic serotonin were increased after DHEA administration [103]. Additionally, DHEAS has been shown to bind to the excitatory *N*-methyl-d-aspartate (NMDA) receptor [104]. Both GABA and serotonin are known to be mood related receptors which both have targeted, prescribable pharmacological agents

(benzodiazepines and selective serotonin reuptake inhibitors respectively) used as antidepressants, whilst NMDA ('ecstasy') is a psychotropic drug of abuse. There is also some evidence from small scale open label studies in healthy elderly human volunteers showing that DHEA supplementation increases β endorphin levels [105], an endogenous opiod which is known to cause an increase in wellbeing. Long term large epidemiological studies in humans have shown that in elderly women mood is correlated to DHEA, with low levels found in those women with depression [106]. Finally, DHEA has been shown to act as an agonist on the σ_1 receptor and reduce the decline in memory associated with β amyloid accumulation [107]. There is further evidence that DHEAS levels are inversely correlated to levels of β amyloid in people with Alzheimer's disease [108]. This is discussed further in the section on cognitive impairment.

There are several reasons why estrogens may play a role in ameliorating the cognitive and emotional disturbances associated with the menopause. Estrogens have been shown to produce an increase in attention span, concentration, libido and memory in postmenopausal women [109]. However in aging men, despite DHEA administration increasing circulating estrogens and androgen metabolites, this beneficial effect on mood has not been a consistent finding [57,110]. This may be because endogenous production of androgens from the testes compensates for the effects of the declining levels of DHEA in men with age [110].

It is for this reason that the subjects in our study were not on any new dose of estrogens for at least six months to ensure a minimizing of any potential bias caused by the estrogens.

In humans, two recent small studies from the same group have shown DHEA to be as effective as more 'traditional' therapies in treating major depression [111,112] however only the latter was randomized whilst the first was an open label study. In addition, other workers have described higher levels of DHEA(S) in clinically depressed subjects when compared with controls [113], and further, that treatment with conventional antidepressants can reduce levels of circulating DHEA(S) [114]. Thus the role of DHEA(S) in mood and affect remains to be clarified.

Preliminary work has shown that a single 500 mg dose of DHEA enhances relaxation by increasing the amount of time spent in REM sleep [115]. This is also implicated to be the time of sleep during which memory is laid down as well as having a key role in language and emotional learning [116]. Work has been done looking at the effects of various glucocorticoids, their biosynthetic precursors and their metabolites on the sleep EEG. This work showed that the effects could be attributed to the mode of action of these neuronally produced steroids. Specifically, steroids such as pregnenolone and DHEA were thought to most likely be produced in glial cells and act in a paracrine fashion, thus modifying the sleep EEG in humans in a manner that suggested they may enhance memory [117]. However, a recent review article has challenged this view, stating that REM sleep is not necessary for the laying down of memory, because in humans, REM deprivation is not associated with memory dysfunction [118]. Thus the effects of glucocorticoids and DHEA(S) on memory and sleep remain to be fully clarified.

As mentioned, part of the reason that the glucocorticoid regime was standardized was to reduce the impact different regimes have on quality of life [76] but

also that glucocorticoids are known to have an effect on sleep patterns and in particular REM sleep [119]. This would imply that memory disturbance and general well being can be related to quality of sleep.

Evidence is also accumulating that high glucocorticoid levels are neurotoxic [120] and that this may be one mechanism for the psychological disturbances seen in hypercortisolism [121]. These changes have a physical effect when tissue cultures are examined in culture media containing the same concentrations of glucocorticoids as found in the csf. DHEA has been shown to modulate this response in vitro [122]. High DHEA(S) levels in the well elderly reduces the cortisol/DHEA(S) ratio and this may act as a mechanism to prevent cognitive decline in these individuals [123].

Clearly, in our study, where subjects have low or absent endogenous circulating cortisol, the cortisol/DHEA ratio is not an issue. However there is a valid argument to suggest that this ratio would now be altered in such a way that a raised DHEA level may have an enhancing effect on cerebral functioning rather than a protective effect.

Other work looking specifically at cognitive function has shown that the reduction in DHEA levels with normal aging did not correlate to cognitive decline in a large prospective observational study [124]. This study also looked at mortality and showed that those subjects at baseline with a DHEA in the lowest quartile were more likely to die by the follow up 15 years later compared with those in the top quartile. This represented a 40% and a 24% increase in mortality in men and women respectively. However, decline in cognitive function was not increased amongst those who died before follow up.

Aging is associated with a general health score decline [125]. It has also been shown that Norwegian men with Addison's disease with a mean age of 39 had a lower self reported subjective health status than the general population of healthy men over the age of 70 years. Women with hypoadrenalism have also been found to have greater subjective feelings of both total and physical fatigue than men [22]. However, the same study showed that mental health was deemed to be less in men than women. However, it was in this study that general health perception was found to be lower in hypoadrenal women. In both sexes, the numbers of patients out of work and receiving benefits was much higher in those with hypoadrenalism than those without (24% vs 10% in the general population 18 to 67 years old, and 41% vs 17% in the age range 40 to 67) [22].

A more recent study from the same authors gave a dose of 25 mg of DHEA for 9 months to 19 hypoadrenal women aged between 18 and 70 [126]. The authors showed that whilst androgen levels increased appropriately, there were no statistically significant differences in any of the parameters that they measured when compared with the 20 women randomized to placebo. They used a standardized questionnaire regarding general wellbeing. These variables included physical and social functioning, bodily pain, general and mental health, and others. They also found no differences in total, physical or mental fatigue scores between the two groups. These results are in conflict with those previously reported who both used doses of 50 mg of DHEA in cross over designs [20,21].

It can be seen that subjects with hypoadrenalism who are on replacement therapy have a reduced self reported perception of general health and vitality. Whilst

this population is heterogeneous, with many subjects well-being falling under the 'normal' range, a substantial proportion have a reduced quality of life. This is mainly due to the perceived reduction in mental and physical well being.

The increase in IGF 1 levels has been put forward as one of the reasons for the improvement in well being with DHEA(S) replacement [57,59,127,128]. In one study this increase in IGF 1 was restricted to those women with primary adrenal insufficiency [20] suggesting that the effect of DHEA(S) on IGF 1 production is growth hormone dependant.

A summary of the various results is given in Table 5. It is clear from the reported studies that no consensus is available. DHEA replacement in hypoadrenal people seems to lead to an improvement in mood in a significant proportion of the studies. The effect on depression and other conditions appears to be dose dependent, and is probably also related to the duration of administration.

Our study adds to the evidence showing that there is benefit in general health perception, arousal and learning efficiency, but little effect in other parameters measuring well being in hypoadrenal Caucasian women.

Type of Subject	Age (years)	Type of Study	Dose (mg/day)	Duration on DHEA	Sex and Number	Summary of Results	Reference
Healthy Elderly	Over 65	O	N/A	N/A	M and F (622)	Low DHEAS levels associated with depression - significant in women, trend in men	Berr et al [106]
Healthy Elderly	40 to 60	O	N/A	N/A	F (141)	DHEA levels positively correlated to wellbeing	Cawood et al [129]
Healthy Elderly	50 to 90	O	N/A	N/A	F (699)	DHEAS levels positively correlated to wellbeing	Barret-Connor et al [130]
Healthy Elderly	Mean age 69	P, R	50	2 weeks	M (25) F (15)	Non significant trend to improvement in mood in women	Wolf et al [131]
Hypoadrenal	26 to 69	P, R, C	50	3 months	M (15) F (24)	Significant improvement in mood	Hunt et al [21]
Hypoadrenal	23 to 59	P, R, C	50	4 months	F (24)	Significant improvement in mood	Arlt et al [20]
Hypoadrenal	24 to 70	P, R	25	9 months	F (39)	No change in mood	Løvås et al [126]
Healthy	40 to 70	P, R, C	50	3 months	M (13) F (17)	Improvement in mood	Morales et al [57]
Healthy elderly	50 to 69	P, R, C	50	4 months	M (22)	No change in mood	Arlt et al [110]
Anorexic	14 to 28	R	50	12 months	F (61)	Significant improvement in mood	Gordon et al [132]
Healthy Elderly	Over 50 in men, over 55 in women	O	N/A	N/A	M (270) F (167)	DHEAS levels not correlated with cognitive decline	Barrett-Connor et al [124]

Healthy and Institutionalized Elderly	55 to 104	O	N/A	N/A	M (111)	DHEAS levels significantly lower in those with AD or MID than controls	Rudman et al [133]
Demented Elderly	80	O	N/A	N/A	M (35) F (51)	DHEAS levels significantly lower in those with AD or MID than controls	Näsman et al [134]
Healthy Elderly and Elderly with AD	Healthy mean 75 AD mean 76	O	N/A	N/A	M (22) F (32)	Women with AD had significantly higher DHEA levels	Rasmuson et al [135]
Healthy Elderly and Elderly with AD	69	O	N/A	N/A	M (30) F (40)	DHEAS levels not correlated with cognitive function	Schneider et al [136]
Subjects with Depression	51 to 72	OL	90	6 weeks	M (3) F (3)	DHEA(S) significantly improved all measures of mood and wellbeing	Wolkowitz et al [111]
Healthy Subjects with Midlife Dysthymia	45 to 63	P, R, C	90, 450	Each dose for 3 weeks	M (12) F (3)	DHEA significantly improved all measures of mood and wellbeing	Bloch et al [137]
Subjects with Depression	33 to 53	P, R	90	6 weeks	M (12) F (10)	DHEA significantly improved all measures of mood and wellbeing	Wolkowitz et al [112]
Subjects with AD	67 to 84	P, R	100	6 months	M (30) F (28)	No effect of DHEA on any cognitive assessment scores	Wolkowitz et al [138]

Table 5 Summary of Human Studies Looking at the Effect of DHEA on Mood, Wellbeing, Cognition and Memory.

O = Observational, OL = Open label, P = Placebo controlled, R = Randomized trial, C = Cross-over design, N/A = Not applicable, AD = Alzheimer's disease, MID = Multi infarct dementia

Cortisol Neurotoxicity Prevented by DHEA and Effects on Memory

In vitro work looking at rat embryo hippocampal cultures has shown a decline in cell numbers, a change in morphology and the production of the stress activated Protein Kinase 3 in those cultures exposed to corticosterone [139]. With aging the rate of loss of hippocampal neurones in rats is raised, with the addition of chronic glucocorticoid exposure this loss is greatly accelerated [140]. All of these changes were attenuated when DHEA was added to the culture [122]. In addition, there is an accelerated decline in cell numbers when cultures are exposed to the excitatory amino acids NMDA and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) [141]. This decline in cell number is not seen when DHEA is added, whilst DHEA alone did not increase the number of cells in culture [141]. Some authors take this further and suggest that in addition to this apparent protective role DHEA(S) also stimulates specific signal transduction pathways involved in cell survival [142,143].

Stress and aging are known to be associated with neuronal vulnerability and also degeneration. The hippocampus is known to be important in regulating the activity of the hypothalamo-pituitary-adrenal (HPA) axis by suppressing its activity. Damage to this area, therefore, leads to a lesser ability to shut off HPA function during and after times of stress so leading to glucocorticoid hypersecretion. This is what is found in both rat and human studies of stress [139]. This may be one of the mechanisms of a failure of suppression of the dexamethasone suppression test in depressed or stressed individuals. There is evidence for the role of hypercortisolemia in disorders of memory [144]. In addition, a small study has been done showing that

lowering the raised cortisol levels found in depressed individuals has a beneficial effect [145].

Estrogens have been shown to have beneficial effects on both psychological and neurological disorders [146]. This is possibly due to effects on the levels of choline acetyltransferase [147] or, like DHEAS, reducing the effects of NMDA [148]. Activation of hippocampal NMDA receptors have been shown to be important in retrieval of memory in mice [149], however work to look at the effects on memory of DHEA(S) activity on these receptors has not been done.

Recent work has shown that estrogen administration to ovariectomized rats rapidly enhanced visual and place memory [150]. It has also been shown that learning is impaired if the estrogen receptor is disrupted [151]. This is consistent with the in vivo studies using aging rats, which showed that DHEAS administration improved memory [152]. It is unknown if this is a direct effect of DHEA or if it is permissive effect allowing the actions of other molecules to take place. Possible mechanisms for this improvement have been proposed. Racci et al raised the possibility that alterations in Protein Kinase C activity were responsible for the decline in memory seen with aging [153]. They provide animal data, and suggest that these changes in Protein Kinase C activity can be reversed by the addition of DHEA, thus this serves as a potential mechanism to prevent the age related decline in memory. However as these authors used a rat model, it is difficult to extrapolate these results to humans.

The mechanism of DHEA(S) neuroprotection is unknown as it has been shown not to alter cortisol binding with it's receptor in hepatocytes [154]. Whether there are different cortisol receptors in the brain that can be antagonized by DHEA(S) is

unknown. However, it has been shown that in rat brains, levels of the immediate precursor to DHEA(S) production, pregnenolone sulfate, are highly correlated with spatial memory performance [155]. It is possible that the effect of DHEA(S) on memory in humans occurs by the same mechanism as pregnenolone sulfate in rats.

While glucocorticoids are detrimental to the hippocampus and dentate gyrus, there is evidence that the adrenal steroids are neuroprotective. In the developing rat embryo the rates of cell birth, migration and survival are highest when levels of adrenal steroids are highest. In the first two weeks of development when adrenal steroid levels are lowest, the rate of neuronal loss is highest [156]. In the rat, the administration of adrenal steroids at this time reduces the magnitude of cellular loss. In addition, as the birth, death and migration of neurones is ongoing for about a year in rats this dependence on adrenal steroids is ongoing. Whether this occurs in humans is unknown, however, in a post-mortem study of a single of Addisonian subject there was evidence of dentate gyrus neuronal loss, suggesting a similar requirement of adrenal steroids [157].

Because adrenal steroids are normally buffering and protecting against disturbances that can lead to affective disorders, further investigation of their counter regulatory effects may shed light on the chemical imbalances that lead to an effective illness. The current literature on human studies is summarized in Table 5.

Cognitive Impairment

The current literature is summarized in Table 5. Alzheimer's dementia (AD) and multi-infarct dementia (MID) are relatively common in the aging population. There is some evidence that AD is due to hippocampal damage induced by free radicals, resulting in increased lipid peroxidation and alteration in free radical defence mechanisms [158]. Animal studies using the centrally administered $\beta_{25\text{-}35}$-amyloid peptide as a model for Alzheimer's disease have shown that the administration of DHEA reduces the rate of decline of cognitive function [107]. In addition, there is some work to suggest that DHEA(S) can, in vitro, reduce this oxidative stress induced damage [159], however, how this protection is afforded has yet to be fully established. Furthermore, the use of DHEA(S) in vivo for this purpose seems limited as the doses used in this study were highly suprapharmacological.

There is some conflicting evidence about the relationship between DHEA(S) levels, AD and MID [133,135]. There was some early data to show that low DHEA(S) levels were associated with both AD and MID. Rudman et al compared DHEA(S) levels between 50 independently-living community men, aged 55 to 94 years old and 61 nursing home men, aged 57 to 104 years old [133]. These authors showed that there was an inverse relationship between DHEAS levels and the presence of either AD or MID [133]. In addition, there was also an inverse relationship between DHEAS levels and the degree of dependence in activities of daily living. Further, plasma DHEAS was lowest in 80% of the nursing home men who required total care. In total care patients with either AD or MID the prevalence of low DHEAS was 68% and 100% respectively [133]. This later finding is consistent with that of other workers who have

found low DHEAS levels in elderly subjects with organic brain disease [134]. Näsman et al additionally found that the cortisol/DHEAS ratio was also high. However, other work has shown that there are no differences in DHEAS levels between those subjects with or without AD [136].

Other workers have suggested that it might be the DHEA rather than DHEAS that is the cause of these dementias. In another study looking at elderly subjects with dementia and their aged matched controls, serum concentration of DHEA among patients with AD and patients with cerebrovascular disease did not significantly differ from that of controls [160]. However, patients with AD and patients with cerebrovascular disease were found to have lower concentration of serum DHEAS and a lower DHEAS/DHEA ratio compared to normal control individuals [160]. This has yet to be confirmed by other groups.

Recent work has supported the hypothesis regarding the link between low DHEA levels and Alzheimer's disease. Luchsinger et al reported that reducing caloric intake might reduce the risk of Alzheimer's disease in individuals carrying the apolipoprotein E epsilon 4 allele [161]. People with apolipoprotein E epsilon 4, (apoE4), are more vulnerable to Alzheimer's disease. They develop Alzheimer's disease at an earlier age [162]. Roth et al found that caloric restriction extends the time at which high levels of DHEAS are seen in nonhuman primates, and suggest this may be the case in humans [1]. This suggests that reducing caloric intake extends the availability of DHEA and may be a causative factor in the delay or prevention of AD.

Raber, et al found that apoE4 contributes to cognitive decline by reducing androgen receptor levels in the brain [163]. Whilst DHEA does not bind to androgen

receptors directly, there is some evidence that it may be a competitor for androgen receptor - like components in cytosol [164]. Because people with apoE4 are generally older, they are affected more by the decline in DHEA. In addition, recent work from France has looked at DHEAS levels in post-mortem specimens from elderly subjects with and without AD. This group found a significant correlation between areas of the brain that have high levels of both β amyloid protein and the pathological tau proteins seen in the patients with AD, and low levels of DHEAS [108]. This suggests that DHEAS may have a neuroprotective role in the prevention of AD.

The probability of AD increases directly with age. DHEA declines to very low levels in old age. It is plausible that AD results from reduced maintenance of brain function as a result of declining DHEA. Individuals who carry the apoE4 gene are at increased risk because apoE4 reduces the availability of DHEA to their brains below that of their age.

One of the few randomized controlled trials to be carried out in the AD population randomized men and women in their 8th decade of life to 50 mg DHEA twice daily or placebo [138]. These authors failed to find any statistically significant differences in any of the cognitive assessment scales they used over 6 months of treatment.

The data suggesting that DHEA(S) levels are low in organic brain disease conflicts with very recent work suggesting that DHEA(S) levels are raised in subjects with AD and MID [135]. Thus, the role of DHEA(S) in this area remains to be clarified.

Androgens and Sexual Function in Oophorectomized Women

The current literature is summarized in Table 6. The role of androgens in the sexuality and sexual functioning of adrenalectomized women was first demonstrated in 1959 by Waxenberg et al [165]. The role of testosterone in the sexuality and sexual functioning of hypogonadal women has most recently been demonstrated in a randomized cross over study involving 75 oophorectomized women by Shifren et al [166]. They showed that testosterone supplementation in women already on adequate estrogen replacement significantly improved sexual function and psychological well being. Work done several decades ago had shown that surgical castration of women by oophorectomy had little or no effect on sexuality or sexual function, or that estrogen replacement in these women had any effects on these variables [167]. Taken together, these studies suggest that the role of estrogens in the psychological aspects of sexual wellbeing is limited. However, estrogens have been shown to be related to vaginal elasticity and lubrication and they are believed to be associated with pelvic blood flow [168]. There is then the apparent indirect relationship between low estrogen levels and disorders of female sexual arousal due to poor lubrication and dysparunia leading to decreased desire and orgasm difficulties. Subsequent work has revealed an association between the multidimensional relationship of sexual physiology of desire, arousal, and orgasm with androgen levels.

There is some suggestion that androgens are important in genital smooth muscle relaxation and genital sensation [169]. Due to these, and other reasons, the use of androgens for treating sexual dysfunction in women has gradually increased,

especially after it became apparent that estrogen replacement had little or no effect [170].

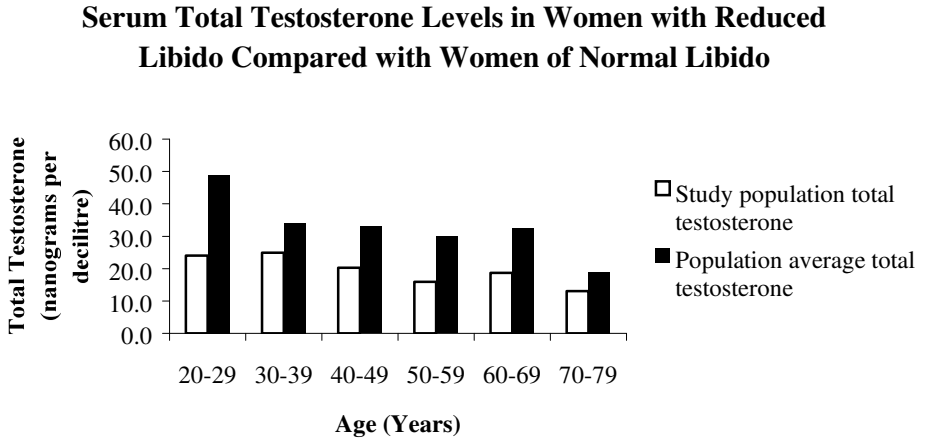
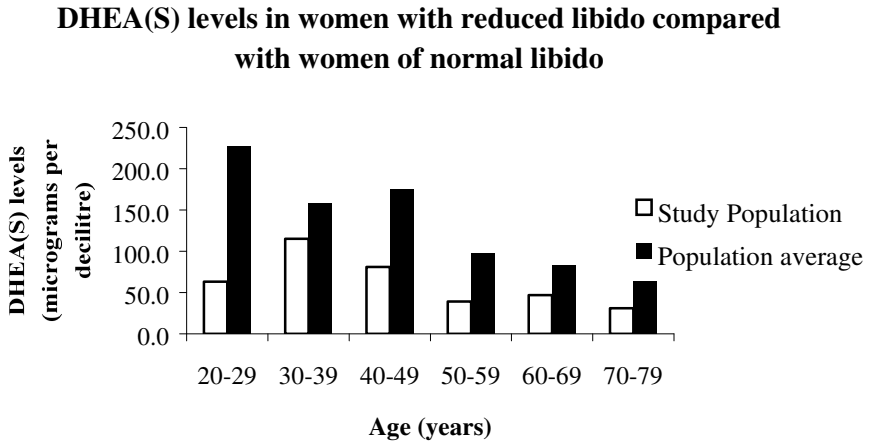


Figure 28 Low Serum DHEA(S) Levels Found In Women of All Ages With Reduced or Absent Libido

$P < 0.05$ in all groups. Data adapted from reference 171.

There is inherent difficulty in establishing the 'normal' range for free and bioavailable testosterone in women. This is because it is only recently that the ultrasensitive assays have become available. Many of the standards used previously have not been able to detect any circulating testosterone. In addition, data suggest that up to 43% of women between 18 and 75 years of age have some form of sexual difficulty [172,173]. However, much of the initial data used to create the 'normal range' may not have taken this into account, and so it is highly likely that many of the women used to establish 'normal' values had some form of sexual dysfunction, with a large proportion having low testosterone levels. Other issues arise in postmenopausal

women on hormone replacement therapy. At least one study has shown that free testosterone and DHEA(S) levels are reduced by estrogen replacement therapy [174].



Studies in very small numbers in premenopausal women on oral contraception have also found this, but no conclusive inferences can be drawn from such small numbers [171].

Figure 29 Low Free Testosterone Levels Found in Women of All Ages With Reduced or Absent Libido

$P < 0.05$ in all groups. Data adapted from reference 171.

Recent studies have shown that there is a correlation between serum androgen levels and decreased libido in young women with decreased libido and absent sexual desire [171,175]. This is illustrated in Figures 28 and 29. Furthermore, other work has confirmed this by showing that sexual dysfunction and low libido occurred most frequently in both pre and postmenopausal women with low androgen levels, and that replacement of DHEA(S) using either 50 mg or 100 mg restored sexual function [176]. Sexual function in this context consists of sexual distress, sexual desire, arousal,

lubrication satisfaction, and orgasm. Sexual dysfunction is characterized by alterations in sexual desire and the psychological and physiological changes associated with sexual response [177].

The simplified steroid synthesis pathway shown in Figure 2 illustrates that both DHEA(S) and testosterone are derived from the precursor 17-hydroxypregnenolone by the action of 17, 20 lyase. As mentioned earlier, it may be that senescence is associated with a decline in activity of this hormone resulting in low levels of both DHEA(S) and testosterone and thus a decline in sexual function [42].

Gonadal derived hormones play a part in the sexual function of premenopausal women, but how this is done is not clear. As levels of ovarian derived androgens vary with the menstrual cycle in women, indices of sexual function (sexual activity, sexual arousal and sexual fantasy) also vary [178]. Levels of androgens are highest during the middle of the cycle, when fertility is highest. Thus there is evolutionary pressure to be most sexually active at the time when the chance of conception is highest. This relationship between hormonal levels and sexual function is not seen with the varying level of estrogens.

Conflicting evidence on the effects of estrogen replacement on the indices of sexual function have been found in postmenopausal women [179,180]. Studies have been done involving surgically castrated women looking at the effects of estrogens given together with androgens compared to either estrogens alone or placebo. These studies have shown that 'sexual motivation' (i.e. sexual desire, sexual fantasies, sexual arousal, frequency of sexual encounters and sexual gratification) increases significantly in those women given the estrogen and testosterone combination [181,182].

Johannsson et al gave either 20 mg or 30 mg of DHEA for six months to women of ages between 25 to 65 years with hypopituitarism [183]. This group showed that at the higher dose indices of sexual function improved by 50% compared with no improvement in those taking the lower dose [183]. The higher DHEA dose was given to the women less than 45 years old. However, whilst there was a trend, this improvement was not statistically significant as there were a few subjects on the placebo arm who also showed an improvement.

The results from Johannsson et al were in contrast to a more recent study that looked at acute effects of a single 300 mg dose of DHEA to 16 sexually active postmenopausal women and compared the effects of mental and physical sexual arousal with placebo [184]. Whilst there were clear methodological differences between the studies, Hackbert et al showed a significantly greater mental ($p < 0.016$) and physical ($p < 0.036$) sexual arousal visual stimulation with erotic videos with DHEA vs. placebo. Physical effects were measured using measurements of vaginal pulse amplitude and vaginal blood flow. Both of these parameters showed a positive affect during the erotic video across drug conditions. Vaginal pulse amplitude and vaginal blood volume demonstrated a significant increase ($p < 0.001$) between neutral and erotic film segments within both conditions (DHEA and placebo) but did not differentiate drug conditions. However, work done by the same group in premenopausal women given 300 mg of DHEA 60 minutes prior to exposure to an erotic film segment showed that DHEA had no effect on sexual response [185].

A more recent study looking at 39 hypoadrenal women aged between 24 and 70 randomized to either 25 mg of DHEA or placebo for 9 months showed no

statistically significant differences in any of the sexuality related measurements using a validated questionnaire [126].

No work looking at the relationship between IGF 1 levels in adrenalectomized / hypoadrenal individuals and sexual function has previously been done. There are studies looking at the involvement of IGF 1 in women with hyperandrogenism. These show that women in whom the serum free testosterone and free androgen index normalize after gonadotrophin suppression have most of their excess androgens derived from the ovary. This is in contrast to hyperandrogenic women in whom the androgens are derived from adrenal precursors. These women do not normalize their androgen levels after gonadotrophin suppression. It is in the group who derive their androgens from adrenal precursors that serum IGF 1 levels are also raised with normal levels in the group who derive their androgens predominantly from the ovaries [186].

Hyperandrogenic women in whom the ovary was the primary source of the excess androgens, had lowered IGF BP 1 and IGF BP 3 levels [187], with the hyperandrogenism persisting after puberty [188]. These decreases in IGFBP 1 and BP 3 may be responsible for the enhancement of IGF 1 bioavailability which may be responsible for the increased ovarian and adrenal androgen secretion [187,189].

Our study showed a significant increase in IGF 1 with no change in levels of its main binding protein, IGF BP 3. Our study is in contrast to previous work in aging men that showed an increase in IGF 1 levels by growth hormone treatment led to improvement in mood and wellbeing [190].

Type of Subject	Age (years)	Type of Study	Dose (mg/day)	Duration on DHEA	Sex and Number	Summary of Results	Reference
Healthy women with decreased libido	24 to 78	O	N/A	N/A	F (105)	70% of subjects had low DHEA levels	Guay et al [171]
Healthy women with decreased libido	31 to 48	OL	50 to 100	Not given (minimum 8 weeks)	F (8)	6 of 8 women regained normal sexual desire	Guay et al [176]
Healthy premenopau-sal women	24 to 34	P, R, C	300	Single dose	F (12)	No effect on sexual arousal	Meston et al [185]
Healthy postmenopa-usal women	51 to 68	P, R, C	300	Single dose	F (16)	Increased sexual arousal	Hackbert et al [184]
Women with sexual dysfunction	Mean 43.5	OL	50	4 ($\pm$) 2 months	F (113)	Improvement in sexual wellbeing	Munarriz et al [169]
Hypoadrenal	23 to 59	R, C	50	4 months	F (24)	Improvement in sexual wellbeing	Arlt et al [20]
Hypoadrenal	25 to 65	R (OL)	30 (<45 years old), 20 ($\geq$ 45 years old)	6 months	F (38)	Non significant trend towards improvement in the 30 mg group only	Johannsson et al [183]
Healthy	40 to 70	P, R, C	50	3 months	M (13) F (17)	No improvement in sexual function	Morales et al [57]
Hypoadrenal	24 to 70	P, R	25	9 months	F (39)	No improvement in sexual function	Løvås et al [126]
Hypoadrenal	26 to 69	P, R, C	50	3 months	M (15) F (24)	No improvement in sexual function	Hunt et al [21]

Table 6 Summary of Human Studies Looking at the Effect of DHEA on Sexual Functioning

O = Observational, OL = open label, P = Placebo controlled, R = Randomized trial, C = Cross-over design, N/A = Not applicable

Assumptions, Limitations and Criticisms of the Study

Our assumption was that the actual population that we sampled was representative of hypoadrenal women in general. The limitations of our actual sample were that it was limited to women seen at Mayo Clinic in the 5 years previous to the start of recruitment (n = 23) or women who were subscribed to internet self help groups who had never been previously seen at Mayo Clinic (n = 10). Thus there is an element of respondent or volunteer bias. This latter category assumed some degree of computer literacy and so may not have been representative of the hypoadrenal population in general, although this is possibly now less likely in North America. One advantage of internet recruitment is that the volunteers are not limited to subjects seen at a tertiary referral centre. The median distance travelled to the study centre was 286 miles (interquartile range = 59.5 to 358.5 miles). This wide geographical distribution of volunteers may decreases the generalizability of the results as it suggests that many of those seen here were tertiary referrals, and thus our results are open to referral bias. However, as a substantial minority of our patients were not patients of Mayo Clinic, it is likely that our results may be more applicable to a wider population. It is accepted, however, that these results are only directly applicable to Caucasian women with hypoadrenalism due to Addison's disease or bilateral adrenalectomy. Whether these results can be applied to other categories of hypoadrenal subjects, e.g. men or non-Caucasians, remains to be determined. It is also possible that those hypoadrenal women seen at Mayo in the 5 years prior to the start of the study who did not respond to the first two sets of invitation letters to participate in the study were in some way systematically different to those who did respond. A similar bias may have been

present when considering those women who answered the internet advertisement. There was no method to minimize or evaluate this potential source of bias in this study. Whether a difference in adrenal hormonal status makes a difference to motivation is unknown.

It has been assumed that the cortisol/DHEA ratio is important in understanding the neuroprotective effects of DHEA(S). There has been some work showing that there are higher ratios in depressed individuals and in those in who recovery from major depression was delayed [191], but this work remains to be confirmed in larger trials.

There is evidence to show that DHEA(S) is produced within the brain in the glial cells. It is for this reason that they are termed neurosteroids [192]. Also there is evidence to show that the levels of serum DHEA do not correlate but DHEAS levels do, with those found in cerebrospinal fluid with much variation in the levels [193]. In this group of subjects who were undergoing insertion of ventriculo - peritoneal or lumbar - peritoneal shunts, levels were 5.4% ± 0.03% of that in plasma of adults ($r = 0.65$, $p < 0.01$) but in juveniles there was no correlation ($r = 0.62$, $p > 0.05$).

For DHEAS, levels were only 0.15% ± 0.79 of that seen in plasma, however there was a correlation in both adults ($r = 0.62$, $p < 0.01$) and juveniles ($r = 0.88$, $p < 0.01$) between csf and plasma.

Due to the much higher abundance of DHEAS in serum compared with that of DHEA (over 130 fold), there was only a 2.9 fold increase in csf levels making the DHEA/DHEAS ratio 0.01 in serum, but 0.52 in the csf. The reason for the relative differences in blood and csf may be the fact that DHEA is largely conjugated to fatty

acids in serum which may limit it's transport into csf [194]. DHEAS levels may be low due to its poor transfer across the blood brain barrier due to its lipophobic nature (levels rise in conditions where the blood brain barrier integrity is breached e.g. Guillain-Barre Syndrome or carcinomatous meningitis compared to healthy controls [192,195]). But despite this, levels are still 5 times that of DHEA. The time taken for equilibration between blood and csf was not taken into account in this study and work on this has not been previously reported. The assumption was made that csf levels of DHEA(S) would have reached steady state within the time period of the study and in addition, would have had time to exert any effect on the psychological aspects under consideration.

Levels of csf DHEA(S) in elderly subjects reflect the reduction in serum levels compared with young individuals, with there being about 50% reduction in 60 to 85 year olds compared to 19 to 40 year olds (corresponding serum levels are about one third).

Cortisol however shows a strong correlation between serum and csf, even in those on exogenous cortisol. As serum cortisol essentially remains stable throughout life and does not show the decline seen in DHEA(S) levels, the serum cortisol/DHEA(S) ratio goes up. As in the study by Guazzo et al the rise in csf cortisol with age and the relative stability of DHEA(S) meant the cortisol/csf ratio in those individuals undergoing cranial surgery was raised [193]. Looking at the cortisol/DHEA(S) ratio of csf has also been done in normal healthy women [196]. This showed no correlation between aging and csf DHEA(S) levels – i.e. whilst the serum levels fell with aging, the csf levels remained the same. One theory for this is the increasing 'leakiness' of

the blood brain barrier. In addition, however there was a rise in csf cortisol leading to a rise in the cortisol/DHEA(S) ration as well as a decline in the potentially neuroprotective estrodiol.

Different glucocorticoid replacement regimes can have effects on both subjective and objective measures of mood and well being [76]. Whilst efforts were made to standardize subjects onto one regime – hydrocortisone 10 mg on rising, 10 mg at 4 pm and 5 mg at bedtime it was not possible to do this with all subjects. This was because some subjects were unwilling to change from their current regime or that they were already on a lower dose of hydrocortisone. In addition, some subjects were on prednisolone (prednisone) the equivalent dose of hydrocortisone was lower than 10 mg / 10 mg / 5 mg. This is a potential confounding effect when interpreting the psychological evaluations.

During the recruitment phase of the study the Women's Health Initiative (WHI) was published which suggested that postmenopausal women who had a uterus and were on combined estrogens and progestins were at a slightly increased risk of developing cancers of the breast and bowel [197]. One of the inclusion criteria for the study was that subjects had steady estrogen status for 6 months prior to entering the study. The WHI made this very difficult and so recruitment included subjects who may have stopped estrogens only a few weeks prior to joining the study. As estrogens levels are known to affect cognitive performance [198] this is also a potential confounding variable when considering the psychological evaluations. One subject began taking estrogen replacement at 9 weeks into the first arm of the trial on the

advice of her gynecologist. This was not discussed with the primary investigator, and her data is not included in the final analysis of the psychometric tests.

Another subject was excluded from the final analysis for the psychometric testing. She was found to have been recruited despite a protocol violation. She had not been on a steady dose of her antidepressant drugs (a selective serotonin reuptake inhibitor). She had stopped it a few weeks prior to joining the study, and thus had not had a steady dose for over six months. During the study she became depressed, and her drug was restarted. At the initial psychometric evaluation she had a raised Beck score (17), and at her second and third evaluations these had continued to rise (23 and 33 respectively). It is therefore difficult to know what effect, if any was due to the reintroduction of the antidepressant, or due to DHEA/ placebo. Her results are not included in the final psychometric analysis.

One subject had her 11week psychometric tests within a week of the first anniversary of her parents' death. The subject's parents had died within a few days of each other from old age. However, at the time of the psychometric tests, this was not apparent and was only told to the primary investigator one week after the end of the 12-week visit. Her data is included in the analyses.

One subject experienced the unexpected death of her mother 2 weeks prior to her initial 11-week visit. As the Beck depression index scores individuals as how they felt in the previous two weeks, it made interpretation difficult, as the results showed her level of depression had increased from her initial visit (8 to 15). Her data is included in the analyses.

Two volunteers had previously been on DHEA at various doses. Both had stopped at least 6 months prior to starting the study, however, it is possible that these women had a 'memory' effect and knew what effects to look for when on the DHEA.

Hypoadrenal women have been shown to have virtually no circulating androgens 5 years after the menopause [199]. The validity of the findings of our study would have been increased had we recruited only postmenopausal, hypoadrenal women, as the ovaries would not have been producing any endogenous androgens.

For the statistical assumptions it is clear that subjects were not randomly selected as they were mainly from the Mayo Clinic records. However, this study included a wide range of ages and the results should therefore be applicable to hypoadrenal women over 18 years old and are likely to be representative of the female hypoadrenal population as a whole. Whether these results can be applied to other groups, such as males or those with low DHEA levels with normally functioning adrenal glands remains to be seen.

There were a few potential confounders for interpretation of the results of the psychometric tests. It was for this reason that a total of 33 volunteers were recruited, so that unbiased psychometric test results were available on 26 subjects. Of the subjects in whom the psychometric testing was invalid, one was unable to speak or read much English. Even with the aid of an interpreter, her psychological testing results were questionable. The interpreter had no experience with psychometric testing and had to be briefed as to some of the things to look out for. The understanding of the subject's language by the psychometrist was very limited, so to insure accuracy and reliability against the interpreter's calculations was difficult (i.e.

AVLT). The subject was uncomfortable with having a male interpreter assist her in translating the "Changes in Sexual Functioning Questionnaire". She tried her best (her understanding was questionable), and left 3 items blank. The AVLT delay was longer than 30 minutes. On the 2nd list of the AVLT - the word "Ranger" has no equivalent translation in Italian. The interpreter and psychologist used the word "Policeman" or "Guardia" in its place. How this change effects the validity of the test is unknown. The subject had a difficult time understanding the scales or continuums. She would reverse their value assignment from question to question.

Further possible confounding is due to the fact that 6 of the subjects recruited were recruited form 2 internet self help groups (http://healinglight.com/cgi-bin/addisons.pl, and http://groups.yahoo.com/group/Addisons_Disease/). Whist the participants did not know each other individually, many had shared experiences and thought with others on these websites. This makes the individuals not truly 'independent' of each other. In addition during the course of the study, these individuals often communicated with each other on these self-help websites.

There has been discussion about the validity of conducting a cross over study when psychological outcomes are being assessed, as there is a risk of unblinding [200]. There is also the difficulty regarding concerns about sample size. However, with the single centre, cross over design the inherent variability of the psychological results are reduced and thus the sample size can be smaller when compared to either multicentre studies, or parallel group studies.

Further anecdotal evidence for the potential psychological effects of DHEA came from several of the subjects who described a variety of withdrawal effects when

coming off DHEA. These were usually described as ‘feeling down’ (one subject lost her job as a result of continuous crying shortly after stopping the drug). Others felt that their skin became very dry, others felt very tired and easily fatigued. Further work to formally assess this should be done using the questionnaires to assess mood and well being after drug withdrawal.

Adverse Effects and Potential Limitations of DHEA Use

Adverse effects were common in most studies, and were minor in nature. These were usually in women and were due to the androgenic effects of the DHEA metabolites. In this study, all side effects were noted anecdotally. There were no consistent findings. As in the current study, the most common adverse effects previously reported were an increased skin sebum production leading to perceived 'greasiness' and acne [72]. However, many women have previously reported that this change is beneficial and that prior to DHEA replacement their skin was excessively dry. This effect has been reversible when the DHEA was withdrawn.

Of greater concern, are the reports of mild elevations in serum transaminases. These occur within a few weeks of starting the DHEA. These increases have not led to any cases of subjects having to withdraw from a study. In addition, effects have either been reversible when the drug has been stopped, or have become normal after a few weeks on the drug [20]. In our study, one subject had a rise in Alanine Transaminase to 139 U/l (reference range 9 – 29 U/l) after her 12 weeks on DHEA. This returned to normal within 2 weeks of stopping the drug.

Nonsignificant rises in hemoglobin and hematocrit have been reported in some trials, possibly due to the androgenic effects of DHEA metabolites [183]. We did not find such an increase in either hemoglobin or hematocrit.

Other, milder adverse effects include increase in perspiration and body odour [73,126,183]. An increase in body hair – especially facial, axillary and pubic hair [20,21,183]. Rarely, hair loss has also been reported [20].

Other side effects include abdominal pain, intermenstrual bleeding, fatigue, insomnia, skin rash, weight gain, and breast tenderness [72,169]. These side effects occurred at higher doses of DHEA (100 mg and 200 mg). All of these effects were transitory and were reversible on withdrawal of the drug. None of these side effects were observed in our study.

There are more serious potential risks with the use of DHEA. While there are several rodent models showing that the use of DHEA prevents tumourigenesis,[201] the use of suprapharmacological doses of DHEA also has resulted in an increase in hepatocellular carcinoma [202]. Because of the conversion of DHEA into androgens and estrogens, use of supplemental DHEA in individuals with a history of sex hormone dependent malignancy such as prostate, breast or endometrial cancer remains a valid concern. This issue has yet to be fully addressed in long term human studies.

Availability of DHEA Within the United States

DHEA in dietary supplements is synthetic, manufactured from plant chemicals found in soybeans and wild yam. DHEA has been banned by the International Olympic Committee because of its conversion to sex hormones, and so be used as a drug of abuse. In the USA, the Food and Drug Administration also banned the substance until the passage of the Dietary and Supplement Health and Education Act of 1994, when this ruling was overturned. DHEA is now freely available in pharmacies and health food shops, where it is classed as a food supplement. This is despite the fact that DHEA is not a food, does not naturally appear in the human food chain, and no foodstuff can carry out the physiological role of DHEA. It can be sold directly to the public as long as no claims are made about therapeutic efficacy. In the USA food supplements are not required to undergo strict safety and efficacy testing and as a result in these over-the-counter products, there are problems with quality control [203]. These authors showed that the quantity of DHEA from different manufacturers in a variety of different doses, varied from 0% to 150% of what the label claimed was in the product. One further private company has reported quality control on commercially available DHEA (http://www.consumerlab.com/results/dhea.asp). This company found that 3 of the 17 products tested by them contained significantly less DHEA than claimed. One product boasting "Pharmaceutical Quality" and "...produced and packaged in [an] OTC approved facility" was found to have only 19% of the claimed DHEA. Another product was found to have only 79% of the claimed DHEA. Another product indicated that its raw material met United States Pharmacopoeia standards. Our

supply of DHEA was pharmaceutical grade and manufactured specifically for the study, however, once the study was completed, those subjects who felt better on the DHEA who wanted to continue on it, were advised to purchase it commercially. They were, however, warned of the findings quoted above.

In an attempt to reduce the potential abuse of DHEA, a bill has recently been put before the US House of Representatives that aims to restrict the over-the-counter sale of DHEA and other androgenic steroid precursors [204]. How this will effect those people who may derive benefit from DHEA, such as hypoadrenal and elderly subjects, remains to be determined.

Potential Future Studies

The study could be repeated with only hypoadrenal women who were at least 5 years past the menopause to ensure that any circulating androgens present during the study would be due to administered DHEA(S) only.

Looking at csf cortisol/DHEA(S) levels and correlating this with psychiatric conditions.

Looking at the effect of DHEA(S) replacement in adrenalectomized / hypoadrenal men.

In vivo and in vitro studies of mitochondrial function studies in a variety of tissues with DHEA(S) replacement assessing prevention of radical oxygen species damage.

Longer term studies of DHEA(S) replacement, looking at C – Reactive Protein, cardiovascular outcomes, etc.

One of the reasons for the failure to improve insulin sensitivity is that DHEA is a precursor to both estrogens – which are known to improve insulin sensitivity and androgens – which are known to exacerbate insulin resistance. A further test may be to infuse or give DHEA orally but at the same time give an androgen blocker to see if the beneficial effects of DHEA are being masked by the androgens.

Looking at the effects of different glucocorticoid replacement regimes and the possible reasons for differences seen. It may be the rates of absorption of oral cortisone acetate and hydrocortisone are different leading to a delay in cortisol clearance [78,205]. Alternatively, defective 11β-hydroxysteroid dehydrogenase reductase

activity has been described [206]. This enzyme is responsible for the conversion of cortisone to cortisol and may explain treatment failure in some cases.

In August 2002 Genelabs Inc in California were granted FDA approval for a New Drug Application on a compound (Prestara™) that contains prasterone, a synthetic form of DHEA as its active ingredient. Thy had previously carried out several studies looking at the effects of DHEA in patients with systemic lupus erythematosus that had shown beneficial effects in this condition [72,207,208]. This, or similar products could assess effects of DHEA(S) in other conditions.

As two of the women had previously been on DHEA it may have been more appropriate to use DHEA naïve individuals.

Summary and Conclusions

In summary we have found that 50 mg of DHEA given once daily to hypoadrenal Caucasian women aged between 20 and 80 years standardized onto a single glucocorticoid had a measurable effect on general health perception, arousal and learning efficiency. It remains to be determined what the clinical impact of these small but statistically significant differences are. These results, together with the findings of others, suggest that DHEA replacement may have some appreciable effects on mood, memory and psychological wellbeing in hypoadrenal women, but further evaluation is needed before DHEA replacement can be routinely recommended in this population.

DHEA and DHEAS remain intriguing hormones. Their metabolites have a variety of effects in a number of physiological systems, and yet at present, little is known about the role of either DHEA or DHEAS in normal physiology. It has not yet been clearly identified if it is correct to classify aging as a DHEA 'deficient' state. In hypoadrenal subjects, DHEA deficiency has been associated with a lower quality of life. But it is clear that these hormones are not essential for life, as adrenalectomized or hypoadrenal subjects who have little or no circulating DHEA do not have shortened live spans [209].

This study has added to the tantalising evidence to support the use of DHEA in hypoadrenal subjects (Tables 5 and 6). The lay press has widely promoted the use of DHEA in normal healthy individuals, and bodybuilders promote its use as a method of increasing muscle mass. However, many of the claims made on the internet websites ('fountain of youth', 'prevents diabetes', 'prevents aging', 'boosts

the immune system', etc,) fail to mention that most of these studies were carried out either in vitro or in animals. These reports are further misleading as they also fail to state that the results were usually a response to highly suprapharmacological doses of DHEA. There is also concern regarding the degree of quality control of the substances currently marketed. Finally, there remain valid concerns about the use of DHEA in individuals with a history of sex hormone dependent malignancies. Larger scale human studies are needed to answer many of these intriguing questions.

Publications Resulting From This Research

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Dhatariya K. Is there a role for dehydroepiandrosterone replacement in the intensive care population? Intensive Care Medicine 2003;29(11):1877-1880.

Dhatariya K, Bigelow ML, Nair KS. The effects of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women. (Submitted for publication).

Dhatariya K, Smith GE, Nair KS. The effect of dehydroepiandrosterone replacement on mood, memory, well-being and sexual function in hypoadrenal women. (Submitted for publication).

Dhatariya K, Bigelow ML, Nair KS. The effect of dehydroepiandrosterone replacement on muscle strength and physiology in hypoadrenal women. (Submitted for publication).

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