Brief Report | April 01, 1999
Double-Blind Treatment of Major Depression With Dehydroepiandrosterone
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Am J Psychiatry 1999;156:646-649.
Article
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Abstract
OBJECTIVE: This study was designed to assess possible antidepressant effects of dehydroepiandrosterone (DHEA), an abundant adrenocortical hormone in humans. **METHOD:** Twenty-two patients with major depression, either medication-free or on stabilized antidepressant regimens, received either DHEA (maximum dose=90 mg/day) or placebo for 6 weeks in a double-blind manner and were rated at baseline and at the end of the 6 weeks with the Hamilton Depression Rating Scale. Patients previously stabilized with antidepressants had the study medication added to that regimen; others received DHEA or placebo alone. **RESULTS:** DHEA was associated with a significantly greater decrease in Hamilton depression scale ratings than was placebo. Five of the 11 patients treated with DHEA, compared with none of the 11 given placebo, showed a 50% decrease or greater in depressive symptoms. **CONCLUSIONS:** These results suggest that DHEA treatment may have significant antidepressant effects in some patients with major depression. Further, larger-scale trials are warranted.
Dehydroepiandrosterone (DHEA) is a major circulating corticosteroid in humans, but its physiological role is unclear. In addition to serving as a precursor to testosterone and estrogen, DHEA and its sulfated metabolite, DHEA-S, likely have important biological roles (1, 2) and may be involved in regulating mood and sense of well-being.
Open-label or single-blind treatment studies as early as 1952 noted that DHEA treatment improved mood, energy, confidence, interest, and activity levels in patients with "inadequate personality" or "emotional and constitutional immaturity" (3–6). In a 1994 double-blind trial, Morales et al. (7) demonstrated a significant DHEA-induced increase in sense of well-being in middle-aged and elderly healthy volunteers. Subsequently, our group presented open-label data showing that DHEA had antidepressant effects in patients with major depression and that antidepressant responses were directly correlated with treatment-induced increases in plasma DHEA and DHEA-S levels (8).
The current report presents data from what we believe is the first double-blind, placebo-controlled trial of DHEA’s antidepressant efficacy in major depression.

METHOD

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Twenty-two subjects with DSM-IV major depression (20 unipolar and two bipolar type II, depressed phase) participated in the study; written informed consent was obtained from all participants after complete description of the study. Subjects with rapid cycling or mixed bipolar disorder or seasonal affective disorder were excluded. Subjects were not the same as those who participated in our previous open-label trial (8). Twelve subjects were male, and 10 were female; six men and five women were randomly assigned to each drug condition. Subjects ranged in age

from 33 to 53 years (mean=44.0, SD=8.0); age did not significantly differ between the two groups.
All subjects had pre-study ratings of 16 or greater on the 17-item Hamilton Depression Rating Scale (9) (mean=19.9, SD=2.1) and either were medication-free or had been receiving stable doses of antidepressant medication for 2 or more months (mean=7.7 months, SD=9.7). Three subjects in the DHEA group and four subjects in the placebo group were medication-free. Before random assignment to the two groups, all subjects received single-blind placebo capsules for 1 week; those who showed an improvement of 20% or more in depression ratings (placebo responders) were not advanced to the randomization phase. One subject (not included among the 22 subjects in the study) was excluded on this basis. The remaining subjects were randomly assigned to receive either DHEA (N=11) or placebo (N=11) for 6 weeks in a double-blind manner. Study medication was dispensed in identical-appearing 30-mg capsules, and subjects were instructed to take 30 mg/day for the first 2 weeks, then 30 mg b.i.d. for 2 weeks, and then 30 mg t.i.d. for the final 2 weeks. For subjects on prestabilized antidepressant regimens, the study drug was added to that regimen, and no changes in the concurrent antidepressant medication were allowed during the study period. The 17-item Hamilton depression scale was used to rate depressive symptoms at the beginning of the double-blind phase (baseline) and at the end of week 6.
Data were analyzed by using two-factor (drug-condition-by-time) repeated measures analysis of variance. All probability values are for two-tailed tests. Treatment responders were characterized descriptively as those who improved at least 50% from baseline to the end of week 6 and who achieved an end-of-study Hamilton depression scale score of 10 or less.

RESULTS

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DHEA-treated subjects showed a significantly greater antidepressant response than did those who received placebo, as indicated by change in Hamilton depression scale ratings (group-by-time interaction: $F=5.21$, $df=1, 20$, $p<0.04$). The mean percentage change in Hamilton depression scale ratings in the DHEA group was 30.5% (SD=29.1), compared with 5.3% (SD=20.2) in the placebo group. Five of 11 DHEA-treated subjects were considered treatment responders, compared with none of 11 placebo-treated subjects. Subgroup analyses revealed no differential effect of sex (sex-by-drug-by-time interaction: $F=0.14$, n.s.) or of preexisting medication status (medication-free versus stabilized antidepressant regimen: $F=0.47$, n.s.). DHEA was well tolerated by all subjects, and none dropped out because of side effects.

DISCUSSION

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In this double-blind, placebo-controlled trial, DHEA had statistically significant antidepressant effects; nearly half of the DHEA-treated subjects showed clinically meaningful improvement (defined as treatment responders). This is noteworthy because the majority of subjects in this study were at least partially resistant to treatment with traditional antidepressant medication

alone. Although the number of subjects in this study was insufficient to compare DHEA's efficacy alone with its efficacy as an antidepressant adjunct, no consistent differences were apparent.

As in previous clinical studies (7, 8), the doses of DHEA used in the present study (up to 90 mg/day) were chosen to increase subjects' circulating DHEA and DHEA-S levels to the high end of the physiological range of healthy 20–30-year-old adults (the age at which DHEA and DHEA-S levels typically peak in humans). It is unknown if higher or lower doses would produce greater or lesser effects or if greater duration of treatment with DHEA would result in greater cumulative antidepressant effect.

The present results are consistent with the treatment studies we reviewed (3–8) as well as with anecdotal or open-label data from treatment trials in other patient groups, e.g., those with multiple sclerosis (10, 11) and systemic lupus erythematosus (12) and elderly patients with general illness (13, 14). In these studies, DHEA appeared to improve energy, stamina, libido, and sense of well-being. Two studies employing relatively brief trials of DHEA in different study groups, however, failed to note beneficial effects. Wolf et al. (15) failed to discern a strong mood effect of a brief (2-week) course of DHEA administration in healthy volunteers, and an older double-blind study of DHEA, given for 3 weeks to patients with "constitutional inferiority," "vulnerable personalities," or "depressive psychopathy," failed to note positive effects (16).

Epidemiologic data support a direct relationship between DHEA and DHEA-S levels and positive mood. For example, elderly women with nondetectable serum DHEA-S levels had higher depression ratings than did women with detectable levels (17), and low DHEA-S levels were significantly associated with depressive symptoms in a sample of elderly French women (18). In institutionalized elderly men and women, DHEA-S levels were lower in those being treated for depression (19), and low levels of DHEA and DHEA-S have been associated with higher ratings of perceived stress (20) and trait anxiety (21). Conversely, higher serum levels of DHEA and DHEA-S have been associated with greater amount, frequency, and enjoyment of leisure activities (22); higher "dominance" (23) and "expansive personality" (24) ratings; and greater "sensation-seeking" attributes (25). Nonetheless, the literature examining endogenous DHEA and DHEA-S levels in major depression is inconsistent, with reports of increased (26, 27), decreased (19, 28, 29), or unaltered (30, 31) levels. In one of these reports (26), imipramine treatment lowered urinary DHEA-S levels, but in another report (28), ECT increased DHEA-S levels. Two additional studies suggested that the ratio of DHEA and DHEA-S to cortisol may more accurately discriminate depressed from nondepressed individuals, with lower ratios seen in those who were depressed (32, 33).

Mechanisms by which DHEA might have mood-elevating or antidepressant effects remain unclear, but several intriguing possibilities exist. In addition to being partially metabolized to testosterone and estrogen (both of which may have mood effects of their own), DHEA may modulate the bioavailability of testosterone by means of allosteric changes in albumin's affinity for testosterone (1). Further, DHEA and DHEA-S antagonize certain effects of cortisol (34, 35), stimulate or antagonize brain $GABA_A$ receptors (36), alter *N*-methyl-D-aspartic acid neurotransmission (37), bind to sigma receptors (38), and increase serotonin levels in certain brain regions (39).

Although DHEA treatment was well tolerated in this study, the full risk-to-benefit ratio, especially at higher doses and for longer periods of time, is unknown (40). Side effects reported with DHEA in the clinical literature include oily skin, acne, and, less frequently, hirsutism or voice deepening. Anecdotal reports have also suggested the possibility of DHEA-induced

overactivation, disinhibition, aggression, mania, or psychosis (6, 41). Additionally, animal studies have documented both pro- and antitumor effects of DHEA (e.g., references 42 and 43); the relevance of such preclinical data to human treatment is unknown (44, 45). Nonetheless, DHEA, by virtue of its metabolism to testosterone and estrogen, theoretically has the potential to exacerbate hormone-sensitive tumors, such as malignant melanoma or tumors of the breast, cervix, uterus, or prostate.

The present data, although based on a small number of subjects, suggest that DHEA, used alone or as an adjunct to antidepressants, has antidepressant effects in patients with major depression. This finding adds to the growing body of literature indicating that hormonal dysregulation may be causally related to depressive illness and that certain hormonal treatments can have antidepressant effects (46–49). Further, larger-scale controlled trials with DHEA are clearly warranted. Until more is learned about potential long-term risks, however, such trials should remain under medical supervision.

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