Dehydroepiandrosterone Monotherapy in Midlife-Onset Major and Minor Depression

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Context: Alternative and over-the-counter medicines have become increasingly popular choices for many patients who prefer not to take traditional antidepressants. The adrenal androgen and neurosteroid dehydroepiandrosterone (DHEA) is available as over-the-counter hormonal therapy and previously has been reported to have antidepressant-like effects.

Objective: To evaluate the efficacy of DHEA as a monotherapy treatment for midlife-onset depression.

Design: A double-blind, randomized, placebo-controlled, crossover treatment study was performed from January 4, 1996, through August 31, 2002.

Settings: The National Institute of Mental Health Midlife Outpatient Clinic in the National Institutes of Health Clinical Center, Bethesda, Md.

Patients: Men (n=23) and women (n=23) aged 45 to 65 years with midlife-onset major or minor depression participated in this study. None of the subjects received concurrent antidepressant medications.

Intervention: Six weeks of DHEA therapy, 90 mg/d for 3 weeks and 450 mg/d for 3 weeks, and 6 weeks of placebo.

Main Outcome Measures: The 17-Item Hamilton Depression Rating Scale and Center for Epidemiologic Studies Depression Scale. Additional measures included the Derogatis Interview for Sexual Functioning. Results were analyzed by means of repeated-measures analysis of variance and post hoc Bonferroni t tests.

Results: Six weeks of DHEA administration was associated with a significant improvement in the 17-Item Hamilton Depression Rating Scale and the Center for Epidemiologic Studies Depression Scale ratings compared with both baseline (P<.01) and 6 weeks of placebo treatment (P<.01). A 50% or greater reduction in baseline Hamilton Depression Rating Scale scores was observed in 23 subjects after DHEA and in 13 subjects after placebo treatments. Six weeks of DHEA treatment also was associated with significant improvements in Derogatis Interview for Sexual Functioning scores relative to baseline and placebo conditions.

Conclusion: We find DHEA to be an effective treatment for midlife-onset major and minor depression.

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Midlife in both men and women is characterized by a decline in the production of the adrenal androgen dehydroepiandrosterone (DHEA). An association between DHEA secretion and depression has been suggested by alterations in DHEA secretion (increased and decreased) in depressed patients compared with control subjects (at midlife and other ages) and by the mood-elevating effects of DHEA in depressed and nondepressed men and women. In the first randomized, controlled trial of DHEA in depression, Wolkowitz et al reported the beneficial effects of DHEA in a parallel-design study of 22 patients with major depression; however, only 3 of the subjects who received DHEA were not simultaneously receiving antidepressants. A preliminary report by Bloch et al suggested that DHEA also may be an effective monotherapy in midlife-onset depression. Predictors of a therapeutic response to DHEA administration have not been identified, with the exception that the magnitude of the increase in DHEA sulfate (DHEA-S) levels from baseline after treatment correlated with mood improvement. Although sex differences are reported in the pattern of DHEA metabolites (eg, increased testosterone [T] levels in women but not men), the existence of a dimorphism in treatment response is not clear. Because of the rela-
tively small sample in our preliminary report and the underrepresentation of women, we recruited twice as many subjects as in the original study (31 vs 15) to achieve similar-sized samples of men and women.

Herein we report the results of a randomized, placebo-controlled, double-blind, crossover trial in which men and women with midlife-onset depression were treated with 2 dosages of DHEA, 90 mg/d (low dosage) and 450 mg/d (high dosage), for 3 weeks each. Data from 15 subjects of the 46 described herein were published in our preliminary report.9

METHODS

PATIENT SELECTION

Men and women aged 40 to 65 years who reported the onset of depression within the past 5 years presented for evaluation at the National Institute of Mental Health (NIMH) Midlife Clinic, Bethesda, Md. All patients were symptom free for at least 2 years before the onset of the current episode of depression.

Patients undergoing screening for the study were physically healthy and were recruited through newspaper advertisements or through their personal physician. All subjects except 7 were free of medication, including antidepressants, hormones, and oral contraceptives, for a minimum of 4 months. No subject previously had taken DHEA therapy. Six subjects had previously received antidepressants for the current episode of depression; of these, 4 reported a partial response; 1 reported no response; and 1 discontinued her selective serotonin reuptake inhibitor therapy because of adverse effects. The 4 partial responders wanted an alternative therapy for their depression. As described in the previous report,1 the subjects' eligibility for the study was determined during a 6-week screening period (4 biweekly clinic visits), which included a psychiatric evaluation and a complete medical workup. Exclusion criteria included symptoms of prostatism; family history of premenopausal breast cancer, bilateral breast cancer, or multiple family members with breast cancer; systemic diseases; abnormal laboratory results; and abnormal mammogram or gynecological examination findings.

A structured diagnostic interview was administered to all patients. To ensure the stability of symptom ratings, cross-sectional rating forms were administered during the 4 screening visits and included the Beck Depression Inventory13 and the section form. Enrollment began on an open-label basis with administration by their private physician, underwent monitoring for up to 1 year. Nine subjects underwent evaluation with the structured diagnostic interview, and 4 (the first 4 subjects), with the HDRS-17 only.

OUTCOME MEASURES

Primary outcome measures consisted of 2 of the most commonly used standardized depression rating scales in depression treatment studies11 and investigations of midlife and perimenopausal depression,10,11 ie, the HDRS-17 and the Center for Epidemiologic Studies Depression Scale.20 Additional outcome measures included the following: (1) the Beck Depression Inventory11, (2) the modified Cornell Dysthymia Scale,21 and (3) the modified Derogatis Interview for Sexual Functioning (DISF),22 a self-report measure of sexual functioning that consists of 3 subscales measuring levels of sexual fantasy, sexual arousal, sexual activity, quality of orgasm, and sexual drive and the quality of the sexual relationship (separate forms exist for men and women). In addition, we used the unidimensional measures of depression that were used by Bech et al23 and Faries et al,13 including items selected from the original HDRS-17 and reported to be more sensitive to identifying differences between drug and placebo in pharmacological trials of depression.

Blood samples for DHEA and its sulfated metabolite DHEA-S were drawn before 10 AM at the beginning and at the 3- and 6-week visits of both treatment phases, whereas samples for total T, free T, sex hormone–binding globulin, estradiol, androstenedione, and 3α-androstenediol glucuronide were drawn only at baseline and at the end (week 6) of each treatment phase.

STATISTICAL ANALYSIS

We performed the statistical analysis using the Systat 10.0 (SPSS Inc, Chicago, Ill) and the NCSS (Number Cruncher Statistical Systems, Kaysville, Utah) software programs. Based on predicted group differences,4 power analyses (NCSS/PASS; Number Cruncher Statistical Systems) determined appropriate sample sizes of 19 (for α = .05) and 28 (for α = .01) with 80% power for the outcome measures. With an estimated 20% attrition rate, it was estimated that approximately 26 subjects should be enrolled to yield the proper sample size of completers. Effects of DHEA and placebo on outcome measures were determined by analysis of variance with repeated measures (ANOVA-R). The within-subjects variable was treatment condition (baseline vs DHEA vs placebo), and the between-subjects variable was sex. Post hoc testing was performed with Bonferroni t tests. Response to treatment (DHEA vs placebo) was defined as a 50% reduction from baseline score in the HDRS-17 or the Center
A total of 115 women and 69 men underwent screening for this study (Figure 1). Fifty-two patients were randomized, 23 of 28 women and 23 of 24 men completed the trial. Characteristics of the 46 subjects who completed the study are listed in Table 1. Nineteen women and 9 men met criteria for major depression; all other subjects met criteria for minor depression. Sixteen women and 10 men reported a past depression. Baseline HDRS-17 scores did not differ between those receiving DHEA first compared with those receiving placebo first (13.7±3.6 vs 13.3±4.4, respectively; f<sup>2</sup>=0.3 [P=NS]).

The Structured Clinical Interview for DSM-IV-TR was administered, supplemented with the minor depression module form of the Schedule for Affective Disorders and Schizophrenia–Lifetime Version in the first 15 subjects; in the remaining subjects, we administered the SCID-IV, which included the module for DSM-IV minor depression. We reviewed the original SCID interviews in the first 15 men and women (published previously) who met criteria for dysthymia and determined that they would have also met criteria for DSM-IV minor depression. For consistency, the diagnoses of the previous subjects are reported as minor depressions, not dysthyrias.

All but 7 patients were medication free. One man received enalapril maleate (Merck & Co, Inc, Whitehouse Station, NJ), 25 mg/d, for borderline hypertension for 2 years before the onset of his depressive symptoms. Two women took stable doses of levothyroxine sodium (50 and 100 µg/d, for 3 and 20 years, respectively) for hypothyroidism, and 4 subjects (3 women and 1 man) received proton pump inhibitors for gastroesophageal reflux.

Outcome measures are described in Figure 2 and Table 2.

### Table 2

Treatement with DHEA significantly improved mood scores compared with baseline and placebo conditions on the HDRS-17 (F<sub>3,44</sub>=20.2 [P<.001]; DHEA vs baseline, P<.01; DHEA vs placebo, P<.001), the Center for Epidemiologic Studies Depression Scale (F<sub>3,50</sub>=11.2 [P<.001]; DHEA vs baseline, P<.01; DHEA vs placebo, P<.01), and the scales used by Bech et al and Fairley et al, whereas no significant effects were observed on these.
same scale scores during the placebo compared with baseline conditions (Table 2). Similarly, significant improvements were observed in the other outcome measures (Beck Depression Inventory and modified Cornell Dysthymia Scale), although the DHEA-placebo differences were less robust in these outcome measures. A nonsignificant trend for an effect of dosage of DHEA (90 vs 450 mg/d) was observed \(F_{2,88}=0.5\) \(P=.37\), reflecting significantly lower HDRS-17 scores after DHEA compared with baseline \(13.3\pm0.9\) vs \(7.5\pm1.2\, t_{122}=5.3\) \(P<.001\) but not after placebo \(13.5\pm0.8\) vs \(11.8\pm1.1\, t_{122}=0.5\) \(P=NS\). The HDRS-17 scores after DHEA were significantly lower than after placebo \(t_{64}=3.6\) \(P<.01\).

In the crossover study, 23 subjects (12 women and 11 men) had a 50% or greater decrease on their HDRS-17 scores after 6 weeks of DHEA treatment, compared with 13 subjects receiving placebo \(\chi^2=4.6\) \(P=.03\). Only 16 subjects (9 women and 7 men) met criteria for responders to DHEA after placebo treatment. Limiting the analysis of responders to only the first 6 weeks of treatment (parallel design), we observed a significantly greater number of responders after DHEA compared with placebo treatment \(\chi^2=6.2\) \(P=.01\), with 10 of the 22 subjects first receiving DHEA responding and only 3 of the 24 subjects first receiving placebo meeting the 50% reduction in HDRS-17 response criterion.

In the 29 subjects who received SCID interviews after completing each treatment, significantly fewer subjects receiving DHEA (8 subjects) than placebo (18) met diagnostic criteria for depression \(\chi^2=4.4\) \(P=.04\). After the first 6 weeks of treatment (parallel comparison), only 8 of 14 subjects receiving DHEA vs 14 of 15 receiving placebo met diagnostic criteria for depression (Fisher exact test, \(P<.04\)). Twelve (43%) of the 28 subjects with major depression were classified as responders compared with 11 (61%) of the 18 subjects with minor depression \(\chi^2=1.5\) \(P=.37\).
There were no significant main or interaction effects of a past major depression on HDRS-17 scores ($F_{1,44}=0.02$ [$P=.88$]; and $F_{2,88}=1.2$ [$P=.30$], respectively).

**RESULTS OF FOLLOW-UP STUDY**

Ten of the 13 patients who responded to DHEA and who elected to continue with an open-label trial of over-the-counter DHEA (dosage range, 25-50 mg/d) remained asymptomatic (ie, no SCID diagnosis or HDRS-17 score $<10$) (7 were followed up for 12 months; 3, for 6 months). The remaining 3 patients met SCID criteria for depression or had HDRS-17 scores greater than 16 (followed up for 2 weeks, 2 months, and 12 months). None complained of adverse effects, with the exception of 1 woman who experienced a moderate but tolerable increase in oily skin.

**BLOOD HORMONE LEVELS**

Plasma levels of DHEA, DHEA-S, androstenedione, and 3α-androstanediol glucuronide increased significantly after DHEA treatment in men and women compared with the baseline and placebo conditions (Table 3). There was no significant difference in levels of DHEA or DHEA-S between the placebo and baseline conditions or between the baseline and washout conditions. Total $T$ levels nonsignificantly increased in women and decreased in men during DHEA treatment compared with the baseline and placebo conditions. Free $T$ levels were increased after DHEA treatment relative to baseline and placebo conditions in women ($P<.01$) and to a lesser extent in men ($P=.05$). The increase in free $T$ levels after DHEA treatment represented a greater than 500% increase in women, but only a 17% increase in men relative to baseline. Finally, sex hormone-binding globulin levels decreased in women ($F_{2,88}=25.7$ [$P<.001$]; $t_{88}=7.9$ [$P<.01$]) but not significantly in men ($t_{88}=1.4$ [$P=.NS$]), and no significant changes in estradiol levels were observed in men or women.

**PREDICTORS OF RESPONSE**

The discriminant function analysis included 16 subjects who responded to DHEA but not placebo and 17 subjects who responded to neither treatment. None of the variables included in the analysis (ie, age, sex, reproductive status, baseline mood ratings, and blood hormone levels at baseline, after treatment, and change [before vs after DHEA treatment]) showed a significant effect that distinguished responders to DHEA from nonresponders. Finally, Pearson product moment correlations examining the relationship between differences in the HDRS-17 or the DISF scores before and after DHEA treatment and blood levels of DHEA, DHEA-S, and free $T$ were nonsignificant ($r=0.1-0.3$ [$P=.3$ to $>.99$]).

**COMMENT**

Complementary and alternative medicine is a multimillion dollar industry, reflecting a growing number of people who avoid traditional medications, including antidepressants. In addition, alternative medicines have potential as second- or third-line treatments for the 50% or more depressed men and women who are not responsive to first-line traditional treatments. Thus, con-
controlled evaluations of these potential therapeutic agents should be a public health priority.

We demonstrated 3 main findings. First, DHEA is an effective monotherapy for the treatment of both major and minor depression of moderate severity occurring at midlife in men and women. Second, DHEA treatment increased plasma free T levels in both men and women. Finally, despite initial suggestions of a sexual dimorphism in the therapeutic actions of DHEA, the response to DHEA did not differ between men and women.

We observed improvements in the primary outcome measures after DHEA treatment compared with both placebo and baseline conditions. The beneficial effects of DHEA compared with placebo were observed for both rating scale scores and the numbers of subjects meeting the 50% response criterion in the HDRS-17. The efficacy of DHEA also was confirmed in a subsample who, on the basis of structured interviews after each treatment, no longer met diagnostic criteria for depression after DHEA treatment. Our demonstration of the antidepressant efficacy of DHEA is similar to the findings of Wolkowitz et al and of Bloch et al, which is a preliminary report of the present study. In the study by Wolkowitz et al, 15 of 22 patients were simultaneously taking antidepressants; consequently, although the therapeutic efficacy of DHEA monotherapy was suggested, it remained to be documented.

A significant therapeutic effect of DHEA was observed in major and minor depression as well as in both men and women, and no significant interaction between these factors and clinical response was evident. The severity of major depressions in this study was at most moderate, and therefore we are unable to suggest a role for DHEA in severe major depression. Depression scores were significantly lower after 6 weeks of DHEA therapy compared with placebo and baseline conditions. The beneficial effects of a longer duration of DHEA treatment, in keeping with previous reports of antidepressant efficacy...
with DHEA at dosages substantially lower than 450 mg/d. Finally, the observed antidepressant effects of DHEA are consistent with reports of the beneficial effects of DHEA on mood in depressed patients with human immunodeficiency virus. The high dosage of DHEA that we administered is comparable to that used by Rabkin et al12 and considerably lower than the 1600 mg/d used by Mortola and Yen.31 Moreover, the subjects in the open-label follow-up study remained stable on relatively lower dosages of DHEA. Nonetheless, it is possible that lower dosages of DHEA would not have the same antidepressant effects as those we observed. The reported beneficial effects of DHEA on mood in other medical contexts are far less uniform. Some22,31 but not all34 studies of symptomatic women with adrenal insufficiency have reported a beneficial effect of DHEA on mood. Similarly in symptomatic perimenopausal and postmenopausal women, Morales et al9 but not Barnhart et al35 observed mood enhancement after DHEA treatment, and Arlt et al40 failed to observe mood improvement after DHEA administration in aging men with low plasma DHEA levels. In none of these studies was the presence of depressive syndromes confirmed; consequently, the severity, persistence, and placebo responsiveness of mood symptoms in these subjects may differ considerably from those in our depressed subjects.

Our use of a crossover trial could be confounded by the presence of carryover effects. We deliberately chose a crossover design to permit the identification of those subjects who responded to DHEA but not placebo to facilitate prediction of response specifically to DHEA (ie, uncomplicated by placebo response). After a 2-week washout (before crossover), DHEA and DHEA-S levels returned to those observed at baseline; however, there was a difference between HDRS-17 scores before crossover and those obtained at baseline. Thus, we confirmed our findings in the crossover design by restricting our analysis to the first 6 weeks of the trial (parallel design). We observed the identical pattern of results for individual outcome measures and the 50% response criterion as that observed in the crossover trial. Thus, we were able to demonstrate the efficacy of DHEA treatment in this depressed sample, and our findings were not significantly altered by carryover effects.

Treatment with DHEA increased blood levels of DHEA, DHEA-S, and free T in both men and women. Our findings that DHEA increases total and free T levels and decreases sex hormone–binding globulin levels in women and increases levels of the androgen metabolites androstenedione and 3α-androstenediol glucuronide in both sexes are consistent with several previous reports.7,11,32,33,35,37-41 A DHEA-related increase in total T levels in men is reported more variably, with some studies reporting an increase but most reporting no change.7,11,32,37,41 Only 1 study (our preliminary study findings by Bloch et al9) reported a decrease in total T levels in men after DHEA treatment.

In addition to improvements in mood, measures of libido showed significant improvements after DHEA. Similarly, improvement in libido after DHEA therapy was reported in some12,32,60 but not all studies of women with adrenal insufficiency or Addison disease and in depressed men and women with human immunodeficiency virus. In all reports, this improvement in libido was paralleled by improvement in well-being. In fact, no report describes libido as improving independent of mood symptoms. Finally, Johansson et al40 reported that the beneficial effects of DHEA on mood and libido correlated with blood androgen levels, a relationship not observed in this study.

We examined several factors for their ability to predict a response to DHEA. None of these measures significantly predicted response to DHEA as defined in this study. The failure of DHEA or DHEA-S levels to predict the beneficial effects of DHEA on mood is consistent with previous data by Rabkin et al12 in depressed men and women with human immunodeficiency virus, but not our earlier observations in a smaller sample or reports from Wolkowitz et al40 and Strous et al.24 Our inability to show a correlation between DHEA-S levels and therapeutic response may reflect the obscuring influence of peak levels of DHEA in some of our subjects. Our data suggest that the antidepressant effects of DHEA do not reflect the correction of a simple deficiency state of DHEA secretion in depression. It is possible that DHEA serves as some form of replacement therapy in that, despite ostensibly adequate levels, individual differences may exist in the level of DHEA that is required. Thus the benefits of DHEA could be secondary to restoring DHEA levels to each individual’s “normal” level. However, the absence of measured DHEA levels before the onset of each person’s depression prevents us from addressing this possibility further.

Our failure to find a relationship between DHEA levels and antidepressant response converges with inconsistent reports of lower DHEA levels in depression in suggesting that correction of a putative DHEA deficiency does not underlie the antidepressant efficacy of DHEA.1-5,44 As a neurosteroid, DHEA may act directly as a psychotropic agent. Although no specific DHEA receptor has been identified, DHEA actions may be mediated through the androgen receptor. Recent studies in mouse brain demonstrate that DHEA can increase the number and transcriptional activity of androgen receptors. It may also serve as a prohormone, metabolized at the tissue level or systemically into hormones with psychotropic effects. In the present study, DHEA treatment increased free T, androstenedione, and 3α-androstenediol glucuronide levels in men and women. Thus, it is possible that the effects of DHEA were mediated by increasing androgen levels. Free T has been implicated in mood and in the regulation of libido and cognition.8,7,54 However, although free T levels were uniformly increased in women, the effect of DHEA on free T levels in men was varied. Moreover, in neither sex were the observed clinical responses consistently associated with changes in any of the androgen levels measured. Theoretically, the antidepressant actions of DHEA could be mediated by estrogen receptors, because the dihydrotosterone (and possibly DHEA) metabolite 3α-androstan-3β,17β-diol is an important ligand for estrogen receptor-β.8,55 Finally, DHEA could influence the activity of several classic neurotransmitter systems or other physiological systems implicated in the mechanism of antidepressant action. Specifically, DHEA has been reported to be active in the γ-aminobutyric acid,
serotonin, N-methyl-d-aspartate (possibly mediated through sigma receptors), and noradrenergic systems. More recently, findings suggest the importance of neuroproliferation in the mechanism of antidepressant action, perhaps mediated through proliferative and antiapoptotic pathways in the central nervous system (eg, cyclic adenosine monophosphate–response element binding or Bcl-2 systems). Dehydroepiandrosterone has neuroprotective and proliferative effects. For example, DHEA stimulates neurogenesis and synapse spine formation in the rat hippocampus and prevents corticosterone-induced neuronal damage, however, opposite effects of DHEA-S also have been reported.

Despite the overall beneficial effects of DHEA, which were sustained in several patients during follow-up, we observed only a 50% response rate using standardized criteria. At present, there are no predictors of response, and with a 50% response rate one would obviously select more reliable first-line treatments for this condition. However, in the 50% of depressed outpatients who do not respond to first-line antidepressant treatment, or in those unwilling to take traditional antidepressants, DHEA may have a useful role in the treatment of mild to moderately severe midlife-onset major and minor depression. Treatment with DHEA was well tolerated, with signs and symptoms of increased T levels (ie, acne or oily skin) being the most common adverse effect and in our experience responsive to dosage adjustment. As a caution, the use of DHEA in the treatment of patients with antidepressant-resistant depression has not been determined, and the magnitude of the antidepressant effects of DHEA compared with those of traditional antidepressants needs to be empirically demonstrated. As a final caveat, the long-term effects of DHEA have not been fully documented. The potential to exacerbate or initiate hormone-responsive tumors exists, and those prescribing DHEA should familiarize themselves with the means to evaluate a patient for DHEA therapy and to monitor DHEA therapy appropriately. Androgenic adverse effects could occur with longer-term use of DHEA and, similarly, we cannot infer the lack of significant consequences of the long-term administration of DHEA. Finally, it is possible that the response to DHEA simply reflects the effects of T replacement, and future studies examining the antidepressant efficacy of the nonaromatizable androgen dihydrotestosterone may help determine whether the beneficial effects of DHEA on mood are mediated through the androgen receptor.

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