Dehydroepiandrosterone Monotherapy in Midlife-Onset Major and Minor Depression

Peter J. Schmidt, MD; Robert C. Daly, MD; Miki Bloch, MD; Mark J. Smith, MD, PhD; Merry A. Danaceau, RN; Linda Simpson St. Clair, RN; Jean H. Murphy, RN, MSN; Nazli Haq, MA; David R. Rubinow, MD

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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Author Affiliations: Behavioral Endocrinology Branch, National Institute of Mental Health, Rockville, Md (Drs Schmidt, Daly, Bloch, Smith, and Rubinow, and Mss Simpson St Clair, Murphy, and Haq); and Clinical Center Nursing Department, National Institutes of Health, Department of Health and Human Services, Bethesda, Md (Ms Danaceau).

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)[1-5] and by the mood-elevating effects of DHEA administration in depressed and nondepressed men and women.[6-9] In the first randomized, controlled trial of DHEA in depression, Wolkowitz et al[10] 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[9] 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.[9,10] Although sex differences are reported in the pattern of DHEA metabolites (eg, increased testosterone [T] levels in women but not men[7,11,12]), 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,[9] 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 Inventory[13] and the 17-item Hamilton Rating Scale for Depression (HDRS-17).[14] Patients met structured diagnostic criteria for dysthymia, minor depression, or major depression and had scores of at least 10 on the Beck Depression Inventory or the HDRS-17. However, subjects were excluded if they met criteria for major depression of greater than moderate severity (as indicated by the severity scale in the Structured Clinical Interview for *DSM-IV* [SCID-IV]), were suicidal, or required immediate treatment after clinical assessment.

This study was approved by the Intramural Review Board of the National Institute of Mental Health. All subjects provided oral and written informed consent before study participation.

STUDY DESIGN

A National Institutes of Health pharmacist who was not a study investigator randomly assigned subjects (random number table) into 1 of 2 groups defined by the order in which DHEA and placebo were administered. Each treatment phase lasted 6 weeks, with a 1- to 2-week washout before crossover (1 week in the first 15 patients and 2 weeks in the others). Patients were treated with DHEA (obtained from Diosynth Biotechnology, Chicago, Ill, and National Biochemicals Corporation, Twinsburg, Ohio), 30 mg 3 times a day for 3 weeks, followed by 150 mg 3 times a day for 3 weeks (total of 6 weeks). The length of placebo treatment also was 6 weeks. The DHEA and placebo were administered in identical capsules formulated by the National Institutes of Health Pharmacy, Bethesda. Women received a 10-day course of 5 mg of medroxyprogesterone acetate at the end of the trial to cause menses and shedding of possible endometrial growth stimulated by DHEA or its metabolites.

After 3 and 6 weeks of each treatment, subjects were seen in clinic, and outcome measures were obtained. Prescribing physicians, subjects, and all raters were blind to group assignment.

Thirteen subjects who were identified to be responders to DHEA during the trial and elected to continue DHEA therapy (on an open-label basis) with management by their private physicians, 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 studies[15] and investigations of midlife and perimenopausal depression,[16-19] ie, the HDRS-17 and the Center for Epidemiologic Studies Depression Scale.[20] Additional outcome measures included the following: (1) the Beck Depression Inventory,[13] (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 5 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 al[23] and Faries et al,[15] 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-androstanediol 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,[9] power analyses (NCSS/PASS; Number Cruncher Statistical Systems) determined appropriate sample sizes of 19 (for $\alpha = .05$) and 28 (for $\alpha = .01$) 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 or placebo) was defined as a 50% reduction from baseline score in the HDRS-17 or the Center
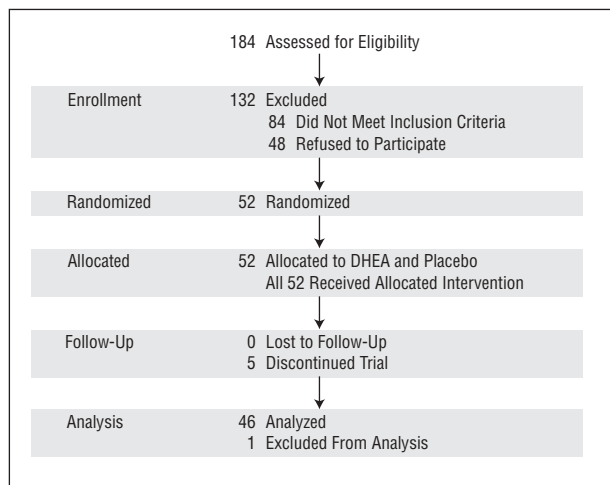
Figure 1. Flow diagram of the study population. Of the 5 women who discontinued the trial, 3 were randomized to receive dehydroepiandrosterone (DHEA) first and dropped out during the DHEA treatment phase. Severe acne and oily skin (reported previously[9]) developed in the first subject; a contact dermatitis believed to be unrelated to the medication developed in the second; and a transient elevation of liver function test results considered to be part of a preexisting intermittent liver condition in remission for several years (steatohepatitis) developed in the third. The remaining 2 women were randomized to placebo and dropped out during the placebo phase; one who discovered a breast lump at manual examination, and the other who became noncompliant after a family member was involved in the events of September 11, 2001. One man was randomized and received DHEA and placebo but was excluded from the analysis. He had no measurable increase in plasma DHEA or DHEA sulfate level and was admittedly noncompliant.

for Epidemiologic Studies Depression Scale score after 6 weeks of each treatment. The SCID interviews were not repeated as an outcome measure in the first sample (15 subjects). However, to determine the effects of DHEA and placebo on the syndrome-based measures, we readministered the SCID in 29 subjects in the second sample at the end of each treatment condition. Differences in the number of subjects meeting the response criteria or an SCID diagnosis of depression after DHEA and placebo were compared by separate χ^2 analyses or Fisher exact tests.

Potential order effects were examined by analyzing the HDRS-17 score by ANOVA-R, with the order of treatment (ie, DHEA first vs placebo first) as the between-subjects variable and treatment condition as the within-subjects variable. The presence of carryover effects was examined by comparing baseline and washout HDRS-17 scores before each treatment phase with a paired t test. In addition, an ANOVA-R of HDRS-17 scores was repeated comparing the effects of the first 6 weeks of the trial only (DHEA vs placebo) relative to baseline HDRS-17 scores (parallel design).

To evaluate the effects of the high and low dosages of DHEA, we performed ANOVA-R on HDRS-17 scores at baseline and after 3 and 6 weeks of DHEA and placebo treatment. In addition, we examined the potential effects of a past major depression on HDRS-17 scores with separate ANOVA-Rs, with history of depression as a between-subjects variable. Finally, we used the χ^2 test to examine the number of responders in men compared with women and in subjects with major depression compared with those with minor depression.

A stepwise forward discriminant function analysis was performed on variables (predominantly continuous) that were potentially related to treatment response, with the presence or absence of response to DHEA as the dependent variable. Subjects who respond to both placebo and active drug may account for 30% of a sample of depressed subjects, therefore complicating identification of measures that predict response to active drug alone. A crossover design allowed us to evaluate an individu-

al's response to both active and placebo treatments. In the discriminant function analysis, responders were defined as those subjects who met response criteria during DHEA but not placebo treatment, and nonresponders were those who did not respond to DHEA or to placebo treatment. Variables entered into the discriminant function included the following: age, sex, reproductive status, baseline mood ratings, and blood hormone levels at baseline, after treatment, and change (before vs after DHEA treatment). Three previous treatment studies observed a significant correlation between plasma levels of DHEA and/or DHEA-S and symptom ratings.[8,9,24] Thus, we specifically examined, with Pearson correlation coefficients, the relationship between posttreatment plasma DHEA-S levels and the differences in HDRS-17 scores between baseline and after 6 weeks of DHEA treatment. Finally, because of a reported relationship between plasma DHEA, DHEA-S, and free T levels and sexual desire, we examined possible associations between these measures in our sample with Pearson correlation coefficients. Data are reported as mean±SD unless otherwise indicated.

RESULTS

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; $t_{44}=0.3$ [$P=NS$]).

The Structured Clinical Interview for *DSM-R-III*[26] was administered, supplemented with the minor depression module form of the Schedule for Affective Disorders and Schizophrenia–Lifetime Version[27] in the first 15 subjects; in the remaining subjects, we administered the SCID-IV,[28] which included the module for *DSM-IV* minor depression. We reviewed the original SCID interviews in the first 15 men and women (published previously[9]) 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 dysthymias.

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**.

Treatment with DHEA significantly improved mood scores compared with baseline and placebo conditions on the HDRS-17 ($F_{2,88}=20.2$ [$P<.001$], DHEA vs baseline, $P<.01$; DHEA vs placebo, $P<.01$), the Center for Epidemiologic Studies Depression Scale ($F_{2,88}=11.2$ [$P<.001$]; DHEA vs baseline, $P<.01$; DHEA vs placebo, $P<.01$), and the scales used by Bech et al[23] and Faries et al,[15] whereas no significant effects were observed on these

	Women (n = 23)	Men (n = 23)
Age, y		
Mean (SD)	49.0 (4.4)	52.9 (6.6)
Range	41-57	42-63
Married	16 (70)	18 (78)
Current minor depression	4 (17)	14 (61)
No. of criterion symptoms met, mean (SD)	3.7 (0.6)	3.3 (0.7)
Current major depression	19 (83)	9 (39)
No. of criterion symptoms met, mean (SD)	6.1 (0.8)	5.9 (0.9)
History of affective disorder		
Minor depression	4 (17)	4 (17)
Major depression	12 (52)	6 (26)
BMI, mean (SD)	24.8 (3.1)	25.6 (4.2)
Weight, mean (SD), kg	68.2 (2.6)	82.2 (13.0)
Smoking history	2 (9)	0
Randomized to placebo first	13 (57)	11 (48)
Reproductive status†		
Postmenopausal	6 (26)	
Perimenopausal	5 (22)	
Premenopausal	12 (52)	
Plasma T level, ng/dL		
<300		4 (17)
≥300		19 (83)
Baseline HDRS-17 score, mean (SD)	14.3 (4.1)	12.7 (3.8)
Baseline CES-D score, mean (SD)	27.0 (7.8)	24.7 (6.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CES-D, Center for Epidemiologic Studies Depression Scale; HDRS-17, 17-Item Hamilton Depression Rating Scale; T, testosterone.

SI conversion factor: To convert T to nanomoles per liter, multiply by 0.0347.

*Unless otherwise indicated, data are expressed as number (percentage) of subjects.

†Reproductive status was characterized but was not a selection criterion. Women were grouped into premenopausal, perimenopausal, and postmenopausal phases of reproductive life according to the Stages of Reproductive Aging Workshop criteria.[25]

Figure 2. Six weeks of dehydroepiandrosterone (DHEA) treatment significantly improved 17-item Hamilton Depression Rating Scale (HDRS-17) scores compared with the baseline and placebo conditions ($F_{2,88}$=20.2 [P<.001]; DHEA vs baseline, P<.01; DHEA vs placebo, P<.01), whereas no significant effects were observed on HDRS-17 scale scores after 6 weeks of placebo compared with baseline conditions. Limit lines indicate standard error.

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 ($F_{2,86}$=2.9 [P=.06]), reflecting significantly lower HDRS-17 scores after 6 weeks of DHEA (7.5±5.4) compared with 3 weeks (9.6±5.3) (t_{129}=3.0 [P<.05]).

Treatment with DHEA also significantly improved total DISF scores ($F_{2,70}$=8.9 [P<.001], relative to baseline [P<.01] and placebo [P<.05]), whereas there was no significant improvement on DISF scores after placebo. Each subscale of the DISF showed a similar pattern of effects, with the exception of section 4 (quality of orgasm), which showed only a trend for an improvement during DHEA treatment.

There were no significant interactive effects of sex on any of the outcome measures.

We found no significant interaction between the effects of DHEA and order of drug administration
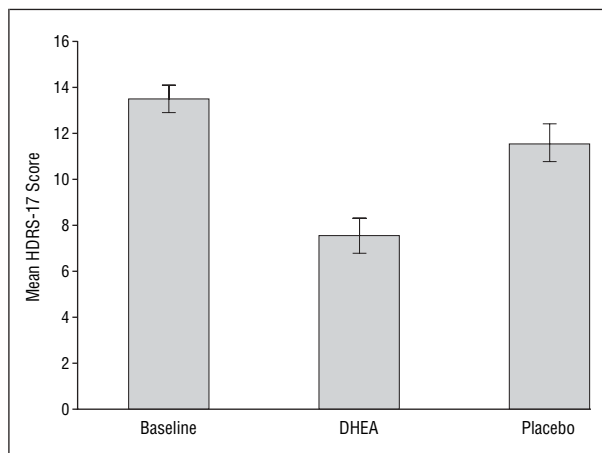
(hormone × group interaction, $F_{2,88}$=0.02 [P=.98]). Nonetheless, HDRS-17 scores at baseline were slightly, but significantly, higher compared with washout (before crossover) (13.5±4.0 at baseline compared with 10.5±4.2 after washout [paired t, P<.001]). Thus, to exclude the possibility that carryover effects confounded our results, we repeated the analysis of HDRS-17 scores using only baseline scores and those after the first 6 weeks of treatment (ie, DHEA or placebo, parallel design). A significant effect of drug condition ($F_{1,42}$=98.3 [P<.001]) reflected the significant decrease in HDRS-17 scores after DHEA compared with baseline (13.3±0.9 vs 7.5±1.2, t_{42}=5.3 [P<.01]) but not after placebo (13.5±0.8 vs 11.8±1.1, t_{42}=0.5 [P=NS]). The HDRS-17 scores after DHEA were significantly lower than after placebo (t_{84}=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 (χ^2=4.6 [P=.03]). Only 16 subjects (9 women and 7 men) met criteria for response during DHEA but not placebo treatment. Limiting the analysis of responders to only the first 6 weeks of the study (parallel design), we observed a significantly greater number of responders after DHEA compared with placebo treatment (χ^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 (χ^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 (χ^2=1.5 [P=.37]).

Table 2. Symptom Ratings at Baseline and After 6 Weeks of DHEA and Placebo Treatment

Rating Scale	Symptom Ratings, Mean (SD)			ANOVA, F (*P* Value)*
	Baseline	After 6-Week DHEA Treatment	After 6-Week Placebo Treatment	
HDRS-17†	13.5 (4.0)	7.5 (5.4)‡§	11.5 (5.9)	20.2 (<.001)
Bech et al[23]	6.6 (2.3)	4.0 (3.5)‡§	6.7 (4.0)	11.2 (<.001)
Faries et al[15]	6.6 (2.3)	3.5 (3.1)‡§	5.7 (3.8)	15.0 (<.001)
CES-D	25.8 (7.3)	16.6 (9.3)‡§	21.8 (11.5)	14.1 (<.001)
BDI	17.2 (5.1)	10.1 (6.3)‡‖	13.3 (6.6)	19.0 (<.001)
CDS	37.0 (9.2)	18.1 (12.5)‡§	27.2 (13.2)¶	31.6 (<.001)
DISF				
Fantasy	131.1 (98.8)	196.0 (105.6)§	157.8 (111.0)	5.4 (.006)
Arousal	136.3 (96.3)	198.5 (121.9)§	165.5 (103.8)	7.8 (.001)
Activity	101.0 (75.9)	152.6 (97.0)§	127.5 (86.9)	8.7 (<.001)
Orgasm	231.7 (177.2)	294.9 (182.3)‖	247.1 (186.6)	3.1 (.052)
Drive and relationship	126.5 (76.7)	179.9 (86.2)‡§	150.2 (82.2)	15.1 (<.001)
Total#	726.5 (455.1)	1021.8 (525.5)§**	848.1 (511.7)	8.9. (<.001)

Abbreviations: ANOVA, analysis of variance; BDI, Beck Depression Inventory; CDS, modified Cornell Dysthymia Scale; CES-D, Center for Epidemiologic Studies Depression Scale; DHEA, dehydroepiandrosterone; DISF, Derogatis Interview for Sexual Functioning; HDRS-17, 17-Item Hamilton Depression Rating Scale.

*For the ANOVA, *df* = 2,88, with the exception of DISF (*df* = 2,70) (baseline DISF ratings were not completed by 2 women and 7 men). *P* values were calculated using post hoc Bonferroni *t* tests.

†Indicates effect size with pooled standard deviation; DHEA vs placebo, d = 0.71.

‡*P*<.01, DHEA vs placebo.

§*P*<.01, DHEA vs baseline.

‖*P*<.05, DHEA vs baseline.

¶*P*<.01, placebo vs baseline.

#Because of rounding, total may not equal the sum of the individual subscale ratings.

**P*<.05, DHEA vs placebo.

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 repre-

sented 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,[29] 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.[30] Thus, con-

Table 3. Plasma Hormone Levels at Baseline and After 6 Weeks of DHEA and Placebo Treatment*

	Plasma Level, Mean (SD)			ANOVA-R $F_{2,88}$ (*P* Value)
	Baseline	**DHEA**	**Placebo**	
DHEA, ng/dL				
Men	411.8 (280.2)	1047.2 (709.1)†	377.7 (189.8)	74.0 (<.001)
Women	359.7 (169.9)	1058.5 (413.4)	437.4 (230.8)	
DHEA-S, µg/dL				
Men	162.7 (76.9)	864.8 (607.6)†	153.0 (55.6)	77.8 (<.001)‡
Women	85.9 (46.2)	646.5 (382.0)	81.3 (48.9)	
Total T, ng/dL				
Men	411.2 (175.3)	371.2 (146.8)	398.5 (153.9)	0.6 (.57)§
Women	21.1 (7.0)	57.9 (19.4)	20.8 (5.7)	
Free T, pg/mL				
Men	42.5 (31.7)	49.9 (35.8)	39.7 (26.9)	28.4 (<.001)‖
Women	2.3 (1.5)	14.1 (7.8)	2.4 (1.4)	
E_2, pg/mL				
Men	28.0 (9.4)	30.9 (8.9)	28.7 (7.9)	0.5 (.59)
Women	98.1 (91.4)	82.7 (79.8)	72.7 (82.5)	
Androstenedione, ng/dL				
Men	98.5 (29.3)	244.1 (124.6)†	85.6 (28.2)	67.9 (<.001)
Women	92.3 (30.3)	289.4 (135.9)	94.7 (31.6)	
3α-Androstanediol glucuronide, ng/dL				
Men	354.1 (186.6)	4184.3 (3844.6)†	402.4 (252.1)	60.6 (<.001)
Women	99.7 (80.0)	4130.6 (2900.0)	105.3 (115.5)	

Abbreviations: ANOVA-R, repeated-measures analysis of variance; DHEA, dehydroepiandrosterone; DHEA-S, DHEA sulfate; E_2, estradiol; T, testosterone.

SI conversion factors: To convert androstenedione to nanomoles per liter, multiply by 0.0349; DHEA to nanomoles per liter, multiply by 0.0347; DHEA-S to micromoles per liter, multiply by 0.027; E_2 to nanomoles per liter, multiply by 3.671; T to nanomoles per liter, multiply by 0.0347; free T to picomoles per liter, multiply by 3.47.

*Blood samples were assayed under batched conditions with samples from the same person run within the same batch at the Mayo Clinic Laboratories, Rochester, Minn (first 15 subjects for DHEA, DHEA-S, E_2, and T), and Endocrine Sciences, Calabasas Hills, Calif (all remaining samples), and interassay coefficients of variation (CV) in the range of the measured values were as follows (Mayo Clinic Laboratories CV in parentheses): DHEA = (7.0%) 8.4%; DHEA-S = (8.0%) 8.4%; E_2 = (10%) 9.2%; total and free T = (9.5%) 8.9%; androstenedione = 9.1%; and 3α-androstanediol glucuronide = 11.0%. The measures of total T, free T, and sex hormone–binding globulin were performed on serum samples, whereas the remaining hormone levels were measured in plasma.

†Values on DHEA were significantly different from baseline and placebo, by Bonferroni t_{88} (range, 9.8-11.3); P<.01.

‡For ANOVA-R effect of sex, $F_{1,44}$ = 4.9 (P=.03). Plasma DHEA-S levels were significantly higher in men compared with women across treatment condition).

§For ANOVA-R interaction of treatment with sex, $F_{2,88}$ = 7.6 (P = .001). Plasma T levels were nonsignificantly higher in women and lower in men during DHEA treatment compared with baseline (women, t_{88} = 2.2 [P<.10]; men, t_{88} = 2.4 [P<.10]) or placebo treatment (women, t_{88} = 2.2 [P<.10]; men, t_{88} = 1.6 [P = NS]).

‖For ANOVA-R interaction of treatment with sex, $F_{2,88}$ = 4.8 (P = .01). Plasma free T levels increased during DHEA treatment compared with baseline (women, t_{88} = 4.0 [P<.01]; men, t_{88} = 2.5 [P = .05]) and placebo treatment (women, t_{88} = 3.9 [P<.01]; men, t_{88} = 3.4 [P<.05]).

trolled 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[10] and of Bloch et al,[9] which is a preliminary report of the present study. In the study by Wolkow-

itz et al,[10] 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 3 weeks, but the drug × time interaction on ANOVA did not reach statistical significance (P=.06). Consequently, although this suggests that a longer duration of therapy or a larger dosage of DHEA (ie, 450 compared with 90 mg/d) is necessary for optimal antidepressant effects, our data cannot confirm the superior efficacy of the larger dosage of DHEA. However, posttreatment plasma levels of DHEA and DHEA-S did not predict symptom response. Thus, our findings probably reflect the effects of a longer duration of DHEA treatment, in keeping with previous reports[8,10,24] 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.[12] The high dosage of DHEA that we administered is comparable to that used by Rabkin et al[12] 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. Some[32,33] but not all[34] 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 al[7] but not Barnhart et al[35] observed mood enhancement after DHEA treatment, and Arlt et al[36] 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-androstanediol 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[38] but most reporting no change.[7,11,12,37,42,43] Only 1 study (our preliminary study findings by Bloch et al[9]) 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 some[12,32,40] but not all studies[33,34,36] of women with adrenal insufficiency or Addison disease and in de-

pressed 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, Johannsson et al[40] 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 are consistent with previous data by Rabkin et al[12] in depressed men and women with human immunodeficiency virus, but not our earlier observations in a smaller sample[9] or reports from Wolkowitz et al[10] 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,[45] 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[46] 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-androstanediol 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.[47-53] 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 dihydrotestosterone (and possibly DHEA) metabolite 5α-androstane-3β,17β-diol is an important ligand for estrogen receptor-β.[54] 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.[55-59] 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[60-62]; however, opposite effects of DHEA-S also have been reported.[63]

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,[30] 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.[64,65] 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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