ORIGINAL ARTICLE

Dehydroepiandrosterone Augmentation in the Management of Negative, Depressive, and Anxiety Symptoms in Schizophrenia

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Context: Negative symptoms of schizophrenia are a prominent feature of the illness, and frequently remain refractory to treatment. Dehydroepiandrosterone (DHEA), along with its sulfated form, DHEA-S, is an important circulating neurosteroid with several vital neurophysiological functions, including the regulation of neuronal excitability and function.

Objective: Since the administration of DHEA has demonstrated improvement in mood, sense of well-being, interest, activity, and energy in several subpopulations, we investigate the efficacy of DHEA in the management of the negative symptoms of schizophrenia.

Design: Thirty *DSM-IV*–diagnosed schizophrenic patients with prominent negative symptoms (inpatients in a large referral state hospital) were randomized to receive either DHEA or placebo in double-blind fashion, in addition to regular antipsychotic medication, dose-stabilized prior to study entry. The DHEA was titrated up to a dose of 100 mg in divided doses during 6 weeks.

Results: Results indicated significant improvement in negative symptoms ($P<.001$), as well as in depressive ($P<.05$) and anxiety ($P<.001$) symptoms in individuals receiving DHEA. This effect was especially noted in women. The improvement in negative symptoms was independent of improvement in depression. No differences were noted on the positive symptom subscale of the Positive and Negative Syndrome Scale (PANSS) or on the total PANSS score as compared with placebo. Subjects receiving DHEA demonstrated a significant increase in DHEA ($P<.05$) and DHEA-S ($P<.01$) plasma levels, without changes in cortisol levels. Increases in DHEA and plasma DHEA-S levels were correlated with improvement in negative symptoms ($P<.05$), but not with improvement in depressive and anxiety symptoms. No obvious adverse effects were experienced by participating subjects.

Conclusions: Our preliminary observations report for the first time in double-blind fashion the efficacy of DHEA augmentation in the management of negative, depressive, and anxiety symptoms of schizophrenia. The findings from this study raise important issues regarding the role of neurosteroids in general, and DHEA in particular, in the ongoing symptomatology and pharmacotherapy of schizophrenia.

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NEGATIVE SYMPTOMS, including avolition, anhedonia, amotivation, and alogia, in addition to the more treatment-responsive positive symptoms such as delusions and hallucinations, remain a prominent feature in many individuals with schizophrenia.[1] More recently, the introduction of atypical antipsychotic medication has provided additional hope in the management of negative symptoms[2]; however, success remains limited.

Dehydroepiandrosterone (DHEA) is a major circulating corticosteroid in humans and serves as a precursor for both androgenic and estrogenic steroids.[3,4] Its sulfated form (DHEA-S) is the most abundant steroid found in the body.[5,6] It is considered both a neurosteroid, being produced in the brain, as well as a neuroactive steroid, produced in the adrenals and having its effect on the brain.[5,7] In contrast to the more classically known but slower gene expression ("genomic") mechanisms of steroid activity, neuroactive steroids such as DHEA and DHEA-S are now known to regulate neuronal function by means of influence on neuronal excitability ("nongenomic" mechanisms occurring via membrane-bound, ligand-gated ion channel receptors).[8,9]

Interestingly, in humans, DHEA has demonstrated efficacy in the improvement of mood, with increased energy, interest, confidence, and activity levels in various populations.[10,11] More

Demographic Data of Participating Subjects Meeting Criteria for at Least 4 Weeks of Study Participation

Variable	DHEA Group	Control Group
No. of subjects	15	12
Mean (SD) age, y	38.1 (13.7)	36.6 (10.3)
Sex (M/F)	9/6	3/9
Schizophrenia subtype		
Paranoid	9	5
Disorganized	1	1
Undifferentiated	4	3
Residual	1	3
Mean (SD) duration of illness, mo	200.6 (133)	202.9 (121.7)
Mean (SD) current episode, mo	14.5 (21.7)	17.6 (24.3)
Antipsychotic medication		
Haloperidol	3	0
Fluphenazine	1	1
Zuclopenthixol	1	1
Risperidone	1	1
Olanzapine	5	5
Clozapine	4	3
Benzodiazepine medication	4	5
Anticholinergic medication	3	2

Abbreviation: DHEA, dehydroepiandrosterone.

specifically, DHEA has been shown to increase the sense of physical and psychological well-being in middle-aged and elderly individuals,[12] and in patients with systemic lupus erythematosus.[13] In addition, several studies have demonstrated the efficacy of DHEA in the management of both dysthymia and major depression.[14,15] These observations offer the intriguing possibility that the positive effects observed with DHEA administration may also extend to the management of negative symptoms in schizophrenia. Surprisingly, to our knowledge, this has yet to be tested in a double-blind fashion, despite the study observation in the early 1950s, prior to the advent of antipsychotic medication, of the positive effect of diandrone (dehydroisoandrosterone) in treating individuals with schizophrenia. In these few patients, improvement was noted with regard to "timidity, lack of social confidence, feelings of inferiority, apathy, vagueness, and rapport" as well as "improved reality contact and desire to engage in more appropriate social interactions."[16,17] These are features that very closely resonate with modern-day descriptions of the negative symptom cluster in schizophrenia.

The aim of the current study was to investigate the efficacy of DHEA in the improvement of negative symptoms in schizophrenia. Furthermore, previous studies investigating DHEA blood levels in psychosis have demonstrated low DHEA levels,[18,19] observed by some particularly in the morning[20]; higher DHEA-S levels in males[21]; as well as abnormal DHEA diurnal rhythms[22] and no differences in DHEA levels.[23] In addition, correlations between low serum DHEA levels and higher psychopathology ratings have been observed.[24] We therefore determine prestudy and poststudy plasma levels of DHEA and DHEA-S, and analyze any relationship between plasma levels and clinical response to DHEA administration.

METHODS

STUDY POPULATION

The study population consisted of in-patients with long-term schizophrenia (as defined by *DSM-IV* criteria) at the Beer Yaakov Mental Health Center (a large state referral institution in Beer Yaakov, Israel), all with illnesses of longer than 2 years' duration and between the ages of 18 and 70 years. Two board-certified psychiatrists verified patients' diagnoses arrived at by means of a structured interview according to the *Structured Clinical Interview for DSM-IV Axis I, Patient Edition* guidelines.[25] Patients were enrolled by 2 of us (R.L. and M.L.). To qualify for study participation, patients met criteria for negative symptoms as defined by the demonstration of a score of at least 25 (cut-off score selected to recruit subjects with at least a moderate severity of negative symptoms) on the Scale for the Assessment of Negative Symptoms (SANS).[26] Patients with any significant medical (including prostate illness) or neurological illness, or who were pregnant, were excluded from the study. The absence of medical or neurological illness was verified by means of a routine laboratory investigation (including prostate-specific antigen level in males older than 50 years), physical and neurological examination, treating physician report, and medical records. Prior to study entry, all subjects provided written informed consent after receiving a full explanation regarding the nature of the study and the potential risks and benefits of study participation. The study was approved by the Beer Yaakov Mental Health Center Institutional Review Board and the Ministry of Health Ethical Review Board.

STUDY DESIGN

This "between groups" study design required participating subjects to have been administered a stable dose of their current "typical" or "atypical" antipsychotic medication for at least a month prior to study commencement. Patients were required to continue taking their regular medications for the duration of the study. Aside from antipsychotic medication (**Table**), concurrent medications allowed included medications that were clinically required prior to study recruitment to maintain and stabilize clinical status (eg, anticholinergic medication and benzodiazepines). Patients being administered mood-stabilizers or any steroid or hormonal supplement (eg, estrogen) were excluded from study participation. No change in dose or addition of any other psychoactive medication was permitted during the study. All patients entered a 1-week, single-blind, placebo lead-in phase to the study. Patients completing the placebo lead-in and who continued to demonstrate the above criteria for negative symptoms, without any meaningful change in the SANS score (defined by a change of >20% in clinical ratings score),[15] qualified to enter the study treatment phase. Patients were then randomized (by means of random number generation) to receive either DHEA (Biosynergy, Boise, Idaho) or placebo, each for 6 weeks in a double-blind manner (administered and monitored by a hospital pharmacist). The DHEA medication was administered orally in the following fashion: 25 mg/d for the first 2 weeks (8 AM), 50 mg/d in equally divided doses for the second 2 weeks (8 AM and 8 PM), and then 100 mg/d in equally divided doses for the final 2 weeks (8 AM and 8 PM). As in previous studies, these doses of DHEA were selected to increase the patient's circulating DHEA and DHEA-S levels to the range of the typical physiological peak in healthy 20- to 30-year-olds.[11,15]

LABORATORY TESTING

Blood samples of DHEA and DHEA-S were collected between 8 AM and 9 AM on 2 occasions immediately prior to the first

dose of study medication and immediately prior to the last dose of study medication at the completion of the study. Subjects were instructed to abstain from unusual physical activity or stress for a period of 24 hours prior to blood sampling. Levels of DHEA were tested with a DHEA coated-tube radioimmunoassay (RIA) kit (DHEA-DSL 9000 Active DHEA; Diagnostic Systems Laboratories, Webster, Tex) with a sensitivity of 0.7 nmol/L and a cross-reactivity with DHEA-S of 0.88%. The DHEA-S level was tested with a DHEA-S coated-tube RIA kit (DHEA-S-DSL-3500 Active; Diagnostic System Laboratory) with a sensitivity of 4.6 nmol/L. Cortisol level was measured using the TKCO1 Coat-A-Count kit (Diagnostic Products Corporation, Los Angeles, Calif), with a sensitivity of 13.8 nmol/L. Hormone levels in all samples were measured simultaneously to avoid interassay variability. The intra-assay variability values for DHEA, DHEA-S, and cortisol were 5.6% to 10.6%, 6.3% to 9.4%, and 3% to 4.8%, respectively, according to the level both between and within runs.

PATIENT MONITORING

Since the study was carried out in an in-patient setting, patients were closely monitored and assessed daily for any adverse events or clinical deterioration. Furthermore, patients were formally assessed weekly by a physician member of the research team for any DHEA medication adverse effects. Guidelines for the study stipulated immediate termination from the study for any evidence of worsening clinical state or serious adverse effects.

CLINICAL ASSESSMENTS

Patients were rated at baseline as well as weekly for the 7-week duration of the study, by means of the Positive and Negative Syndrome Scale (PANSS),[27] the SANS, the Hamilton Scale for Depression (HAM-D),[28] the Hamilton Scale for Anxiety (HAM-A),[29] and the Clinical Global Impression Scale (CGI) (severity [CGI-S] and improvement [CGI-I]).[30] The SANS rating scale was chosen a priori to test for effects on negative symptoms since the research team considered it to be a more extensive and sensitive measurement of negative symptoms than the negative symptom subscale of the PANSS. However, the PANSS was administered in addition, to provide an indication of positive symptoms and general psychopathology. The HAM-D and HAM-A were selected considering previously reported effects of DHEA on depression and general well-being in nonschizophrenic individuals.[15] Each subject was evaluated by the same research physician (R.L. or M.L.) for the duration of the study, to preserve continuity and uniformity of assessments.

STATISTICAL ANALYSIS

The method of last observation carried forward (LOCF) was used to impute data for subjects who had completed at least 3 weeks (selected a priori) of the randomized medication phase but who failed to complete the full 7 weeks of the study. Scales data were analyzed by using 2×7 repeated-measures analyses of variance (ANOVAs), with a main factor of "treatment" (placebo, DHEA) and a repeated measurements factor of "week." Post hoc analyses were carried out in cases of significant outcomes, using the Duncan method. Other models applied $2\times2\times7$ ANOVAs, with either gender or drug treatment being added to the models. Paired and unpaired *t* tests were used to analyze plasma levels of DHEA and DHEA-S. For each subject, the change of clinical assessments was calculated as an absolute difference value (week minus baseline), and as a proportion (week divided by baseline). Similarly, the change in levels of plasma DHEA and DHEA-S was calculated for each subject. The association between plasma levels of DHEA and DHEA-S and the clinical assessments was done using Pearson correlations. We performed 2×7 and $2\times2\times7$ (without and with the gender effect) analyses of covariance (ANCOVAs) on the change measures of the clinical assessments, controlling for the change of DHEA.

RESULTS

The study sample consisted of 30 patients, all of whom completed the 1-week placebo lead-in phase and were equally randomized into the double-blind DHEA/placebo phase. Mean (SD) age was 37.4 (12.1) years (range, 20-67 years). Subsequently, 3 patients were eliminated from the study analysis after failing to complete 3 weeks of the randomization phase, with 50% of the study randomization phase being considered the minimum cutoff period for study drug efficacy. Reasons for the 3 early terminations (all placebo) included (1) adverse effects and (2) unexpected premature patient discharge. Thus, 27 patients (15 male, 12 female) with confirmed *DSM-IV* diagnoses of schizophrenia were included in the final study analysis (Table). Of the 27 subjects, 15 received DHEA, and 12 received placebo. There was no significant gender or age difference between the 2 groups. The allocation into experimental groups was independent of the drugs used by the subjects (classified as typical or atypical), as indicated by χ^2 test ($\chi^2_1=0.22$; $P=.64$).

Missing data of 4 subjects were imputed using LOCF; the missing data were 3 weeks for 1 DHEA subject (clinical deterioration); 2 weeks for 1 DHEA subject (premature patient discharge owing to marked clinical improvement) and 1 placebo subject (clinical deterioration); and 1 week for 1 placebo subject (partial completion of rating scales at week 6 owing to incomplete cooperation). Thus, 27 subjects were included in the data analyses.

POSITIVE, NEGATIVE, AND GENERAL PSYCHOTIC SYMPTOM PROFILE

As indicated in **Figure 1**A, although patients who received DHEA demonstrated more reduction on total PANSS scores compared with placebo subjects, the difference between the groups was not significant.

With regard to analysis of the subscales of positive, negative, and general symptoms, no differences between the 2 groups on any of the subscales were present prior to the study (ie, at week 1 and week 0 [baseline]).

Positive Symptoms

The placebo subjects showed a reduction from a mean score of 1.83 at baseline to 1.65 at week 6, and the subjects receiving DHEA showed a reduction from 1.75 to 1.64. The repeated-measures ANOVA indicated a significant main effect of week ($F_{6,150}=2.4$; $P<.05$) but no group×week interaction. Post hoc analysis of week effect showed that a significant reduction from baseline was present at weeks 3 and 6.

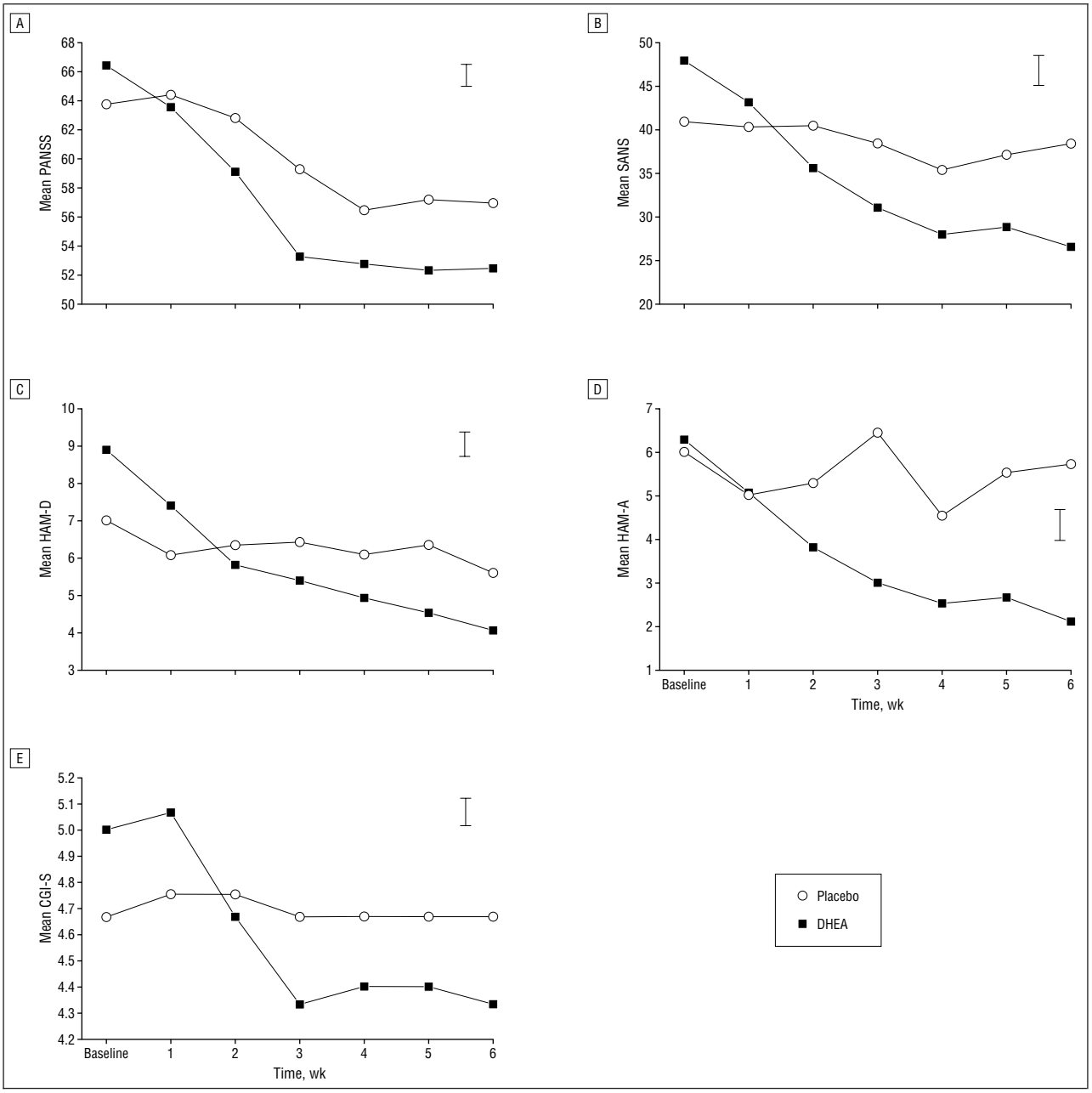

Figure 1. Total Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Negative Symptoms (SANS), Hamilton Scale for Depression (HAM-D), Hamilton Scale for Anxiety (HAM-A), and Clinical Global Impression Scale for severity (CGI-S) scores plotted over time comparing the dehydroepiandrosterone (DHEA) augmentation treatment subgroup (n=15) and the placebo subgroup (n=12). One SE bar appears within the frame of each figure.

Negative Symptoms

The placebo subjects showed a reduction from a mean score of 2.92 at baseline to a score of 2.55 at week 6, with subjects receiving DHEA showing a reduction from 3.13 to 2.30. The repeated-measures ANOVA indicated a significant main effect of week ($F_{6,150}=12.6$; $P<.001$), but no group×week interaction, as both groups showed a pattern of reducing their scores. Post hoc analysis of week effect showed that a significant reduction from baseline was present from weeks 2 onward (week 2, $P<.05$; weeks 3-6, $P<.001$). However, the analysis of the proportional change measure of the negative PANSS subscale shows a main effect of DHEA treatment ($F_{1,25}=5.41$; $P<.05$), indicating that DHEA subjects reduced their scores more than controls. The mean reduction in DHEA subjects was 79.4% of those with negative baseline PANSS scores, and 91.7% of control subjects.

General Symptoms

The placebo subjects showed a reduction from a mean score of 1.91 at baseline to 1.73 at week 6, with subjects receiving DHEA showing a reduction from 2.01 to 1.55. The repeated-measures ANOVA yielded a significant treatment×week interaction ($F_{6,150}=2.3$; $P<.05$). Post hoc

comparisons indicated that placebo subjects reduced general symptoms scores at weeks 4, 5, and 6, compared with baseline (all P values $<.05$), while subjects receiving DHEA showed significant reduction from baseline from week 2 onward (all P values $<.001$). At weeks 3 and 6, subjects receiving DHEA showed significantly lower scores compared with subjects receiving placebo (both P values $<.05$).

NEGATIVE SYMPTOMS

As shown in Figure 1B, the repeated-measures ANOVA indicated a significant main effect of week ($F_{6,150}=14.57$; $P<.001$) as well as a significant group×time interaction ($F_{6,150}=6.82$; $P<.001$). Post hoc analysis indicated that placebo subjects did not reduce their SANS scores compared with baseline scores. In contrast, subjects receiving DHEA showed significant reduction from baseline from week 2 onward (all P values $<.001$). Significant differences between placebo and DHEA subjects were present from week 3 onward (all P values $<.01$). Of the 15 patients receiving DHEA, 12 demonstrated improvement in SANS scores (defined as a >20% improvement).

To control for the possible effect of depression improvement on the results of the SANS, an analysis of covariance (ANCOVA) was used. First, regression models were used to predict each of the 7 SANS measures by the corresponding HAM-D measure, and the residuals were saved. Second, the residuals of SANS were used as the dependent variables in the 2×7 repeated-measures ANOVA. This yielded a significant treatment by SANS measures interaction that was very similar to the outcome without controlling for depression. This outcome convincingly suggests that the effects of DHEA on negative symptoms were independent of the effects on depression.

The influence of DHEA augmentation on the 5 subscales of the SANS was tested with and without controlling for gender. The subscales of "blunting," "alogia," and "anhedonia" showed a significant treatment×time interaction, with DHEA reducing symptoms with no placebo effect noted. No effect was noted on apathy and attention. There was a gender effect noted on the subscales of "alogia," "anhedonia," and "attention," with a treatment×gender×time interaction noted; females were noted as being more responsive.

DEPRESSION

As indicated in Figure 1C, a significant group×time interaction was observed on the HAM-D scale ($F_{6,150}=2.69$; $P<.05$). Post hoc analysis indicated that placebo subjects did not reduce their HAM-D scores compared with baseline scores. In contrast, DHEA subjects showed significant reduction of HAM-D scores from week 2 onward, compared with scores from baseline (all P values $<.01$). A significant difference between placebo and DHEA subjects was present at baseline ($P<.05$), subjects receiving DHEA showing more depression.

ANXIETY

As shown in Figure 1D, a significant group×time interaction was found on the HAM-A scale ($F_{6,144}=4.27$; $P<.001$). Post hoc analysis showed that while DHEA subjects showed significant reduction from baseline scores after 2 weeks (all P values $<.01$), placebo subjects did not show a significant reduction from baseline. In addition, from week 3, DHEA subjects showed significantly lower HAM-A scores compared with placebo subjects (all P values $<.01$).

CLINICAL GLOBAL IMPRESSION

As indicated in Figure 1E, a significant treatment×week interaction was observed on the CGI-S ($F_{6,150}=3.84$; $P<.001$). Placebo subjects did not show any change of CGI-S throughout the study. In contrast, DHEA subjects showed a significant reduction from baseline scores from week 2 onward (all P values $<.05$). The DHEA subjects demonstrated lower CGI-S scores compared with placebo subjects at weeks 3 and 6, but these results only approached significance ($P=.05$ and $P=.06$, respectively). No significant interaction was observed on the CGI-I.

In addition to the analysis of the raw scores of the above 5 clinical rating scales, an analysis of the percent changes from baseline was performed. Only the SANS scores showed significant interaction ($F_{5,125}=2.77$; $P<.05$). Interestingly, total PANSS results were very similar for both groups, as indicated by an interaction ($P=.90$).

GENDER EFFECTS

In general, gender did not show a main effect on the variables. However, most of the dependent variables (excluding CGI-I) showed significant treatment×gender×week interactions (PANSS: $F_{6,138}=3.33$, $P<.05$; SANS: $F_{6,138}=3.91$, $P<.001$; HAM-D: $F_{6,138}=3.31$; $P<.05$; HAM-A: $F_{6,132}=3.94$, $P<.001$; CGI-S: $F_{6,138}=2.7$; $P<.01$). The pattern was quite similar in most cases; the effect of DHEA was more pronounced in female compared with male subjects. This was seen in 2 main aspects. First, the medication response patterns of placebo and DHEA subjects resembled each other more in male than in female subjects; namely, both placebo and DHEA showed some amelioration of symptoms. Second, female subjects receiving DHEA showed a greater decline of measures (starting from higher levels and ending at lower levels) as compared with male subjects.

TYPICAL VS ATYPICAL ANTIPSYCHOTIC MEDICATIONS

Effects of the baseline antipsychotic medication treatment (typical [n=8] vs atypical [n=19]) that were augmented by DHEA or placebo in the study were also tested. No significant main effect or interaction was observed (all P values $>.20$). This is true for the main effect of group (DHEA or placebo), drug (typical or atypical), or the group×drug interaction.

PLASMA DHEA, DHEA-S, AND CORTISOL LEVELS

Change in Plasma Levels

Subjects receiving DHEA who agreed to blood testing both before and after the 6 weeks of study medication, and who

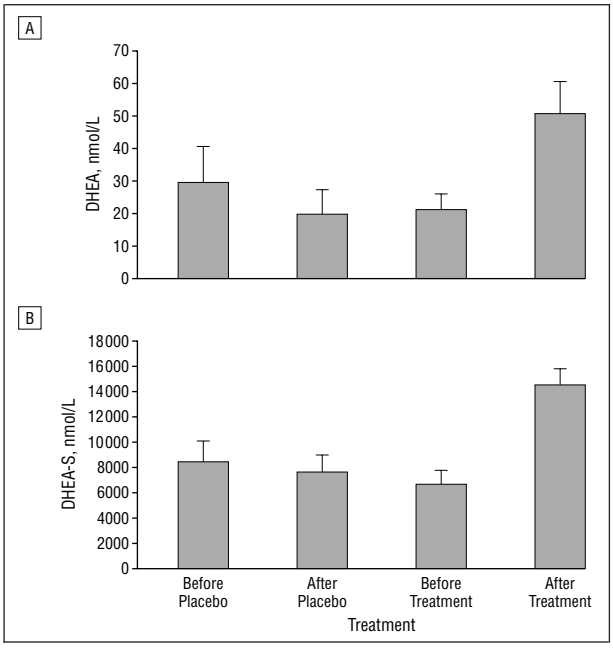

Figure 2. Comparison between the dehydroepiandrosterone (DHEA) augmentation treatment subgroup and the placebo subgroup of the change in plasma DHEA and dehydroepiandrosterone sulfate (DHEA-S) levels before (A) and after (B) completion of the 6-week study period.

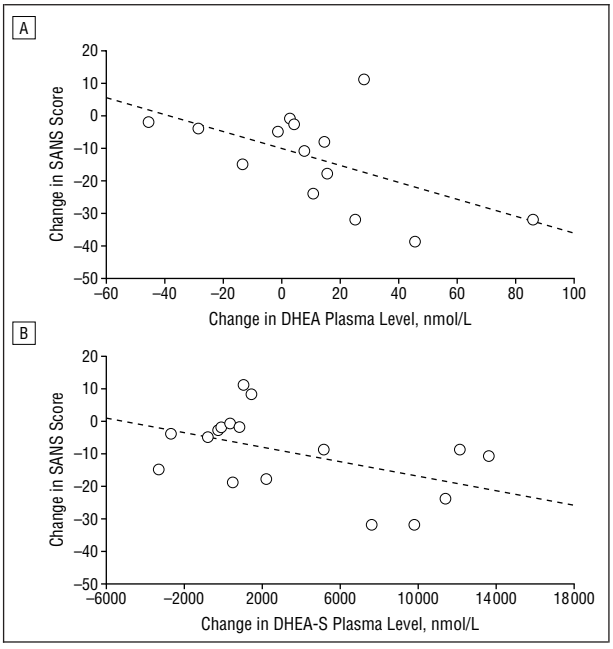

Figure 3. Scatterplot diagram indicating the correlation of absolute change in dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) plasma levels with absolute change in Scale for Assessment of Negative Symptoms (SANS) scores.

were available for phlebotomy on both occasions (n=8), demonstrated significant increases in levels of both DHEA (t_6=2.79; P<.05) and DHEA-S (t_7=5.49; P<.01). This increase was significantly higher than that noted in patients receiving placebo (n=11), in whom levels remained unaltered after the 6 weeks. No differences between placebo and DHEA subjects were present at baseline (both P values >.47), while following treatment, both DHEA (t_{12}=2.85; P<.05) and DHEA-S (t_{15}=3.57; P<.001) levels were higher in subjects receiving DHEA. The increase in plasma levels seemed to be most prominent with DHEA-S (**Figure 2**). Comparisons of the changes (Δ) between before and after the 6-week-study measures, also revealed significant differences in plasma DHEA and DHEA-S levels between subjects receiving placebo and DHEA (t_{12}=2.64, P<.05; t_{15}=4.82, P<.001, respectively). No significant changes over time or between-group differences were noted in cortisol levels (mean [SD] DHEA group baseline=271.5[40.7] nmol/L, endpoint=232.4[38.5] nmol/L, P >.40; mean [SD] placebo group baseline=336.3[41.2] nmol/L, endpoint=274.8[32.9] nmol/L, P >.10).

Since the DHEA-cortisol ratio may be a better correlate of behavioral response than DHEA alone,[31] correlations between DHEA-cortisol ratios and symptomatology were analyzed. Significant negative correlations at study completion were noted with DHEA-cortisol ratios and SANS scores (r=–0.58, P<.05). No associations with PANSS, depression, anxiety, CGI-S, and CGI-I scores were observed. When the analysis was confined to DHEA subjects, the DHEA-cortisol ratio was correlated with the total SANS (r=–0.83, P<.05), negative PANSS (r=–0.75, P<.05), general PANSS (r=–0.75, P<.05), and total PANSS (r=–0.79, P<.05) scores.

Correlation Between Baseline Levels and/or Changes in DHEA and DHEA-S Plasma Levels, and Change in Clinical Symptoms

While there were no significant correlations between baseline DHEA and DHEA-S plasma levels with changes in symptomatology, a tendency toward a significant negative correlation was noted between baseline DHEA-S levels and proportional changes of the SANS (r=–0.65, P=.08), indicating that lower baseline levels of DHEA-S were close to predicting a greater DHEA effect in the amelioration of negative symptoms. In addition, absolute change in plasma DHEA levels was negatively correlated with a change in SANS ratings from baseline to week 6 (r=–0.57, P<.05), indicating the greater the increase in DHEA levels, the more the decrease in SANS scores (**Figure 3**A). Similarly, a change in DHEA-S plasma levels showed negative correlations, with a change in SANS scores from baseline to week 6 (r=–0.49, P<.05) (Figure 3B). Levels of DHEA-S were also negatively correlated with changes in the negative PANSS subscales, global PANNS subscales, as well as total PANSS scores (r=–0.52, P<.05; r=–0.49, P<.05; and r=–0.60, P<.05, respectively). Changes in CGI-S score at week 6 were negatively correlated with change in DHEA-S plasma levels (r=–0.59, P<.05). In contrast, depression, anxiety, and CGI changes did not correlate with any changes of blood measures.

To control for the baseline variance in plasma DHEA levels between the 2 groups (Figure 2), in addition to the correlations analysis, the change of plasma DHEA level as a covariate in the analysis of proportional changes of the clinical scales was assessed. A significant treatment×week interaction was yielded on the general

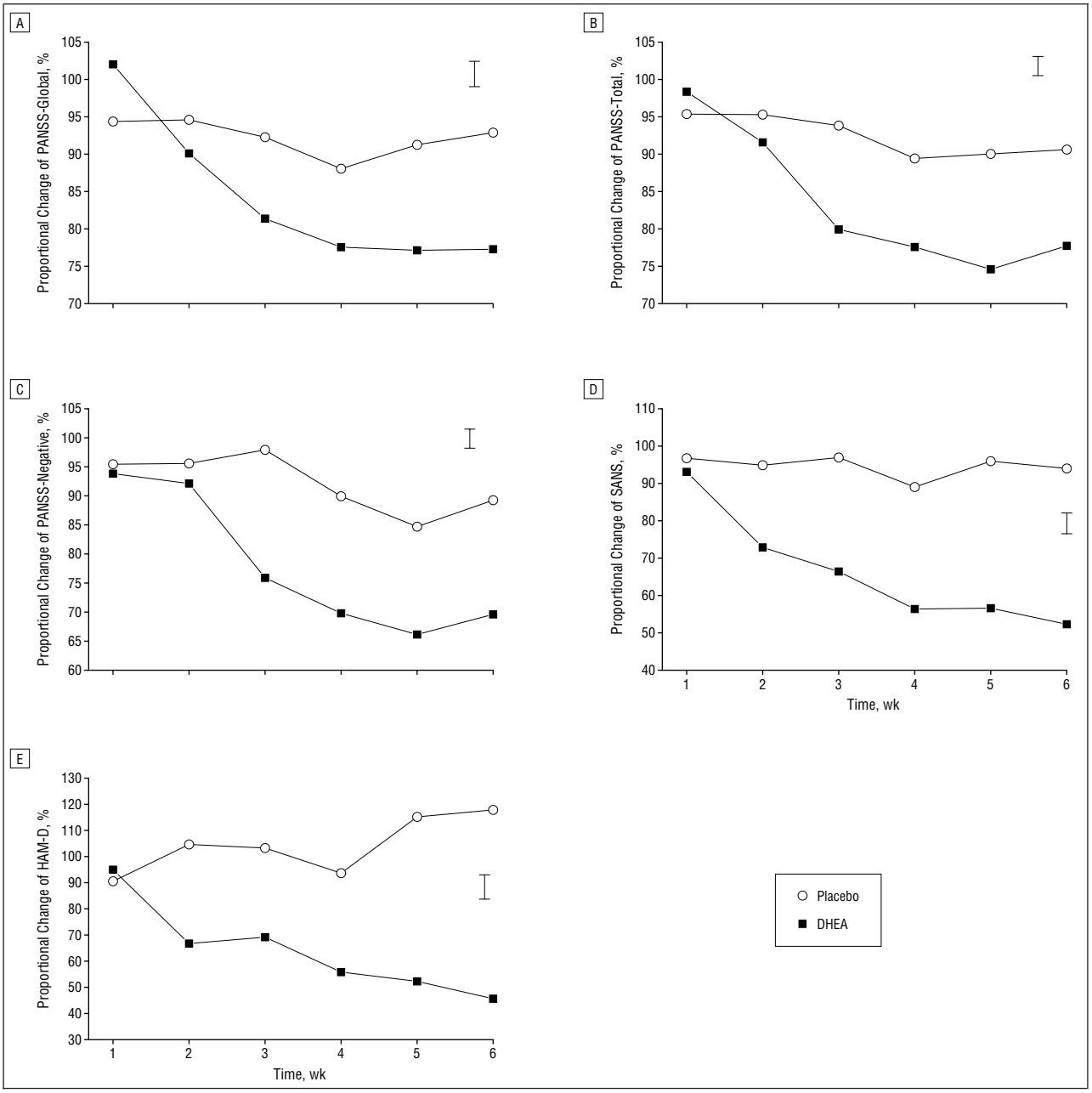

Figure 4. Diagram plotting the change of dehydroepiandrosterone (DHEA) plasma levels as a covariate on the analysis of proportional changes (percentages) of the clinical scales over time (only scales with significant interactions depicted). One SE bar appears within the frame of each figure. PANSS indicates Positive and Negative Syndrome Scale; SANS, Scale for Assessment of Negative Symptoms, and HAM-D, Hamilton Scale for Depression.

symptom subscale and total PANSS scores ($F_{5,60}$=4.76, P<.001; $F_{5,60}$=3.55, P<.01; respectively) (**Figure 4**, A and B), and a tendency to significance was yielded on the negative subscale ($F_{5,60}$=2.21, P=.06) (Figure 4C). In addition, significant treatment×week interactions were seen on the SANS and HAM-D scores ($F_{5,60}$=3.55, P<.01 and $F_{5,60}$=4.55, P<.01, respectively) (Figure 4, D and E, respectively), with subjects receiving DHEA reducing their scores and placebo subjects showing no change from baseline. No significant interactions were noted on HAM-A and CGI scores. When gender was introduced into the analysis, the only significant gender×treatment×week interaction was obtained on the SANS score ($F_{5,50}$=2.47, P<.05), indicating a greater response in females.

COMMENT

The results of this study, while preliminary given the relatively small sample size, suggest the efficacy of DHEA augmentation in the management of negative, depressive, and anxiety symptoms of schizophrenia. However, the observation of negative symptom improvement seems to be independent of depression symptom recovery. No significant difference between treatment and control groups was noted on total PANSS scores, which is not unexpected since both groups continued to take their standard antipsychotic medication, with established beneficial effects on positive symptoms and general symptomatology, for the

duration of the study. Effects of DHEA were more robust in females than in males. The efficacy of DHEA administration in patients with schizophrenia was reflected in the increased levels of plasma DHEA and DHEA-S. Correlations with clinical symptomatology indicated that the greater the change in DHEA and DHEA-S plasma levels, the greater the improvement in negative symptoms, suggesting that the DHEA effect noted was not merely an apparent one. To our knowledge, these findings are the first from a double-blind study reporting the beneficial effect of DHEA administration as an augmenting agent in schizophrenia. Our observations may also provide an indication for the potential range of DHEA dosage for possible augmentation.

Since there is theoretical possibility that DHEA may exacerbate symptoms of psychosis in schizophrenia or result in disinhibition, aggression, overactivation, and mania,[32-34] observations from this preliminary investigation suggest the safety of DHEA administration in this subpopulation. Of the 15 patients randomized to receive DHEA, only 1 had to be withdrawn prematurely from the study owing to early clinical deterioration. While it certainly is possible that the deterioration may be attributable to the DHEA administration, it should be noted that the deterioration occurred before completion of week 3, prior to high doses of DHEA being administered (patient received a dose of 25 mg/d) and may be only an unrelated occurrence. It should also be noted that, despite endogenous DHEA and DHEA-S fluctuations with several medications (eg, alprazolam, carbamazepine, diltiazem, insulin, metformin, morphine, and valproate)[3] no known interactions between DHEA and antipsychotic medications have been described.

In addition to the previously mentioned potential adverse behavioral effects, other adverse effects in the clinical literature noted with DHEA administration have included oily skin, acne, voice deepening, and hirsutism.[15] However, aside from acne and oily skin, DHEA doses administered that resulted in these side-effects have generally been much higher than those used in this study. Furthermore, psychosis associated with DHEA has been reported with endogenous productions of DHEA in severely androgenized females, in whom endocrine testing revealed very high levels of DHEA, unlike those found in our study.[34] There is the theoretical potential for DHEA to exacerbate hormone-sensitive tumors by virtue of its metabolism to testosterone and estrogen.[15] Despite close monitoring of patients in the hospital, no evidence of any of these above adverse effects were noted in subjects participating in the study.

DHEA and DHEA-S demonstrate prominent effects on the GABA (γ-aminobutyric acid) receptor, most notably the GABAa receptor. While studies of DHEA-S indicate that it functions in vitro as a negative noncompetitive modulator of the GABA receptor complex,[35,36] the action of DHEA is less clear, with some demonstrating GABA-antagonistic activity,[36] and others, no activity.[37] It thus becomes possible that DHEA- or DHEA-S–mediated suppression of the GABA inhibitory tone, and DHEA-mediated enhancement of dopamine release in specific brain regions (eg, the frontal cortex) may contribute to improvement of negative symptoms.[38,39] Second, DHEA selectively enhances neuronal response at the NMDA (*N*-methyl D-aspartate) receptor.[40,41] Considering the critical role postulated for the NMDA receptor in the pathophysiology and pharmacotherapy of schizophrenia,[42-46] this specific action of DHEA may have particular importance in the amelioration of negative symptoms. A further related, albeit speculative, effect of DHEA involves the facilitating effects at the sigma receptor, thus potentiating NMDA receptor neuronal excitability.[47-49]

It should also be noted that DHEA demonstrates potent neuroprotective qualities and plays an important role in neurodevelopment.[40,50-55] Whether DHEA administration at an earlier stage of the illness may serve as a protective factor remains unknown and merits further investigation.

While DHEA's precise mechanism of action resulting in the improvement of negative symptoms remains unknown, it should be noted that clozapine, widely considered to be the most efficacious medication in the improvement of negative symptoms,[2] increases levels in the brain of the GABAa-positive modulator neuroactive steroids: progesterone, allopregnanolone and allotetrahydrodeoxycorticosterone, an effect hypothesized to result from interaction with the GABAa receptor.[56] This is in contrast to haloperidol, a "typical" antipsychotic medication that does not cause increases in brain neuroactive steroids. Unfortunately, in that particular study, levels of DHEA and DHEA-S were not determined. These increases in neuroactive steroids, similarly observed with a further "atypical" antipsychotic medication, olanzapine,[57] are being considered as playing a role in the "atypical" psychopharmacological profile that includes the amelioration of negative symptoms. To what extent these findings may be extrapolated to the probable negative GABA neurosteroid activity of DHEA and DHEA-S remains a focus for future study. Furthermore, although speculative, it may also be suggested that DHEA exerts its influence by virtue of its antistress function, thus reducing the "allostatic load" sequelae[31] of chronic and severe psychiatric illness.

Although the results of this study are noteworthy, it would be important to replicate the investigation with an even larger subject cohort, for a longer period of time, and with antipsychotic medication standardization. Although peripheral plasma levels of DHEA and its metabolites were obtained (considering the obvious practical difficulties), brain levels of these neurosteroids were not measured. However, we have no reason to suspect that the levels would not be reflected centrally to a similar extent, and Guazzo et al[58] have demonstrated a linear relationship between the blood and cerebrospinal fluid concentrations of DHEA and DHEA-S.

The role of neurosteroids in the pathophysiology of psychiatric illness is rapidly becoming an important and exciting focus of investigation. We report for the first time, in double-blind fashion, the marked improvement of negative, depressive, and anxiety symptoms in schizophrenia following treatment augmentation with the neurosteroid DHEA. While these findings are certainly intriguing, they remain preliminary given the relatively small sample size. However, they do raise important issues regarding the role of neurosteroids in general, and DHEA in particular, in the pharmacotherapy of schizophrenia. Additional investigation is required to further test and replicate these ob-

servations to definitively declare the value of DHEA when administered in this novel manner.

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