Published in final edited form as:

Psychosomatics. 2012 May ; 53(3): 244–249. doi:10.1016/j.psych.2011.08.005.

DHEA and Cognition in HIV-positive Patients with Non-Major Depression

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Abstract

BACKGROUND—DHEA has been investigated for its potential role in improving cognition in a number of patient populations. Treatment options are limited for HIV-associated neurocognitive disorders.

OBJECTIVE—The authors tested the effect of DHEA administration on the cognitive functioning of HIV-positive subjects with non-major depression.

METHOD—The neuropsychological testing data for 60 HIV-positive patients enrolled in a clinical trial for non-major depression were analyzed to determine if DHEA-treated patients demonstrated improved cognitive functioning versus placebo.

RESULTS—At baseline, 80% of the sample met criteria for asymptomatic cognitive impairment. No benefit in cognitive performance was found on 16 of 17 neuropsychological measures evaluated. One measure showed a modest benefit for placebo-treated patients over DHEA.

CONCLUSION—DHEA treatment was not associated with improved cognitive performance in HIV-positive patients with non-major depression.

BACKGROUND AND SIGNIFICANCE

Dihydroepiandrosterone (DHEA,) an endogenous neurosteroid androgen hormone produced by both men and women, has been investigated for its possible role in mental and physical health across a number of domains. Recent studies have examined its potential to address mood symptoms(1), functional status in the elderly(2), and mouse models of traumatic brain injury(3). Of particular interest, DHEA has come to attention as having possible effects on cognitive performance, although studies in humans investigating the relationship between DHEA and cognition have thus far produced mixed results. In this work, several investigators examining DHEA hormone levels in humans have observed a relationship between higher DHEA levels and better cognitive abilities(4, 5), although others have failed to do so (6–8).

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In addition to studies examining relationships between serum DHEA and cognitive status, a number of clinical trials have examined whether DHEA supplementation can improve cognition in adults. Most focused on elderly populations, and have thus far failed to provide compelling evidence to support the use of DHEA as a pharmacologic intervention for cognition in the healthy elderly(9). Other studies have examined the potential of DHEA to improve cognition in specific populations. For example, one small crossover study found that DHEA supplementation could improve memory among healthy young men(10); however, patients with Addison's disease did not demonstrate cognitive improvement with DHEA supplementation(11). Several studies have looked for cognitive improvement with DHEA in non-impaired individuals as an aspect of overall well-being; for example, a Cochrane review of DHEA supplementation for in the healthy elderly included studies that test for cognitive improvement in non-impaired samples(9).

Patients infected with HIV are a population for whom cognitive disorders represent a major source of morbidity (12). Combination antiretroviral therapy has led to a dramatic reduction in incident HIV-associated dementia cases, but has had far less effect on prevalence of milder cognitive changes. According to the current nomenclature for HIV-associated neurocognitive disorders (HAND), asymptomatic neurocognitive impairment (ANI) is defined as impaired performance (at least 1 standard deviation away from the mean) on a battery of neuropsychological tests involving at least 2 cognitive domains, although the impairment does not interfere with everyday functioning(13). The other category is mild neurocognitive disorder (MND) which is defined similarly in terms of neuropsychological test performance, but in addition produces at least mild interference in daily functioning. In a recent national study of 1316 HIV+ men and women without confounding comorbidities, 45% met criteria for milder forms of impairment (33% for ANI, and 12% for MND), a rate consistent with reports from pre-combination antiretroviral therapy years), while only 2% met criteria for dementia (14). Cognitive impairment may affect motor tasks such as driving(15), as well as antiretroviral medication adherence(16).

Although a number of agents have received attention as potential pharmacotherapeutic candidates (17,18), aside from antiretrovirals themselves no drugs have become established as part of evidence-based standard of care for the treatment of HIV-associated cognitive symptoms. Beyond its potential neurocognitive effects, DHEA was significantly more effective than placebo in alleviating depressive symptoms in a randomized clinical trial of HIV+ patients with non-major depression that our group conducted, examining both clinician and self-rated scales of depression severity(1). Additionally, a smaller trial found that DHEA-treated patients with advanced HIV disease showed significant improvement on a scale measuring mental health and health distress(19).

In order to explore the potential cognitive effects of DHEA in HIV-infected individuals, we examined data from our 8-week placebo-controlled randomized clinical trial of DHEA for HIV+ men and women with non-major depressive disorders, to determine the effect of DHEA, if any, on cognitive functioning. We hypothesized that the DHEA-treated group would show more improvement on neuropsychological measures than the placebo group.

METHODS

Sample and recruitment

Subjects are a subgroup of patients participating in the last two years of a placebo-controlled DHEA study for non-major depression, when neuropsychological testing was added to the protocol at baseline and 8-week follow-up. Eligible patients were HIV-positive, between the ages of 18 and 70, and met DSM-IV criteria for dysthymic disorder or subsyndromal major depression. The parent study's focus on patients with non-major depression emerged from

the observation that lesser forms of depression are prevalent in HIV-positive patients, and are often chronic and associated with significant morbidity. For a diagnosis of subsyndromal depression, subjects were required to meet 4 of 5 criteria for major depressive disorder, and to report a minimum symptom duration of three months. The minimum Hamilton Rating Scale of Depression (HAM-D) score for inclusion was 12. Exclusion criteria comprised any unstable medical illness, recent (within the past three months) initiation of a steroid hormone, substance use disorder in the past six months, or a current DSM-IV diagnosis of major depressive disorder (including major depressive disorder in partial remission.)

Measures

Psychiatric diagnoses and symptoms—The Structured Clinical Interview for the DSM-IV was used to ascertain baseline diagnostic categories. The Structured Interview Guide for the Hamilton Rating Scale of Depression was administered at each visit to assess the severity of depression symptoms.

Cognitive Measures—A battery of seven neuropsychological (NP) tests generating 17 measures was administered to assess memory, attention, language function, executive function, and motor/psychomotor speed. Because of the other demands of the parent protocol, the NP battery was limited to an hour, using tests that represent the domains most vulnerable to impairment associated with HIV infection. The following tests were administered: Rey Auditory Verbal Learning Test (RVLT)(20), Color Trails(21), Stroop Color Interference Test(22), Grooved Pegboard(23), Digit Span and Digit-Symbol Coding from the WAIS(24), and California Computerized Assessment Package (CalCAP)(25).

Biomedical measures—CD4 and HIV RNA viral load were assessed at baseline and Week 8. Serum DHEAS, the sulfated version of DHEA measured in laboratory testing, was assessed at baseline, and at weeks 4 and 8.

Procedures: Full details of study procedures have been previously published (1). Participants received an initial evaluation including medical and psychiatric history, current medications, and blood samples for baseline laboratory studies. After eligibility was established, the patient returned for the baseline study visit, when the study psychiatrist obtained informed consent. Baseline NP tests were administered. Patients were randomized in blocks of 4 according to a computer-generated list provided by the New York State Psychiatric Institute Research Pharmacy, which also packaged the identical-appearing DHEA and placebo tablets. Starting dose was 100mg/day micronized DHEA tablets or placebo, which was titrated in 100mg increments to a maximum of 400mg as tolerated over 4 weeks. At week 8, the HAM-D was administered again to collect follow-up depression severity scores, and the NP tests were repeated.

The study protocol was reviewed and approved by the Institutional Review Boards of the New York State Psychiatric Institute and Weill Medical College of Cornell University. All participants provided written consent. FDA authorization was obtained for the use of DHEA as an investigational drug.

Statistical Analyses: Analyses were performed (χ^2 and t-tests) to test for baseline differences in demographic and medical characteristics between groups. T-tests were also performed to examine for baseline differences in neurocognitive scores between the two groups. Minimum estimated effect sizes were calculated for the given sample, assuming two-tailed tests of significance with $\alpha=0.05$ and $\beta=0.80$. As our primary analyses for this report, differences between DHEA and placebo groups' scores for each separate NP measure at 8 weeks were tested, first as bivariate analyses, and then in models that adjusted for

participants' baseline cognitive scores. We next examined the subset of patients with baseline cognitive deficits, defining "cognitive outliers" as those participants who scored at or greater than 2 standard deviations below the norm on at least 2 subtests of different neurocognitive measures. We conducted separate analyses to determine whether DHEA improved cognitive performance among cognitive outliers. In addition, we tested the effect of DHEA on cognition in models that adjusted for low serum DHEAS at baseline, defined as serum DHEAS below normal laboratory values for age and gender. We also tested models that adjusted for hepatitis C status, which is independently associated with NP impairment.

In order to examine whether DHEA produced an *overall* effect on cognitive performance, we created a single composite cognitive difference score using all of the seven measures. Results of timed tests were reciprocally transformed into speed scores, and differences between baseline and week 8 scores from all cognitive measures were calculated. These difference scores were then transformed to z-scores and summed into a composite. In cases where a given cognitive measure comprised several subtests, we selected a representative subtest to include in the composite. We also used the Global Deficit Score method proposed by Carey et al (26) to calculate the degree of overall impairment for the total sample. Finally, in order to determine whether changes in depression affected cognitive performance in this sample, we tested whether depression response at week 8 of the study was associated with improved cognitive performance. All tests were two-tailed, at $\alpha=0.05$. We did not correct for multiple comparisons, given the exploratory nature of the study.

RESULTS

Sample Characteristics

Baseline demographic and medical characteristics are reported in Table 1; no statistically significant differences in baseline characteristics were found between the DHEA and placebo groups. Average age was 44 and mean education level was 13.3 years; the majority was non-white, and 78% were male. Mean baseline CD4 cell count was in the 400 range. 63 participants had baseline NP assessments, 3 dropped out, leaving 60 for whom complete data are available. No significant differences were found between dropouts and completers. Of the 60 participants in the present analysis, 35 received DHEA and 25, placebo. 80% of the total sample met the criteria for ANI on NP testing; this did not differ significantly between treatment groups. Using the method for calculating a Global Deficit Score (GDS) proposed by Carey et al (26), the mean GDS for our sample was 0.48 (by comparison, in the above paper Carey et al found the GDS for an HIV-negative sample to be 0.22.) In addition, 31% of the sample had a GDS above 0.5, the cutoff found by Carey et al to best predict NP impairment. Mean HAM-D baseline scores were essentially the same for DHEA patients (15.2 [2.99]) and placebo patients (15.6 [3.18]) ($t=0.49$, 58df, $p=0.31$). The groups did not differ with respect to CD4 count, or reported past CD4 nadir.

Neuropsychological test results at baseline

No cognitive differences were found at baseline between the DHEA and placebo groups (Table 2.) We then compared cognitive outliers in the two groups as defined above. Using this classification, we found no differences at baseline between the two groups on any measure.

Neuropsychological tests at 8-week follow-up

The only test to show differential improvement at Week 8, adjusted for baseline scores, was the total score on the Rey AVLT, a test of immediate recall, with the placebo group showing a moderate benefit over the DHEA group ($p=0.015$) (Table 3). Adjusting for hepatitis C status and for low baseline DHEA did not produce additional findings. We also found no

difference between DHEA and placebo group in the composite difference score. Testing whether depression symptom response at week 8 was associated with change in cognitive performance did not produce any significant findings either across or within groups. All effect differences between groups were smaller than the calculated minimal detectable effect sizes.

DISCUSSION

In this report, we examined the effect of DHEA versus placebo on the cognitive performance of 60 HIV-positive patients who participated in a clinical trial of the antidepressant effects of DHEA. We found essentially no differences from baseline to Week 8 between the two groups on 16 of the 17 cognitive indices examined. The one statistically significant result demonstrated a modestly greater improvement by placebo patients on the total Rey AVLT, which is likely a spurious finding given the number of comparisons made and absence of correction for multiple comparisons. Thus, the results did not support the hypothesis that DHEA improves cognitive performance in this sample.

This study focused on a sample of HIV-positive patients who were ambulatory, had access to primary care, and did not demonstrate dementia or significant psychiatric disorders other than depression. Perhaps more severely cognitively impaired patients, or patients with clinically deficient DHEAS levels would have allowed for a greater range of detectable cognitive change. Future studies may benefit from including patients with documented impairments in activities of daily living and other evidence of observable cognitive deficits.

Although DHEA has demonstrated promise in clinical trials for improving mood and well-being, particularly in HIV-positive samples, the evidence to date has suggested less promise with regard to its potential as a cognitive-enhancing agent. In spite of the major advances made in the medical treatment of HIV disease, HAND remains a highly prevalent source of morbidity associated with HIV infection for which no effective interventions have yet been identified (27). As research has not been successful in identifying pharmaceuticals to improve cognition among patients with HAND, future studies will need to continue to expand their focus to new potential candidate agents and medication classes to treat these debilitating conditions.

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Table 1

Baseline demographic and biomedical characteristics

Characteristic	DHEA group (N=35)		Placebo group (N=25)		Analysis	
	Mean (SD)		Mean (SD)		t	df p
Age	44.12 (8.72)		43.68 (9.84)		-0.18	57 0.86
Years of Education	13 (2.91)		14 (2.27)		1.64	58 0.11
Baseline CD4 count	469 (282.50)		420 (185.08)		-0.74	54 0.46
Reported CD4 nadir	213 (180.35)		165 (172.31)		-1.01	53 0.32
	N		N		χ^2	df p
Ethnicity						
White	10		8		2.09	3 0.55
Hispanic	9		9			
Black	13		8			
Other	2		0			
Sex						
Men	27		20		0.10	1 0.75
Reported positive HCV status	9 (26%)		2 (8%)		3.24	1 0.07

Table 2

Differences between DHEA and placebo groups on baseline neurocognitive measure means, and on dichotomized standard deviations from test-specific normed means

Measure	DHEA mean score (SD)	Placebo Mean score (SD)	t	p	Cognitive Outlier status *	p
Rey AVLT 1-5 total	43.82 (8.99)	45.83 (11.42)	0.75	0.45	0.1523	0.696
Rey AVLT delay 1	8.83 (3.36)	9.79 (3.31)	1.09	0.28	0.187	0.665
Rey AVLT delay 2	8.11 (3.84)	9.83 (3.29)	1.78	0.08	0.0339	0.854
Digit symbol	68.86 (15.38)	63.6 (12.16)	-1.42	0.16	0.8358	0.361
Color trails form A	36.57 (15.86)	40.36 (13.72)	0.96	0.34	0.3429	0.558
Color Trails form B	86.49 (33.32)	91.2 (43.60)	0.47	0.64	0.0137	0.907
Stroop word	101.40 (16.08)	94.64 (14.29)	-1.68	0.10	0.2838	0.594
Stroop colors	68.51 (11.25)	67.08 (8.54)	-0.54	0.59	0.7073	0.400
Stroop word/colors	41.20 (7.50)	40.00 (7.23)	-0.62	0.54	0.0106	0.918
Stroop interference	0.80 (7.02)	0.772 (7.59)	-0.01	0.99	2.3241	0.127
Grooved pegboard, dominant hand	68.97 (12.15)	67.92 (10.69)	-0.35	0.73	1.71	1.90
Grooved pegboard, non-dominant hand	72.94 (12.84)	75.16 (11.39)	0.69	0.49	0.9192	0.338
Digit span	16.41 (3.82)	15.8 (3.83)	-0.61	0.55	0.1519	0.697
CalCap simple RT	-1.24 (2.62)	-0.62 (1.38)	1.05	0.30	1.0437	0.593
CalCap choice RT	-0.90 (2.20)	-0.49 (1.22)	0.82	0.42	1.0437	0.593
CalCap Sequential RT 1	-0.25 (1.25)	-0.41 (1.12)	-0.48	0.63	0.3671	0.545
CalCap Sequential RT 2	-0.098 (1.13)	-0.35 (0.783)	-0.94	0.35	0.1575	0.692

* Cognitive Outliers are those subjects who scored greater than 2 standard deviations apart from the mean.

Table 3

Cognitive scores in DHEA and placebo-treated groups at 8 weeks, with analyses adjusted for baseline scores

Measure	Placebo	SD1	DHEA	SD2	F	p	df	N1 placebo	N2 DHEA
Rey AVLT 1-5 total	52.6	11.8	47.2	8.7	6.27	0.015*	1, 54	24	33
Rey AVLT delay 1	11.3	3.3	9.82	2.7	2.06	0.157	1, 54	24	33
Rey AVLT delay 2	10.8	3.4	9.55	2.9	1.55	0.857	1, 54	24	33
Digit symbol	71.0	16.1	73.63	17.1	1.06	0.309	1, 54	25	32
Color trails form A	33.8	16.7	33.58	14.6	0.56	0.457	1, 55	25	33
Color Trails form B	76.7	22.9	74.12	25.7	0.07	0.795	1, 55	25	33
Stroop word	95.4	16.9	101.61	17.2	0.01	0.938	1, 55	25	33
Stroop colors	71.2	11.3	70.61	12.6	1.16	0.287	1, 55	25	33
Stroop word/colors	42.4	9.2	43.03	9.1	0.03	0.859	1, 55	25	33
Stroop interference	1.8	8.4	1.44	7.3	0.03	0.872	1, 54	25	32
Grooved pegboard, dominant hand	64.3	10.3	67.24	12.9	1.11	0.296	1, 55	25	33
Grooved pegboard, non- dominant hand	72.9	12.6	72.55	15.6	0.35	0.557	1, 55	25	33
Digit span	16.6	3.2	16.03	3.8	1.59	0.213	1, 54	25	33
CalCap simple RT	-0.7	1.5	-281	1.0	-1.32	0.193	1, 49	23	32
CalCap choice RT	-1.0	1.8	-750	1.8	7.43	0.342	1, 50	24	32
CalCap Sequential RT 1	-0.3	1.1	-057	1.1	0.28	0.602	1, 50	24	32
CalCap Sequential RT 2	-0.4	1.0	-057	1.0	-2.40	0.128	1, 50	24	32

* p < 0.05