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Effect of dehydroepiandrosterone add-on therapy on mood, decision making and subsequent relapse of polydrug users

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ABSTRACT

A major problem in the treatment of addiction is predicting and preventing relapse following a rehabilitation program. Recently, in preclinical rodent studies dehydroepiandrosterone (DHEA) was found to markedly improve the resistance to drug reuse. In a double-blind, placebo-controlled study, we examined the effect of DHEA on relapse rates in adult polydrug users taking part in a detoxification program enriched with intensive psychosocial interventions and aftercare. During treatment, participants (79 percent males, mean age 28) consumed DHEA (100 mg/day) or placebo daily for at least 30 days. Of the 121 initial volunteers, 64 participated for at least 1 month. While in treatment, DHEA reduced negative affect on the Positive and Negative Affect Scale ($F = 4.25$, $P = 0.04$). Furthermore, in a 16-month follow-up, we found that reuse rates in the DHEA condition were about a third compared with placebo (12 versus 38 percent; $\chi^2 = 5.03$, $P = 0.02$). DHEA treatment also resulted in an increase in DHEA sulfate (DHEA-S) 1 month following treatment, and the level of DHEA-S predicted relapse in the follow-up assessment.

Keywords Cortisol, decision making, DHEA, drug addiction, relapse.

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INTRODUCTION

A major problem in the treatment of addiction is high rates of relapse to drug use after periods of forced or self-imposed abstinence. Prolonged abstinence from substances of abuse is characterized by dysphoria, depression and anxiety, coupled with high stress and craving, which provides a backdrop for the decision to reuse drugs (Lovallo 2007; Froeliger *et al.* 2012; Yadid *et al.* 2012). Most medications currently used for the maintenance of abstinence over time are opioid agonists, such as methadone (Clark *et al.* 2002; Mattick *et al.* 2008), or opioid antagonists such as naltrexone (Ferri, Davoli & Perucci 2006, 2011), and these medications have some effect on reducing stress and anxiety of heroine addicts (Emrich, Vogt & Hertz 1982; Dyer *et al.* 2001). However, relapse rates tend to be quite high even with these medications (Drake *et al.* 1998; Wasserman *et al.* 1998). The present study examined a novel approach for the treatment of addiction through the administration of dehydroepiandrosterone (DHEA), an endogenous neuro-steroid hormone, which is marketed as a food supplement. This approach focuses on boosting the participants' emotional and cognitive resources during the period of treatment. We examined whether DHEA administration affects decision making, mood and quality of life during treatment and has a long-lasting effect on subsequent relapse.

In a simple view, DHEA can be understood as a pro-hormone for the sex hormones. Sex hormones modulate the reward system (Trainor 2011), partly by increasing the density of dopamine (D2) receptors at the striatum and the density of 5-HT binding sites in anterior frontal, cingulate and primary olfactory cortex, and in the nucleus accumbens (Fink *et al.* 1995). Furthermore, DHEA negatively modulates the level of the stress

hormone cortisol (Flood, Smith & Roberts 1998), thus contributing to reduced anxiety and restoration of a stable mood as was demonstrated in animal models (Malkesman *et al.* 2006) and in human adults (Morales *et al.* 1994; Wolkowitz *et al.* 1999). Additionally, DHEA has also beneficial effects on executive functions (Alhaj *et al.* 2006) and it was found to enhance hippocampal neuro-genesis (Suzuki *et al.* 2004).

In human drug addicts, levels of DHEA and DHEA sulfate (DHEA-S) [1] were found to decrease during abstinence (Buydens-Branchey *et al.* 2002; Wilkins *et al.* 2005), and this decrease was found to predict later drug reuse (Wilkins *et al.* 2005). This has led to the suggestion that increased circulating DHEA-S levels may enhance brain resiliency during withdrawal by lowering addicts' distressed mood levels (Wilkins *et al.* 2005; Doron *et al.* 2006a; Doron, Fridman & Yadid 2006b). Protective effects of DHEA administration during drug withdrawal were indeed demonstrated in rodent studies, which showed that chronic exposure to exogenous DHEA (2 mg/kg) attenuated cocaine self-administration and decreased cocaine-seeking behavior of rats up to 20 percent of their maintenance levels (Doron *et al.* 2006a,b).

Most recently, a randomized, double-blind controlled study evaluated the effect of DHEA in human opiate addicts as an add-on to a detoxification and maintenance treatment with buprenorphine (Maayan *et al.* 2008). The results of this study showed a biphasic effect: 34 out of 49 patients showed a significant improvement in withdrawal symptoms and depression and anxiety scores, whereas 15 out of 49 patients demonstrated deterioration in all these measures. However, in that study most patients were only evaluated 3 weeks following the detoxification period due to attrition. Using a double-blind placebo-controlled design, we sought to examine for the first time the long-term effect of DHEA add-on therapy up to 16 months following treatment and also its acute effects on mood and decision making during treatment.

The baseline treatment program in which the study was conducted was a detoxification and rehabilitation program enriched with intensive psychosocial interventions and aftercare. In animal models of addiction, the importance of environmental enrichment has been widely established (Bardo *et al.* 2001; Solinas *et al.* 2008). The therapeutic value of the enriched environment was expected to be facilitated by the augmented emotional and cognitive resources resulting from DHEA administration.

MATERIALS AND METHODS

Participants

One-hundred twenty-one polydrug users from two rehabilitation centers (Retorno and Malkishua, Israel) volunteered to participate in an experimental study on DHEA treatment for drug addiction. The study was approved by the Helsinki Committee of Abarbanel Mental Health Center (Bat Yam, Israel) and by the Israeli Ministry of Health (proposal no. #341). Inclusion criteria were a diagnosis of substance abuse and the provision of a written informed consent. Exclusion criteria were age below 18 and over 50; serious kidney, lung, liver, neurological, prostatic or cardiovascular diseases; and suicide risk, acute psychosis, psychotic disorder, bipolar disorder, severe depressive episode or organic brain syndrome, as well as HIV or hepatitis C. Participants underwent physical examination by a licensed physician to assess their general health conditions. All participants were diagnosed by a senior psychiatrist using DSM-IV criteria, and all were found to have a substance use disorder. For all but one participant the positive diagnosis was for at least one drug other than alcohol, while for the remaining participant the diagnosis was for alcohol use only. The term substance use disorder is the DSM-V definition that combines the substance abuse and substance dependence diagnoses of DSM-IV. As shown in Table 1, the rate of those diagnosed with drug dependence was about equal in the two experimental conditions [2]. Additionally, three participants were diagnosed with alcohol abuse. The psychiatric examination also ruled out the exclusion criteria mentioned earlier. In addition, participants were interviewed by the first author using a structured interview based on the ICD-10 to verify the diagnosis.

From the 121 initial volunteers, 90 participants completed the initial evaluation meeting. The 90 participants who completed the initial evaluation meeting were mostly male (79 percent) and young (mean age of 27.8 ± 1.0). On average they had 10.5 ± 0.2 years of education. Almost all of them were smokers (95 percent) and some reported using alcohol (21 percent). Most of them (85 percent) reported using multiple drugs on a weekly basis, with the most commonly used drugs being cannabis (used by 94 percent), stimulants (used by 50 percent) and heroin (used by 47 percent). On average, participants reported that they had been using drugs for 11.4 ± 1.0 years.

[1] Orally ingested DHEA is converted to its sulfate (DHEA-S) once passing through intestines and liver.

[2] This pertains to addiction to multiple drugs besides alcohol. Information about the two addiction subtypes was recorded for about 40 percent of the participants completing 1 month of treatment.

Table 1 Demographic details of the participants in the DHEA and placebo conditions.

	Baseline		*1 month*		*6 months*	
	Placebo	*DHEA*	*Placebo*	*DHEA*	*DHEA*	*Placebo*
N	45	45	34	30	15	11
Continued study			76%	67%	33%	24%
Gender	22% female	20% female	26% female	23% female	9% female	13% female
Age	26.4 (±1.2)	25.5 (±1.4)	27.0 (±1.5)	25.5 (±1.3)	21.8 (±1.1)	21.9 (±1.4)
Education	10.7 (±0.2)	10.3 (±0.3)	10.7 (±0.3)	10.6 (±0.3)	10.4 (±0.5)	11.4 (±0.3)
Drug use (years)	11.8 (±1.5)	10.9 (±1.3)	14.8 (0.7)	15.4 (±0.6)	15.0 (±0.8)	13.7 (±0.7)
Drug use (age)	15.8 (±0.6)	15.9 (±0.4)	15.7 (±0.7)	15.9 (±0.5)	15.7 (±0.8)	16.3 (±0.8)
Drug dependence	53%	46%	43%	45%	58%	58%
Stay in hostel	26%	25%	24%	27%	20%	18%

Note: Continued study refers to the rate of those who remained in the study from the participants who completed the baseline evaluation meeting. Stay in hostel refers to the rate of those staying in a hostel during the post-rehabilitation period. Drug dependence refers to the rate of those diagnosed with drug dependence (compared with drug abuse).
DHEA = dehydroepiandrosterone.

The placebo and DHEA group did not differ in their demographic or addiction- related indices. Specifically, as shown in Table 1, the two groups did not differ in background variables including gender, age, education, number of years of using drugs and age of onset. A greater rate of DHEA participants used anti-anxiety medications during the rehabilitation (DHEA: 23 percent, placebo: 16 percent) but the difference was not statistically significant ($P = 0.42$). Also, importantly, usage of anti-anxiety medication was not correlated with any of the treatment outcome measures (e.g. rate of reuse: $\chi^2 = 0.64$, $P = 0.66$).

Sixty-four participants (34 placebo, 30 DHEA) participated for at least 1 month following the evaluation meeting. As shown in Table 1, the attrition rates from the initial evaluation meeting were similar in the placebo and DHEA condition ($\chi^2 = 0.87$, $P = 0.48$). Following this period, there was additional attrition, with 49 participants completing at least 4.5 months of treatment (placebo 29, DHEA 20) and 26 participants completing 6 months (placebo 15, DHEA 11). Those who took DHEA/placebo for at least 1 month were included in the follow-up evaluation about 16 months following the treatment. Fifty-five participants were available for the follow-up test (placebo 29, DHEA 26), again reflecting similar attrition rates from those who participated in the evaluation meeting (36 percent in the placebo condition versus 42 percent in the DHEA condition; $\chi^2 = 0.42$, $P = 0.66$). Thus, the differences between groups cannot be attributed to a selection bias. In addition to the rehabilitation center participants, we recruited 15 healthy controls matched by age and gender (by advertisements) to verify the typical blood DHEA, DHEA-S and cortisol levels of the local community.

Study design

The placebo-controlled, double-blind, randomized clinical DHEA trial began 7 days after the patient's arrival at the therapeutic community, after having becoming stabilized from the effects of the drugs and after receiving from the treating doctor a form of informed consent to participate in the study. At this point, each participant was randomly assigned to either the DHEA or placebo condition. Randomization was generated by an independent (blind) researcher using a random number generator for each participant with the sole constraint of having two equal-sized groups. The participants received a detailed explanation of the nature of the study procedures and then provided a written informed consent for participation. The initial evaluation meeting with the participants consisted of two sessions in which they provided demographic details, performed psychological tests and gave blood samples. In addition, further assessments involving psychological testing (see below) and blood samples were collected after 1, 4.5 and 6 months (end of study).

DHEA administration within the treatment program

Both DHEA and placebo were purchased from Bio Synergy Health Alternatives (Boise, ID, USA; http://www.biosynergy.com). The DHEA and placebo treatments were entrusted to a staff member of the rehabilitation center (nurse) and orally administered in a double-blind manner to the patient for six consecutive months. Each capsule had one of four possible colors (two containing placebo and two containing DHEA). As per the double-blind procedure, neither the experimenter nor the nurses were aware of the association between experimental condition and capsule color.

DHEA was administered once a day in the morning after breakfast in a dosage of 100 mg/day. This dose is the minimum therapeutic amount recommended by the manufacturer in order to avoid adverse effects (Strous *et al*. 2005). All adverse effects reported by the study participants were assessed for severity and relationship to study medication.

At baseline, all patients were instructed not to use drugs (benzodiazepines, antidepressants, metadoxine, naltrexone, acamprosate) that would potentially suppress their craving for substances of abuse during the study and follow-up period. At the days of blood collection, all participants were further instructed to avoid morning exercises, caffeine consumption and smoking, which could affect morning cortisol or DHEA/S levels, until blood sampling was completed.

The treatment program

Each patient participating in the experiment received the standard rehabilitation program for the treatment of drug dependence. This program involved counseling using cognitive behavioral therapy, group therapy and psycho-educational sessions addressing problems contributing to or resulting from drug dependence as well as strategies for managing the disorder over time. In addition, participants could take part in a '12-step program' and art therapy.

After being released from the rehabilitation center in which the experiment took place, some of the participants (see Table 1 for details) resided in hostels, where they received support-type treatment including one meeting per day with the other hostel members and a weekly meeting with a social worker. Importantly, the rate of those residing in these hostels was almost identical in the two experimental conditions (see Table 1).

Analysis of blood samples

As noted earlier, serum samples were collected at the initial evaluation meeting, and after 1, 4.5 and 6 months (end of study). The samples were taken between 06:30 and 07:30 AM, before breakfast and were used to analyze levels of cortisol, DHEA and DHEA-S.

DHEA levels were measured with the DHEA-DSL 8900 Active™ DHEA (RIA) kit (Diagnostic Systems Laboratories, Webster, TX, USA). This kit has a sensitivity of 0.21 nmol/L and negligible cross-reactivity to other steroids. Its assay variability is smaller than 8.6 percent between runs, and smaller than 3.8 percent within runs. DHEA-S levels were measured by radioimmunoassay for the *in vitro* determination of DHEA-S in human serum and plasma—IM0729 (Beckman Coulter by Immunotech, Prague, Czech Republic). This kit has a sensitivity of 2.64 µmol/L and extremely low cross-reactivity to other steroids. Its maximal assay variability is 9.3 percent between runs, and 4.9 percent within runs.

Serum cortisol level was assessed by RIA using Cortisol-IMI1841 coated tubes (Beckman Coulter by Immunotech) with a sensitivity of 5 nmol/L and a maximal assay variability of 9.2 percent between runs, and 5.8 percent within runs. Hormone levels in all samples were measured simultaneously to reduce inter-assay variability.

Psychological tests and staff evaluations

To assess their mood and well-being, participants completed the Flourishing scale (Diener *et al*. 2009), the Positive and Negative Affect Scale (PANAS; Watson, Clark & Tellegen 1988), the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q-SF) (Endicott *et al*. 1993), as well as the Trait Anxiety Inventory form-Y2 (Spielberger *et al*. 1983), and the Barratt Impulsiveness Scale (BIS-11) (Patton, Stanford & Barratt 1995).

Additionally, we examined the effect of treatment on decision making using two versions of the Iowa gambling task (IGT; Bechara *et al*. 1994). In this decision task, participants repeatedly select among four decks of cards that yield monetary outcomes. Two of the decks are advantageous, producing small gains and smaller losses, and leading to net (accumulating) gains. The other two decks are disadvantageous, yielding larger gains but much steeper losses, which result in net losses. The two task versions included the original version of the task (Bechara *et al*. 1994) and a simplified version with a feedback method called foregone payoffs (Agay *et al*. 2010) wherein participants see the outcomes not only from the chosen deck but also from the other three decks. This task version will be referred to as the Foregone Payoff Gambling Task (FPGT). The payoff structure of the two tasks is described in the supplementary section. Finally, participants also performed the Forward Digit Span task (Wechsler 1981) as a test of short-term memory capacity.

In addition to these tests, the social worker responsible for each participant reported the person's degree of involvement in rehabilitation center activities on a 0 to 100 scale. In addition, about 16 months (16.3 ± 1.0) following treatment at the rehabilitation center the social worker contacted the participants and evaluated whether each person has been reusing drugs. An evaluation of 'no relapse' was based on two obligatory criteria: (1) The participant' self-report of not using drugs at all since the release from the rehabilitation center until the time of the interview; (2) A report of no drug use during this period from the staff of the hostel in which the participant was residing (for those who resided in hostels). On average, participants remained in the rehabilitation center 2.6 ± 0.3 months following the cessation of the study,

Table 2 Left panes: Mean scores on self-report and cognitive tests for the DHEA and placebo conditions at baseline and following 1 month of treatment (standard errors appear in parentheses).

	Baseline		*1 month*		*ANOVA results*		
	Placebo	*Placebo*	*DHEA*	*DHEA*	*Effect of assessment period*	*Effect of DHEA*	*Interaction DHEA × period*
Self-report tests							
Flourishing scale	5.25 (±0.23)	5.45 (±0.19)	5.09 (±0.32)	4.94 (±0.26)	$F = 0.64$	$F = 0.21$	$F < 0.1$
PANAS positive	3.30 (±0.12)	3.40 (±0.14)	3.14 (±0.12)	2.95 (±0.14)	$F = 1.85$	$F = 3.89$	$F = 0.54$
PANAS negative	2.72 (±0.18)	2.98 (±0.17)	2.55 (±0.17)	2.91 (±0.19)	$F = 0.24$	$F = 0.38$	$F = 4.25^*$
Q-LES-Q-SF	3.29 (±0.10)	3.49 (±0.11)	3.47 (±0.13)	3.13 (±0.13)	$F = 13.18^{**}$	$F = 0.31$	$F = 0.70$
TAI form-Y2	2.53 (±0.09)	2.54 (±0.10)	2.66 (±0.09)	2.85 (±0.10)	$F = 2.32$	$F = 2.11$	$F = 2.69$
BIS-11	2.48 (±0.10)	2.44 (±0.10)	2.49 (±0.10)	2.73 (±0.12)	$F = 4.83^*$	$F = 1.47$	$F = 1.11$
Cognitive tests							
IGT, Dis. Decks	0.55 (±0.02)	0.55 (±0.03)	0.49 (±0.03)	0.58 (±0.02)	$F = 4.21^*$	$F = 0.39$	$F = 3.42$
FPGT, Dis. Decks	0.45 (±0.03)	0.42 (±0.04)	0.44 (±0.04)	0.43 (±0.03)	$F = 0.11$	$F < 0.1$	$F = 0.92$
Digit span	5.32 (±0.30)	5.64 (±0.26)	6.06 (±0.26)	5.60 (±0.31)	$F = 3.25$	$F = 3.02$	$F < 0.1$

Note: Right panes: results of the analysis of variance.
$^{**}P < 0.01$; $^{*}P < 0.05$.
BIS = Barratt Impulsiveness Scale; DHEA = dehydroepiandrosterone; Dis. = disadvantageous; FPGT = Foregone Payoff Gambling Task; IGT = Iowa Gambling Task; PANAS = Positive and Negative Affect Scale; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire; TAI = Trait Anxiety Inventory.

which therefore implies that the evaluation test took place about 19 months after being treated with DHEA/placebo.

Statistical analysis

A mixed ANOVA was used, with experimental condition as a between-subject factor and the assessment period as a within-subject factor. To address the issue of multiple comparisons for the six self-report tests, we first conducted a single multiple ANOVA in which all of these indices were examined together (Feise 2002) [3]. This was followed by separately examining each test in order to identify the source of the difference. This approach guarantees that the overall type I error is not inflated while balancing type I and type II errors for individual tests (see also Zhang *et al.* 1997). We likewise conducted ANOVAs for the IGT and FPGT, with task experience as an additional within-subject factor. Pearson's χ^2 test was used to assess the effect of the manipulation on relapse 16 months following treatment, and Bonferroni corrected *t*-tests were used to examine differences between relapsing and non-relapsing participants. Finally, to identify possible moderators of the effect of DHEA on relapse, we conducted a series of logistic regressions, with drug reuse as the dependent variable and the combination of treatment (DHEA, placebo) and each of the cognitive and self-report tests as predictors. The statistical criterion for successful versus unsuccessful treatment was a two-tailed significance level of $P < 0.05$ for the interaction between experimental condition and the assessment period.

As the number of the participants considerably dropped following the 1-month assessment due to issues of statistical power, we focus on the 1-month assessment and on the follow-up examination [4]. The results and all statistical analyses for the 4.5- and 6-month assessments are available in the supplementary information section.

RESULTS

Baseline assessment and physiological effects

Table 2 shows the baseline assessments for the DHEA and placebo conditions. As can be seen, there were no significant differences in any of the psychological tests, indicating that the random selection process did not bias the sample. No adverse side effects were recorded in either group.

We next examined the effect of treatment on blood DHEA-S, DHEA and cortisol levels. The results are shown in Fig. 1. As can be seen, for DHEA-S there was no difference between conditions at baseline. However, starting from the first month of treatment there was a substantial

[3] In this analysis, the score of 'negative' tests (i.e. the PANAS negative, TAI and BIS-11) was inverted to ensure unidirectionality.

[4] Although there were 49 participants in the 4.5 months assessment, only 27 of them consented to complete the psychological tests. In the 6-month assessment, of the remaining 26 participants, 15 completed the tests.

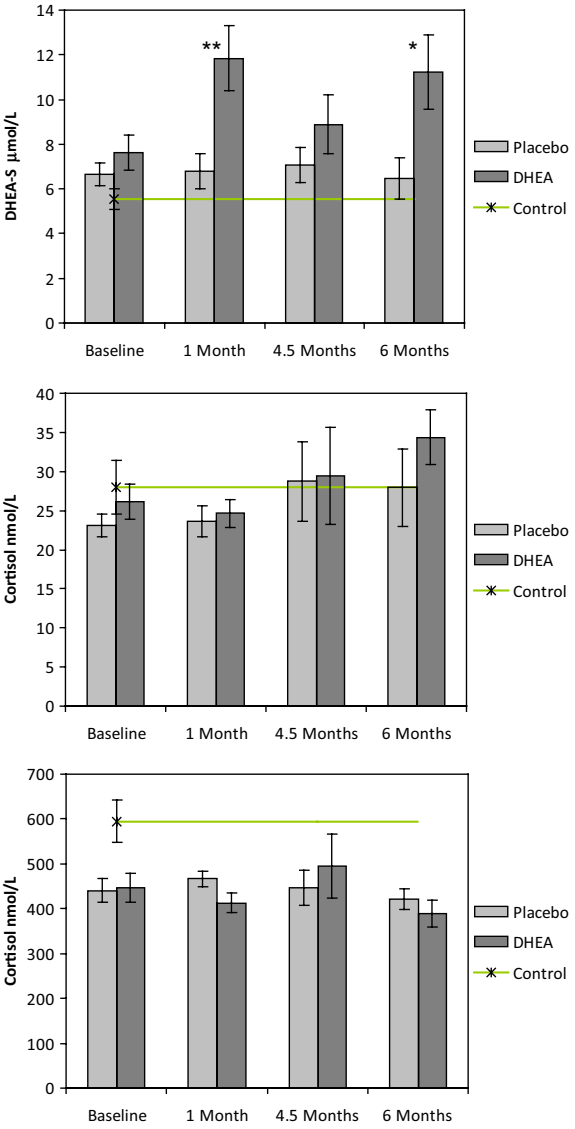

Figure 1 Dehydroepiandrosterone sulfate (DHEA-S), DHEA and cortisol levels during treatment. The control sample of healthy adults was assessed once. Error terms denote the standard errors. $^{**}P < 0.01$; $^{*}P < 0.05$

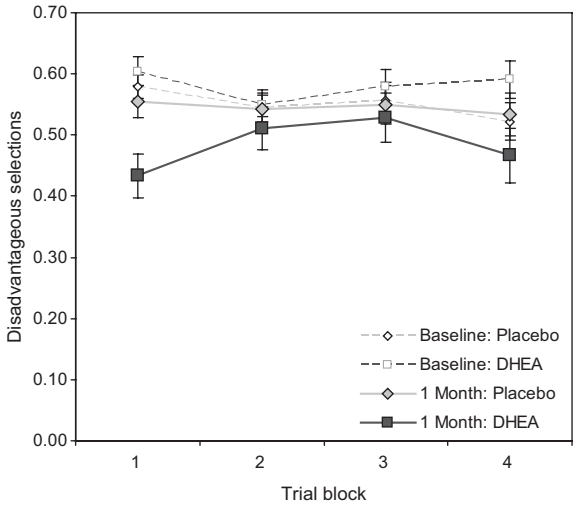

Figure 2 Proportion of selections from the disadvantageous decks of the Iowa gambling task for the dehydroepiandrosterone (DHEA) and placebo conditions at baseline and following 1 month. Error terms denote standard errors

increase in DHEA-S in the DHEA condition (the somewhat smaller difference between conditions following 4.5 months could be due to a selection bias among those who stayed in the study).

Mood and well-being

The results of all psychological tests (see Table 2) were subjected to a mixed analysis of variance, with experimental condition as a between-subject factor and assessment period as a within-subject factor. As noted earlier, we initially examined all psychological tests in a single analysis using ANCOVA. The result of this index showed only a marginally significant effect of the assessment period [$F(1, 38) = 3.51$, $P = 0.07$]. However, there was an interaction of assessment period by experimental condition [$F(1, 190) = 4.28$, $P = 0.04$], suggesting that DHEA differentially affected the tests outcome.

An analysis of specific tests (see Table 2) showed that there was a positive effect of the assessment period on the Q-LES-Q [$F(1,44) = 13.18$, $P = .001$], and a negative effect on the BIS attention scale [$F(1,42) = 4.83$, $P = 0.03$]. Thus, participants reported enhanced well-being and overall life satisfaction and less impulsiveness as a result of their stay in the rehabilitation center, independently of the experimental condition. For the PANAS negative affect scale, there was no main effect, but instead, a condition by assessment period interaction [$F(1, 44) = 4.25$, $P = 0.045$]. *Post hoc* tests showed that at baseline, the two groups were not significantly different on this measure [$t(48) = 0.69$, $P = 0.56$], while after 1 month the DHEA group reported fewer negative emotions [$t(44) = 1.73$, $P = 0.08$].

Decision making

The performance levels on the IGT are shown in Fig. 2 and summarized in Table 2. Following 1 month, the DHEA group chose more advantageously than at baseline, whereas no difference emerged for the placebo group. However, a mixed ANOVA (as above) showed only a marginally significant interaction of condition by assessment period [$F(62) = 3.42$, $P = 0.069$] and a marginally significant three-way interaction of condition by period by trial block [$F(62) = 2.37$, $P = 0.079$]. *Post hoc* tests revealed that for the placebo group, there was no difference in performance between sessions [$t(33) = 0.14$, $P = 0.44$] but for the DHEA group there

were more advantageous selections in the 1-month session than in the baseline session [$t(29) = 2.79$, $P = 0.01$]. Nevertheless, the difference between the DHEA and placebo group in the 1-month assessment did not reach significance [$t(62) = 0.55$, $P = 0.13$].

Relapse to drug use

At the follow-up test conducted about 16 months after treatment, there was a substantial difference in relapse rates between groups. As shown in Fig. 3, the rate of drug relapse in the placebo condition was 37.9 percent while in the DHEA condition it was only 11.5 percent, showing a significant disparity ($\chi^2 = 5.03$, $P = 0.02$). For those in the DHEA condition, the rate of reuse in the follow-up test was similar irrespective of the numbers of month in treatment (1 month: 11 percent, 2 months: 11 percent, 3 months: 13 percent).

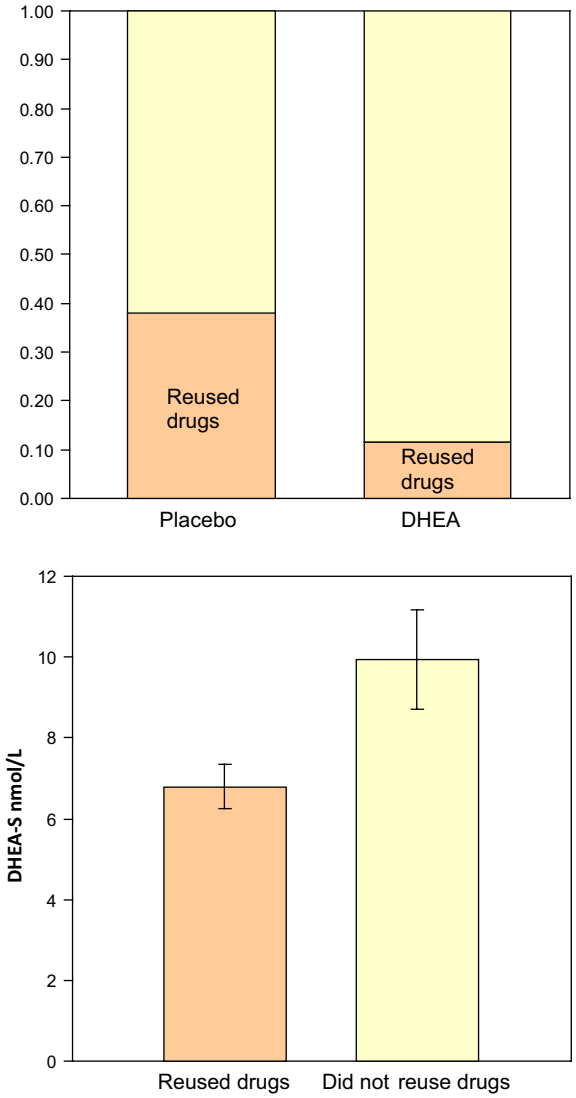

Figure 3 Top: Rates of relapse into drug use approximately 16 months following treatment in the placebo and dehydroepiandrosterone (DHEA) conditions. Bottom: DHEA sulfate (DHEA-S) level 1 month following treatment among those who eventually reused or did not reuse drugs (following 16 months). Error terms denote standard errors

We proceeded by examining whether relapse following treatment was predicted by DHEA-S levels. Compared with their counterparts, individuals who reused drugs following treatment did not show lower DHEA-S levels prior to treatment (placebo: 6.8 ± 0.73; DHEA: 7.43 ± 0.65). However, they had lower levels of DHEA-S following 1 month of treatment [see Fig. 3, bottom pane; $t(34) = 2.34$, $P = 0.03$]. This seemed to be an effect of condition, as the level of DHEA-S was not a significant predictor in the placebo group [$t(20) = 0.16$, $P = 0.87$]. Additionally, we conducted exploratory tests for whether other experimental variables were associated with relapse (using Bonferroni corrected *P*-values). The results are presented in Table 3. The only variable that predicted subsequent relapse was the participants' level of involvement in rehabilitation center activities. Although involvement level was similar in the two experimental conditions (placebo: 73.7 percent; DHEA: 68.2 percent), those who relapsed were less involved in the activities of the rehabilitation center [$t(50) = 3.48$, $P = 0.009$].

Finally, we also examined whether there are moderators for the effect of DHEA on relapse rates. This was tested in a logistic regression with drug reuse at the follow-up test as the dependent variance. None of the experimental variables interacted with the effect of DHEA administration. However, this may be due to the relatively low rate of reuse, which implies low degrees of freedom in any test of interaction.

DISCUSSION

This study has shown for the first time that DHEA add-on administration can substantially improve the recovery process of polydrug users treated in a rehabilitation center. The number of those who eventually relapsed about 16 months following treatment was about a third compared with those who relapsed following placebo (12 versus 38 percent). Additionally, based on the PANAS scale, DHEA seemed to decrease negative affect during treatment. Although these results were obtained with a relatively limited number of participants, it seems that they highlight the potential relevance of findings of animal studies of DHEA (e.g. Doron *et al.* 2006a,b) to the recovery following addiction of human addicts.

Additionally, one of the challenges of rehabilitation centers is to predict the patients' future reuse decisions in order to determine the efficiency of treatment strategies and the required duration of treatment (Sinha 2008). Our experimental approach revealed mixed findings in this respect. Although the baseline level of DHEA-S was

Table 3 Mean scores of self-report and cognitive tests following 1 month of treatment for those who eventually reused or did not reuse drugs following 16 months.

	Reused drugs	*Did not reuse drugs*	t-*test*
Flourishing scale	5.37 (±0.29)	5.00 (±0.36)	$t = 0.81$
PANAS positive	3.44 (±0.16)	3.17 (±0.27)	$t = 0.86$
PANAS negative	3.12 (±0.32)	2.71 (±0.18)	$t = 1.12$
Q-LES-Q-SF	3.59 (±0.17)	3.40 (±0.15)	$t = 0.81$
TAI form-Y2	2.67 (±0.20)	2.50 (±0.08)	$t = 0.78$
BIS-11	2.73 (±0.18)	2.32 (±0.12)	$t = 1.89$
IGT—Dis. decks	0.59 (±0.05)	0.51 (±0.04)	$t = 2.04$
FPGT—Dis. decks	0.46 (±0.07)	0.40 (±0.04)	$t = 0.74$
Involvement	57.15 (±6.32)	81.54 (±3.47)	$t = 3.47$**

Note: Involvement was recorded at the end of treatment. The means and standard errors (in parentheses) are followed by *t*-statistics.
**Bonferroni corrected $P < 0.01$.
BIS = Barratt Impulsiveness Scale; DHEA = dehydroepiandrosterone; Dis. = disadvantageous; FPGT = Foregone Payoff Gambling Task; IGT = Iowa Gambling Task; PANAS = Positive and Negative Affect Scale; Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire; TAI = Trait Anxiety Inventory.

not predictive of eventual outcomes, DHEA-S level following 1 month of treatment was predictive of the decreased tendency to reuse drugs.

Limitations of the current findings include the relatively small sample size, and the fact that there was considerable attrition during the study (about 30 percent in month 1 and about 70 percent in month 6). Still, treatment effects in the current study cannot be attributed to attrition because the rate of those who dropped out during the first month of the study was similar in the two experimental conditions. Moreover, we were able to get relapse results (16 months post-treatment) for most of the participants who remained in the study for 1 month or more, and the analysis of relapse also included groups with similar attrition rates. Furthermore, the findings suggest that the effect of DHEA on drug reuse was relatively robust to the duration of treatment: a 1-month treatment was as effective as a 6-month treatment. Thus, the fact that many participants discontinued their use of DHEA (or placebo) following 1 month was not detrimental. Nevertheless, further studies should be conducted to determine the optimal duration and to assess the consequence of using DHEA for a more extended period.

Another limitation concerns the fact that our measure of relapse was based primarily on self-report (of patients as well as rehabilitation staff and hostel personnel). Although the use of self-report measures for assessing relapse is quite common, a more stringent treatment would have been to conduct urine or blood tests in order to verify this information. Also, our results were not conclusive concerning some of the outcome variables taken during the rehabilitation. We have found that DHEA lowered negative affect on the PANAS, and this is consistent with the previously reported positive effects of DHEA on mood (Morales *et al*. 1994; Wolkowitz *et al*. 1999). However, the PANAS negative affect scale did not predict later relapse, thus suggesting that it does not reliably mediate the effect of DHEA on successful recovery. Additionally, the results for the IGT were somewhat ambiguous. Although an improvement in task score was recorded in the DHEA condition but not in the placebo condition, the interaction between treatment and time was above the 0.05 *P*-value cut-off. Thus, the question of the mechanism driving the observed long-term effect of DHEA on relapse remains open. Possibly, the long-term effect may be to some extent modulated by the effect of DHEA on neurotransmitter receptors, such as γ-aminobutyric-acid type, *N*-methyl-D-aspartate (NMDA) and sigma-1 receptors that contribute to the enduring behavioral effects of substances of abuse (Yadid *et al*. 2010) or by neuro-genesis at the dentate gyrus (Deschaux *et al*. 2014). Future studies should examine the role of these neural mechanisms in mediating the effect of DHEA in human addicts.

Still, despite these limitations, the current findings offer a first confirmation for a potential long-term effect of DHEA on drug reuse. Also, as importantly, the study provides multiple lessons toward conducting a large multisite assessment of the effect of DHEA. First of all, the results suggest that a dosage of 100 mg/day, for which previously (Strous *et al*. 2005) and in the current study as well no adverse symptoms were recorded, is sufficient to have an effect. Second, a 1-month treatment seems to be sufficient to produce a significant effect. Third, the results suggest the value of monitoring DHEA-S levels during treatment, as these seem to be predictive of eventual treatment outcomes. Finally, the results suggest that an effect of DHEA on subsequent relapse can emerge even in treatment centers with an extensive enrichment program. For instance, in the placebo condition, the rate of reuse more than a year after leaving the rehabilitation center was about 38 percent, which is at the low end of the typically observed rates (McLellan *et al*. 2000; NIDA

2010). Indeed, our view is that the present findings reflect the combined influence of DHEA and an intensive psycho-social intervention. The applicability of using DHEA in other types of interventions should be verified.

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Authors Contribution

GY, EY, AW, PR and AMP contributed to the study concept and design. DO coordinated the study with guidance from RM. EY, GY and DO conducted the data analysis and interpretation of findings. EY drafted the manuscript. All authors provided critical revisions of the manuscript. All authors critically reviewed content and approved final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Payoff structure of the Iowa gambling task (Bechara *et al.* 1994)

Table S2 Payoff structure of the Foregone Payoff Gambling Task (*Ert et al.* 2013; Agay *et al.* 2010)

Table S3 Mean scores on self-report and cognitive tests following 4.5 and 6 months of treatment for the DHEA and placebo conditions. Standard errors appear in parentheses

Table S4 Analysis of variance results for the tests taken at 4.5 and 6.0 months