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Gene Narcotic Attenuation Program Attenuates Substance Use Disorder, a Clinical Subtype of Reward Deficiency Syndrome

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ABSTRACT

This study evaluated the effects of a putative activator of brain reward circuitry on outcomes in a 1-y prospective comprehensive outpatient clinical program. As part of the Gene Narcotic Attenuation Program, Haveos (Synaptamine)™ was administered for the treatment of substance use disorder. Seventy-six patients (45 males and 31 females; mean age, 33 y [standard deviation, 7.0]) who had been given a diagnosis of serious substance use disorder were recruited. After exclusion of 15 patients who dropped out before the end of the study, self-reported craving decreased from program entrance to 12 wk (visual analog scale whereby 0 represents no craving and 5, the strongest craving) for 61 compliant patients (mean decrease, 2.85, 95% confidence interval [CI], 2.65, 3.05); this improvement was

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significant ($P<.001$). Building up to relapse scores (each of 5 individual items and summary value) showed similar improvement after 1 y of treatment; the mean decrease in scores was significant for stress (t=3.3; $P=.002$), depression (t=4.0; $P<.001$), anger (t=4.4; $P<.001$), anxiety (t=4.5, $P<.001$), drug craving (t=5.4, $P<.001$), and summary building up to relapse (t=4.1; $P<.001$). Also, recovery score measures of energy level (t=8.4; $P<.001$) and ability to refrain from drug-seeking behavior (t=7.4; $P<.001$) showed significant mean increases from entry to 1 y. During the study, the alcoholic dropout rate was only 7% (4 of 57), which was significantly (Fisher's exact test, $P<.001$) lower than the 73% (11 of 15) dropout rate reported for psychostimulant users. Although these results are significant, any interpretation must await the performance of rigorous double-blind studies.

Keywords: substance use disorder; catecholamine-O-methyltransferase inhibition; enkephalinase inhibition; neurotransmitter precursors; Haveos (Synaptamine)™; reward deficiency syndrome (RDS)

INTRODUCTION

Substance use disorder (SUD) is considered a global epidemic. According to a 2004 report from the Office of National Drug Control Policy, the 2002 estimate for economic cost of drug abuse was $181 billion and the 1998 estimate for alcohol abuse was $185 billion.[1] More recently, the prevalence rates of 12-mo DSM-IV *(Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)* independent mood and anxiety disorders in the US population were 9.21% (95% confidence interval [CI], 8.78, 9.64) and 11.08% (95% CI, 10.43, 11.73), respectively. The rate of SUD was 9.35% (95% CI, 8.86, 9.84). A few individuals with mood or anxiety disorders were classified as having only SUD. Associations between most SUDs and independent mood and anxiety disorders were positive and significant ($P<.05$).[2]

A consensus of the literature suggests that when dysfunction occurs in the brain reward circuitry or cascade (in the mesolimbic region), neurochemical support therapy is warranted. It has been reasoned that dysfunction in this area of the brain may be caused by certain genetic variants (polygenic), especially in the dopaminergic (DAergic) system, causing a hypodopaminergic trait (dopamine [DA] D2 receptor paucity or deficiency at the nucleus accumbens [NAC]), as suggested by Blum et al[3] and Gardner.[4] Carrying the drug-seeking genotype of the brain of that person requires DAergic activation. This trait leads to multiple drug-seeking behaviors[5-8] because alcohol and psychostimulants like cocaine, heroin, marijuana, nicotine, and glucose cause activation and neuronal release of brain DA; this, in turn may help to attenuate craving behavior.[9] In an attempt to explain impairment of the reward cascade due to multiple genes, environmental stimuli (pleiotropism), and resultant aberrant behaviors, Blum et al[10,11] united this hypodopaminergic trait under the rubric of a reward deficiency syndrome (RDS). This is a relatively new concept, and some have embraced the terminology,[12-24] although others have argued its validity.[25] RDS is defined as follows: "A multifactorial condition in which, among other things, stress, environmental influences, and poor lifestyle activities can affect and/or exacerbate inborn genetic predispositions that can lead to imbalances and deficiencies retarding the brain's competent management of the multitude of functions necessary to maintain optimal neurometabolic efficiency."[26]

It is hypothesized that when neurotransmitter synthesis promoters, opioid peptide catabolism inhibitors, brain serotonin synthesis enhancers, and catecholamine-O-methyltransferase inhibitors are combined in a nutraceutical formulation, the product so conceived will significantly reduce aberrant substance-seeking behavior in humans. The mechanism and rationale for this hypothesis have been the subject of a number of earlier studies.[27-33] The present study was undertaken to test this hypothesis.

METHODS

Subjects

In this preliminary outpatient open trial, a total of 76 patients (45 males and 31 females; mean age, 33 y; standard deviation, 7.0) were recruited from the Clark County district attorney's office and judicial system and the US federal court system, and through self-referral. An open-label pilot study was carried out on 76 subjects, comprising 57 alcohol abusers, 11 cocaine abusers, 4 heroin abusers, 14 methamphetamine abusers, and 3 prescription drug abusers. (Note: 13 subjects abused multiple drugs.) Each alcohol abuser had been convicted of at least 1 DUI (charge of driving under the influence) in the prior 2 y, and each psychostimulant abuser (primarily methamphetamine; 2 were habitual cocaine users) had been convicted of at least 2 parole violations over a 1-y period. Each subject had failed several other treatment modalities. (Self-referral participants were accepted only if they had failed other treatment modalities. Failure was confirmed by documentation.)

Each person was given approximately 2 h of instruction on the neurochemical effects of drug dependency and the importance of neurotransmitter restoration in the recovery process. Fifty-seven patients were mandated to participate in the program; 19 were self-referred and volunteered on a cost basis. All patients signed an approved institutional review board (IRB) consent form (registration #IRB00002334). The study population was 75% white, 20% Hispanic, and 5% mixed race. There were no African Americans, Native Americans, or Asians in the study population. Each referral group was further characterized according to drug of choice. Table 1 details the demographic characteristics of the referral groups.

Diagnosis

Upon entry into the program, all patients were screened for SUD with the DSM-IV checklist. A signed consent form was submitted by each participant; a complete history was obtained via a 1-h structured interview, and all patients underwent a complete physical examination performed by an attending physician who approved the use of nutritional supplements on an individual basis. Treatment was then begun.

Treatment

Each patient was seen every day for the first 2 wk, 3 times a week for 8 wk, and 1 time a week for the duration of the program. Abstinence from all psychoactive drugs was required. The use of nicotine and caffeine was not permitted during therapy sessions. Treatment consisted of establishment of sober relationships, a balanced diet, daily exercise, auricular therapy, a 12-step program for spiritual growth, and use of

Table 1. Demographics of Subjects by Drug of Choice

Drug of Choice, n	CCD		CCJ		FCS		SR		Total	
	M=17	F=6	M=13	F=10	M=8	F=3	M=7	F=12	M=45	F=31
EOH	17	6	11	6	7	2	4	4	39	18
COC	0	0	1	2	4	0	2	2	7	4
MET	0	0	2	4	0	1	1	6	3	11
OPI	0	0	0	0	0	0	2	1	2	1
HER	0	0	0	0	0	0	3	1	3	1

CCD=Clark County District Attorney's Office; CCJ=Clark County Judicial System; FCS=US federal court system; SR=self-referral; EOH=alcohol; COC=cocaine; MET=methamphetamine; OPI=opiate; HER=heroin.

nutritional supplements (Formula 1, Formula 2, or Formula 3) selected according to the abused substance of choice. Counseling was also provided.

Measurements and Monitoring

A 3-part inventory was completed daily (suggested 1 h prior to sleep). Section A (visual analog scale [VAS]) measured stress, depression, anger, anxiety, and drug craving; section B (nonstandardized 5-point scale for recovery[26-30]) assessed energy, self-confidence regarding abstinence from drugs, and feelings of well-being; and section C (yes/no) documented level of compliance.

Answers to questions in the self-report were rated as building up to relapse (BUR; reduced stress, depression, anxiety, and drug cravings) or as recovery score (RS; improved energy, self-confidence, ability to refrain from drug-seeking behavior, and feelings of well-being). Continued participation in the program was monitored.

Individual ingredients of treatment products are presented in Table 2. Treatment agents act by means of slow release of dopamine through a controlled time-release process.[28,31,34-38] Ingredients of selected treatment products varied according to the substance of choice. Each patient was instructed to take 3 tablets of the respective reward supplement in the morning 45 min before breakfast and 3 tablets 45 min before dinner (Table 2).

Relapse Criteria

For the first 3 mo of the program, relapse was defined as the use of any psychoactive drug. After the first 3 mo, 3 types of relapse severity were recognized. Relapse A was defined as an isolated episode involving very little drug consumption (ie, 2 drinks for alcoholics, or less than 0.25 g for cocaine addicts and 50 g of heroin for opiate-dependent individuals); the patient was able to stop drug use and remained open to reviewing precipitating events and taking corrective action. Relapse B was defined as the occurrence of more than 1 relapse incident with the patient remaining open about the problem, showing a strong motivation to explore precipitating events, and willing to take corrective action. Relapse C occurred when the patient dropped out of therapy as the result of relapse or rearrest, plea bargain-

ing, or dismissal by the parole officer and had an apparent loss of motivation to continue with the recovery process or to reestablish contact. The overall relapse type based on study criteria was defined as C.

Table 2. Treatment Ingredients*

Ingredients	Formula 1 Daily Amount	Formula 2 Daily Amount	Formula 3 Daily Amount
5-Hydroxytryptophane	20 mg	20 mg	20 mg
DI-phenylalanine	2700 mg	2700 mg	2700 mg
L-glutamine	350 mg	350 mg	350 mg
Rhodiola rosea (3% rosavin)	33 mg	33 mg	50 mg
Chromium dinicotinate glycinate	1000 μg	1000 μg	1000 μg
Dimethylaminoethanol	NA	NA	40 mg
L-tyrosine	NA	750 mg	750 mg
DL-methionine	NA	30 mg	30 mg
Ferulic acid	NA	50 mg	50 mg
Huperzine A	NA	NA	150 μg

*Combination of vitamins (C, E, niacin, riboflavin, thiamin, B_6 [20% pyridoxal-5 phosphate and 80% pyridoxine], folic acid, B_{12}, biotin, pantothenic acid, calcium, magnesium, zinc, manganese) and an herbal cognitive-enhancing blend.

NA=nonapplicable.

Craving Score

Investigators used a modified VAS from 0 to 5, whereby 0 represented no craving and 5 was the strongest craving. On a daily or weekly basis, each patient was assessed for craving behavior for their substance of choice (alcohol, methamphetamine, or heroin). This subjective measure was rated by both the attending clinician and the patient. The mean of the 2 scores was used for the statistical analysis. Craving scores were assessed for 12 mo. Only 12- and 40-wk posttreatment data were used in the statistical analysis.

Statistics

Time-dependent paired processes were evaluated with 1-sample Student *t* tests for scores of interest (T value). Benchmark reference values used to define clinical benefit were derived from mean entry scores. For entry to 12 wk craving change scores and for entry to 1 y BUR change scores, the mean reduction was regarded as clinically significant if it resulted in at least a 50% reduction in the mean entry score. For 12- to 40-wk craving change scores, the null hypothesis was that the mean change

was 0. For entry to 1 y recovery change scores, the mean increase was regarded as clinically significant if it resulted in at least a 100% increase from mean entry score. For each 1-sample Student *t* test, the value of the t statistic was reported, along with its associated *P* value. For all statistical tests, $P<.05$ was considered statistically significant; hence, 95% CIs were reported. Stata 9.2 (Stata Corp, College Station, Tex) was used in the analyses.

RESULTS

Fifteen participants were lost to follow-up; statistical analyses were performed on data from the remaining 61 subjects. Relapse rates are presented in Table 3.

Table 3. Demographics and Relapse Data

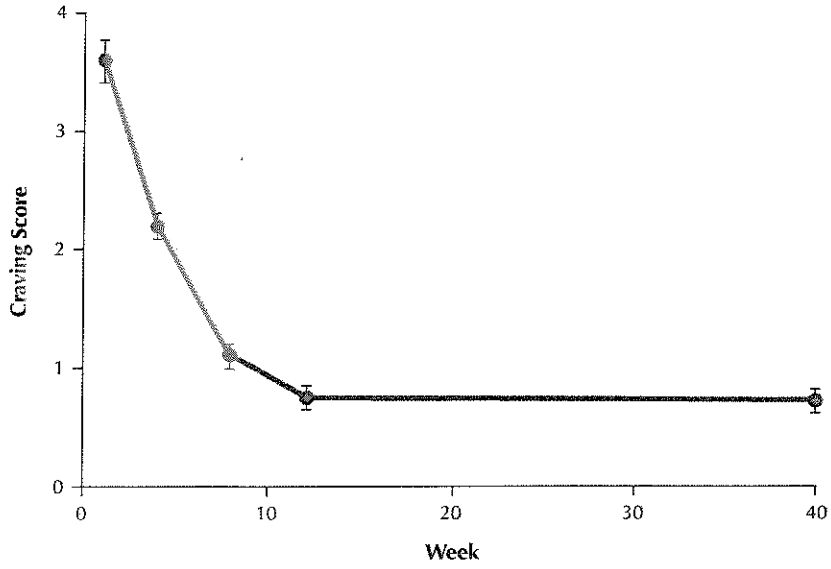
Clark County DA*	Clark County†	US Federal Courts‡	Self Referral§
23 patients	23 patients	11 patients	19 patients
(M, 17; F, 6)	(M, 13; F, 10)	(M, 8; F, 3)	(M, 7; F, 12)
18 stayed for 12 mo	15 stayed for 12 mo	9 stayed for 12 mo	19 stayed for 12 mo
5 patients dropped out	8 dropped out	2 dropped out	0 dropped out
% relapse, 21.7	% relapse, 34.8	% relapse, 18.2	% relapse, 0

*District attorney.
†Clark County—drug-related charges pending in greater Las Vegas, Nevada metropolitan area.
‡US Federal Courts—patient sent by parole and probation for drug-related federal charges.
§Self-referral—no legal charges pending. The subject was in danger of losing job, family, health, etc. Highly motivated because self or family paid for the program (no insurance or third-party payment).

Craving Scores

The average craving score was calculated for the 61 compliant patients. After the second month of treatment, negative craving (a score of 1) for the respective substance of choice remained the same throughout the program (Fig 1 shows entry and 4, 8, 12, and 40 weeks of craving scores). Cravings in the amphetamine group did not consistently drop, which may have contributed to the high dropout rate. No reason has been determined, but it has been suggested that the cause might be dopaminergic genetics in terms of pharmacogenomic response based on genotype and methamphetamine insult to dopaminergic pathways. When mean change in craving score from entrance (mean, 3.6; 95% CI: 3.42, 3.78) was compared with the 12-wk (mean, 0.75; 95% CI: 0.65, 0.85) mark, the reduction in craving score (mean, 2.85; 95% CI: 2.65, 3.05) was significantly greater than the benchmark reference value of 1.8 ($t=10.3$; $P<.001$), indicating clinical improvement. When compared with 40-wk scores (mean, 0.72; 95% CI: 0.62, 0.82), 12- to 40-wk craving change scores (mean, 0.03; 95% CI: –0.07, 0.13) did not significantly differ from 0 ($t=0.6$; $P=.56$).

Fig 1. The graph represents calculated substance of choice craving score means along with 95% CIs for entry and 4, 8, 12, and 40 weeks. A total of 61 subjects were analyzed.



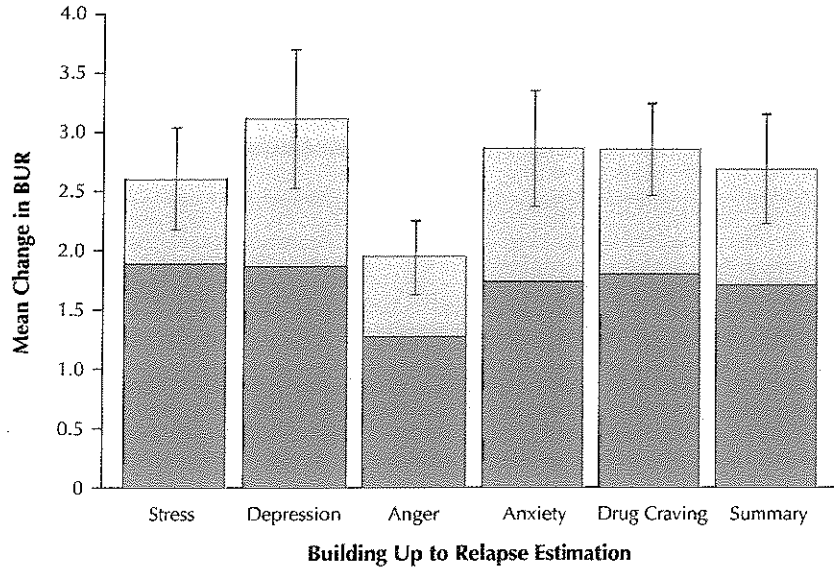
BUR Estimation

Figure 2 depicts the mean changes in BUR scores from entrance until the last month for all compliant patients. BUR scores represent a daily average for stress, depression, anger, anxiety, and drug craving.

On a scale from 0 to 5 (5, most severe), findings were as follows: stress→mean, 3.80 (95% CI: 3.46, 4.14); depression→mean, 3.75 (95% CI: 3.28, 4.22); anger→mean, 2.55 (95% CI: 2.31, 2.79); anxiety→mean, 3.50 (95% CI: 3.12, 3.88); drug craving→mean, 3.60 (95% CI: 3.29, 3.91); and summary BUR score→mean, 3.45 (95% CI: 3.08, 3.82).

The range of possible BUR change (entry minus endpoint) scores is –5 to 5, with 5 representing maximum improvement. Findings were as follows: stress level change→ mean, 2.60 (95% CI: 2.18, 3.02); significantly greater than the reference value of 1.90 (t=3.3; P=.002); depression change→mean, 3.10 (95% CI: 2.51, 3.69); significantly greater than the reference value of 1.88 (t=4.0; P<.001); anger change→mean, 1.95 (95% CI: 1.65, 2.25); significantly greater than the reference value of 1.28 (t=4.4; P<.001); anxiety change→mean, 2.85 (95% CI: 2.37, 3.33); significantly greater than the reference value of 1.75 (t=4.5; P<.001); drug craving change→mean, 2.85 (95% CI: 2.47, 3.23); significantly greater than the reference value of 1.80 (t=5.4; P<.001); and summary BUR score change→mean, 2.68 (95% CI: 2.22, 3.14); significantly greater than the reference value of 1.725 (t=4.1; P<.001). For each behavior, mean score reduction was significantly greater than 50%.

Fig 2. Mean decrease in BUR scores from entrance (pretest) to the last month (posttest) for all compliant patients (n=61).



The benchmark reference value for clinical improvement (50% reduction from the entry mean) is represented by the top of the dark gray portion of the bar. The observed mean BUR score decrease along with 95% CI is represented by the top of the light gray portion of the bar.

Recovery Score

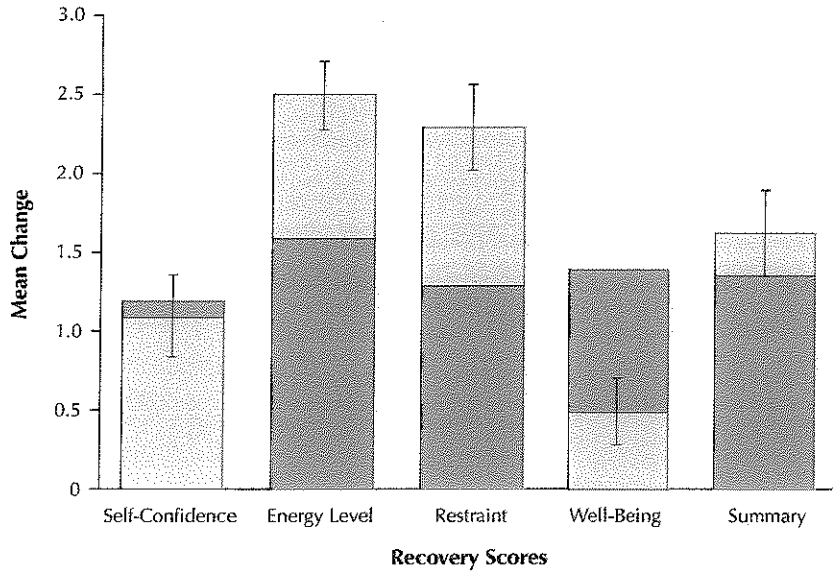
Figure 3 represents mean RS changes from entrance (pretest) to the last month (posttest) for all compliant patients. RS represents a daily average of self-confidence, energy level, ability to refrain from drug-seeking behavior, and well-being.

On a scale from 1 to 5 (5 most positive), findings were as follows: self-confidence level→mean, 1.2 (95% CI: 1.00, 1.42); energy level→mean, 1.6 (95% CI: 1.44, 1.76); ability to refrain from drug-seeking behavior→mean, 1.3 (95% CI: 1.09, 1.51); feelings of well-being→mean, 1.4 (95% CI: 1.21, 1.59); and summary RS→mean, 1.37 (95% CI: 1.17, 1.57).

The range of possible RS change (endpoint minus entry) scores is –4 to 4, with 4 representing maximum improvement. Findings were as follows: self-confidence level change→mean, 1.1 (95% CI: 0.85, 1.35); no significant difference from the reference value of 1.2 (t=–0.8; P=.44); energy level change→mean, 2.5 (95% CI: 2.29, 2.71); significantly greater than the reference value of 1.6 (t=8.4; P<.001); ability to refrain from drug-seeking behavior change→mean, 2.3 (95% CI: 2.04, 2.56); significantly greater than the reference value of 1.3 (t=7.4; P<.001); feelings of well-being change →mean, 0.5 (95% CI: 0.28, 0.72); significantly lower than the reference value of 1.4 (t=–8.2; P<.001); and summary RS→mean, 1.63 (95% CI, 1.36, 1.90); not significantly different from the reference value of 1.37 (t=1.9; P=.064). Except for self-confidence

level and feelings of well-being, recovery change score means were greater than reference values, indicating improvement in energy level, restraint, and summary RS.

Fig 3. Mean increase in recovery scores from the first month (pretest) to the last month (posttest) for all compliant patients (n=61).



The benchmark reference value for clinical improvement (100% mean increase from entry) is represented by the top of the dark gray portion of the bar. The mean observed recovery score increase along with 95% CI is represented by the top of the light gray portion of the bar. For the 2 bars with the lower portion colored light gray and the upper portion colored dark gray, the mean recovery score increase was less than the benchmark reference value.

Compliance and Retention

Patients who participated in this study were grouped according to their drug of choice (ie, alcohol, psychostimulants, or heroin). Because only 4 were heroin users, dropout rates of the 57 alcoholics were compared with those among the 15 psychostimulant users. During the study, the alcoholic dropout rate was only 7% (4 of 57), which was significantly (Fisher's exact test, $P<.001$) lower than the 73% (11 of 15) dropout rate reported for the psychostimulant group. All 4 heroin addicts remained in the program.

DISCUSSION

When relapse rates from the literature (56% for alcoholics; 90% for cocaine- or stimulant-dependent subjects) are compared with the findings reported here,[39,40] earlier results in DUI offenders[32] and results reported here are significant, suggest-

ing a potentially new mode of adjunctive treatment in alcohol, heroin, and psychostimulant dependence. Similar to the first DUI study, in which a variant of Haveos (no chromium, no rhodiola) was used, investigators found that relapse rates during the first 12 wk were not statistically significant at the end of 12 mo. In both studies, relapse usually occurred early on, most often before the 12th week of the program. The study finding of 79.1% recovery is considered significant by the court system.

Observational data on outcomes, which were not subjective but were based on interviews with disciplinary officials, were consistent. Through oral and written reports, the evaluation reported here consistently revealed primarily positive observations. Study results suggest that after a 3-mo treatment period, patients showed great overall improvement.

Investigators hypothesize that motivation of the individual could have affected overall results. Those recruited through the judicial system had a different level of motivation than the self-referral group. Members of the former group were motivated by fear of incarceration, and most did not pay for the program. In contrast, the self-referral group had strong family and job pressures and had to pay for the program themselves because no third party payment was provided.

This study had several limitations. First, this was not a randomized, blinded, placebo-controlled study. Because of the study design, investigators could not differentiate the beneficial effects of the entire gene narcotic attenuation program from those of Haveos alone. Many nutritional supplements are offered on the market for SUD recovery, but only a few[27-33] have been adequately demonstrated to provide a significant clinical advantage when combined with good diet, rest, and recovery strategies (ie, abstinence, cognitive/behavioral therapy, 12-step program participation, and urine testing). Furthermore, without the use of a biomarker, investigators were not assured of the compliance of participants in taking the prescribed study medication.

Another limitation of this trial is that participant data were self-reported and the time of day of data collection was not consistent. Also, scoring scales were not standardized, and this may represent a deviation from normal, resulting in bias and limited information.

Only 2 RS change score means (energy level and restraint) were well above the reference value. These factors are more directly related to drug use than are self-confidence and well-being, which may be kept low by environmental factors for which the patient has begun to rely on defense mechanisms other than substance abuse.

CONCLUSION

It is suggested that future double-blind, randomized, controlled studies are needed to confirm the results of this and earlier studies.[27-33,41] Because it is well known that drug-seeking behavior is due in part to certain genetic antecedents,[10] treatment attenuation of this behavior must be addressed pharmacologically or nutraceutically through incorporation of pharmacogenomic principles (pre-DNA testing to determine drug-seeking genotypes)[42] related to RDS.[21,26]

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DECLARATION OF INTEREST

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