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Enkephalinase Inhibition and Precursor Amino Acid Loading Improves Inpatient Treatment of Alcohol and Polydrug Abusers: Double-Blind Placebo-Controlled Study of the Nutritional Adjunct SAAVE™

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BLUM, K., M. C. TRACHTENBERG, C. E. ELLIOTT, M. L. DINGLER, R. L. SEXTON, A. I. SAMUELS AND L. CATALDIE. *Enkephalinase inhibition and precursor amino acid loading improves inpatient treatment of alcohol and polydrug abusers: Double-blind placebo-controlled study of the nutritional adjunct SAAVE™*. ALCOHOL 5(6) 481–493, 1988.—We investigated the effects of the amino acid and vitamin mixture SAAVE in inpatient, chemically-dependent subjects to evaluate the role of neurotransmitters in facilitating recovery and adjustment to a detoxified, sober state. SAAVE is formulated from amino acids that are precursors for neurotransmitters and neuromodulators thought to be involved in alcohol and drug seeking behavior. In a double-blind, placebo-controlled, randomized study of 62 alcoholics and polydrug abusers, SAAVE patients had a significantly reduced stress response as measured by the skin conductance level (SCL), and significantly improved Physical Scores and BESS Scores (behavioral, emotional, social and spiritual). After detoxification there was a six-fold decrease in AMA rates when comparing SAAVE vs. placebo groups. In this inpatient treatment experience SAAVE facilitated the rate of recovery and allowed patients to respond more fully and more quickly to the behavioral goals of the program, for example as measured by the BESS Score. The use of SAAVE to achieve enkephalinase inhibition and precursor amino acid loading in the acute inpatient treatment environment provides the practitioner with the potential ability to restore the neurochemical changes inherent to alcoholism and drug abuse. These findings increase our understanding of the clinically relevant neurobiological mechanisms which underlie compulsive disease.

Alcohol Nutrition Treatment Amino acid Enkephalinase inhibition

RECENTLY, Blum *et al.* (8) provided the first report of decreased ethanol intake by enkephalinase inhibition. Using strains of mice with a genetic preference for alcohol, they demonstrated an inverse relationship between ethanol intake and brain enkephalin levels. Acute and chronic treatment with hydrocinnamic acid and D-phenylalanine (DPA), known carboxypeptidase (enkephalinase) inhibitors significantly attenuates both volitional and forced-choice ethanol intake (18, 20, 25, 28). Furthermore, DPA, in a double-blind study in humans significantly reduced pain in morphine resistant patients to a higher degree than placebo (1) and significantly reduced the need for benzodiazepines in patients undergoing treatment for alcoholism (14). Since these agents raise brain enkephalin levels (7, 25) and recent experiments of Banks *et al.* (2) showed that circulating met-enkephalin transported from blood to brain by an active carrier, we proposed that alcohol craving could be regulated by altering endogenous brain opioid peptides.

DPA has been administered to mice at a variety of doses and for different durations without untoward effect. The LD_{50} for DPA in rodents is 5,452 mg/kg, a value slightly greater than that for the comparable L-form. For a standard human male this toxicity level translates, on a weight basis, to an LD_{50} dose of 436,160 mg. Allowing for a six-fold difference in metabolically active body mass between mouse and human (17), this still equates to a projected LD_{50} in humans of 908.5 mg/kg or 72,693 mg.

No toxic effects were seen following acute administration of DPA to monkeys of 3000 mg/kg or chronic administration of 1000 mg/kg/day for 30 days (26). Ehrenpreis (personal communication) has carried out acute, 2-month and 6-month oral toxicity studies of DPA in mice. No deaths occurred with acute doses of 10,000 mg/kg. No toxic effects were seen, in a 2-month study, at a dose of 1 g/kg/day. Using this same dose, examining 35 tissues for pathology, mice showed no observable toxic effects after 6 months of chronic oral administration. In addition, no behavioral changes were seen in mice over this time period. Heller (41) has reported comparable results after 2 continuous years of administration at 10 times the equivalent human dose. His study, using several dose levels and examination of 38 tissues, focused on mortality, teratology, carcinogenicity and pathology. No negative findings were reported.

In addition to the importance of enkephalins and other opioid peptides in the alteration and maintenance of alcohol seeking and consumption (6–8, 11, 19, 33, 35, 36, 39, 45, 76, 94), the literature suggests important roles for several aminergic neurotransmitters. For example, in both animals and humans serotonin has been reported to regulate alcohol-related behaviors (15, 30, 32, 47, 52, 61, 75). Similar ideas have been ascribed to the catecholamines (3, 22, 38, 39, 47, 48, 72, 82, 87) and to gamma-aminobutyric acid (GABA) (16, 21, 34, 40, 43, 70, 75, 79, 81, 89, 95). A review of this diverse literature led us to conclude that endorphinergic/enkephalinergic and aminergic deficiencies are key determinants in craving, anxiety, depression, insomnia, and tremulousness, all associated with alcohol withdrawal and abstinence (9, 12, 27).

A common neurobiological pathway has been suggested to underlie uncontrolled use of psychoactive agents including alcohol (97) by activating the opioid-mediated mesolimbic catecholaminergic receptors to provide pleasure or relief from pain (50). This understanding of the neurochemistry of alcoholism (8, 12, 13) and other drug dependencies led us to investigate the effectiveness of a nutritional formula designed to restore brain neurotransmitter balance in both alcoholics and polydrug abusers (91,92). The ingredients selected amounts per capsule and their expected effects are as follows:

D-phenylalanine—230 mg: This amino acid inhibits enkephalinase A and increases the availability of enkephalin in the brain, thereby decreasing craving and depression (8,24). The LD_{50} of D-phenylalanine in rodents is 5,452 mg/kg.

L-phenylalanine—230 mg: This isomer of phenylalanine tends to increase levels of dopamine, which is closely associated with the brain reward system. A second effect is to increase norepinephrine levels, which leads to a decrease in depression (31). The LD_{50} of L-phenylalanine in rodents is 5,287 mg/kg.

L-tryptophan—25 mg: This precursor to the neurotransmitter serotonin plays a role in reducing craving and improving the quality of sleep (99). The LD_{50} of L-tryptophan in rodents is 1,600 mg/kg.

L-glutamine—25 mg: Its effect is to increase brain GABA levels, thereby reducing both craving and anxiety (69). The LD_{50} of L-glutamine in the mouse is 7,000 mg/kg.

Pyridoxal 5'-phosphate—5 mg: This activated form of vitamin B-6 is a cofactor in the production of aminergic neurotransmitters, and enhances the gastrointestinal absorption of amino acids (99).

These ingredients comprise a nutritional supplement known as SAAVE, manufactured by MATRIX Technologies, Inc., Houston, TX. An inpatient double-blind, placebo-controlled study was begun to more fully characterize the effects of SAAVE on both alcoholics and polydrug abusers. The study was conducted at the Chemical Dependency Unit (CDU), Glenwood Regional Medical Center, West Monroe, LA.

METHOD

Group Selection and Dosage Regimen

In this IRB approved, prospective study, four groups of consenting adult patients (excluding pregnant females) were constructed to deal with the different populations of alcoholics and drug abusers found in the typical treatment facility population. All patients were assessed using the Minnesota Multiphasic Personality Inventory (MMPI) and blood analyses (CBC/SMAC-24) were carried out upon admission. No further blood or urine tests were conducted. The groups are: alcohol-SAAVE, alcohol-placebo, polydrug-SAAVE, and polydrug-placebo. Polydrug users typically had used or abused at least three and as many as 13 drugs on a regular basis. Sixty-two patients were divided into appropriate groups randomly and without foreknowledge of diagnosis by the hospital pharmacist.

Four individuals left the program immediately after detoxification within the first six days. Eight more individuals left the program, one at staff request, before completing treatment. For the repeated measure analysis four patients were dropped because of missing data on the BESS score (see below).

Thus, the base set consists of 50 individuals, divided into two groups: 28 on SAAVE and 22 on placebo at the initiation of the study. The alcohol subset consisted of 25 individuals, 15 and 10 each in the SAAVE and placebo subgroups, respectively. The polydrug subset consisted of 25 individuals who were abusing several drugs including alcohol, cocaine, barbiturates, tranquilizers, amphetamines, hallucinogens, and marijuana. This subset was similarly divided so that 13

TABLE 1

PATIENT GROUP DATA DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY

	Alcohol		Polydrug	
	SAAVE	Placebo	SAAVE	Placebo
Mean Age	39.5 ± 16.3	36.2 ± 16.6	29.6 ± 12.8	30.3 ± 14.7
Sex	3F/12M 20% 80%	2F/8M 20% 80%	4F/9M 31% 69%	4F/8M 33% 67%
Race	2B/13W 13% 87%	2B/8W 20% 80%	13W 100%	1B/11W 8% 92%
BAL (mg%)	0.135	0.056	0.016	0.012
Alcohol	15	10	13	12

Subjects

Total Alcohol—25 Total Polydrug—25
Total SAAVE—28 Total Placebo—22

TABLE 2

PHYSICAL SCORE MEASURES

—Flushing response	—Hallucinations
—Muscular coordination	—Nausea-vomiting
—Seizure activity	—Sensorium
—Skin condition and pallor	—Sweating
—Tremors	—Verbalization

TABLE 3

BEHAVIORAL, EMOTIONAL, SPIRITUAL AND SOCIAL (BESS) SCORE

Behavioral	Emotional
—Attitude	—Anger
—Compliance	—Aggressiveness
—Self-image	—Anxiety
	—Depression
	—Reactive responses
Spiritual	Social
—Belief in God	—Cooperation
—Religious involvement	—Group participation

used SAAVE and 12 were provided with placebo. The patient sets are shown in Table 1 (mean±sem).

Blood alcohol level (BAL) upon entry is shown for each of the groups. Patients arrive at treatment facilities with great differences in BAL, some several days from their last drink, others only hours from consuming alcohol. Nevertheless, as a group the alcohol-SAAVE group turned out to have the highest BAL by far and the two alcohol groups were each higher than the polydrug users. Despite these differences the alcohol-SAAVE group will be shown to make the most dramatic improvements. BAL proved not to be a covariate by statistical analysis.

Age, weight, sex, race and entry BAL were tested as possible covariates for the dependent measures. None were found to be significantly different, substantiating the fact that, in terms of these measures, the groups are equivalent.

No one in the CDU, physicians, nurses and subjects, nor the data collector, knew which individuals were receiving SAAVE, and which were receiving the methyl cellulose placebo. The SAAVE capsules and the placebo capsules were identical in appearance.

Two SAAVE or placebo capsules were given three times daily for 21 days to the first 50 patients enrolled. These subjects were observed for an additional seven days without SAAVE or placebo. The purpose of the last seven days (without SAAVE or placebo) was to verify that use of SAAVE did not produce dependency. No evidence of dependency was seen. The protocol was then modified to provide SAAVE or placebo for the 28-day treatment period. This difference is reflected in the analyses below. Presently, the CDU uses SAAVE for the full 28-day treatment period.

Test Measurements

Skin conductance level (SCL). The electrical properties of the skin have been widely utilized in the assessment of emotional response. This technique has proven quite reliable as a measure of stress levels in the patient (for example, extent of anxiety or anger). As such, this is an indirect measure of stress levels in the patient. The SCL, the inverse of the galvanic skin resistance (GSR), monitors absolute skin conductance level as measured in micromhos (23). A correlation exists between orienting and anxiety responses which by sympathetic activation results in increase in skin conductance. Thus, a decrease in conductance is associated with a decrease in autonomic arousal (23, 55, 57).

To make these measurements an Autogen 3000 (Autogenic Systems) was attached to the middle three fingers of the dominant hand of each patient, and a reading obtained. Measurements were carried out approximately 16 times for each patient who completed treatment. Readings were taken on a nonschedule basis, including weekends, between 5:00 and 6:00 p.m.

Clinical measurements. The Physical and BESS Scores are subjective measures applied to each patient during the entire stay in the CDU. The Physical Score includes a number of somatic measures described in Table 2. The com-

TABLE 4
SKIN CONDUCTANCE LEVEL

Treatment Group	Day 3	10	21	28
Alcohol	NS	NS	NS	NS
SAAVE	5923 ± 478	6798 ± 396	7500 ± 312	7340 ± 262
Placebo	7551 ± 150	9013 ± 948	9152 ± 722	8434 ± 595
Polydrug	NS	$p<0.001$	$p<0.001$	$p<0.001$
SAAVE	9470 ± 911	9048 ± 386	8727 ± 285	8693 ± 257
Placebo	14280 ± 162	12738 ± 870	11686 ± 519	11295 ± 447
Total	NS	$p<0.001$	$p<0.001$	$p<0.001$
SAAVE	8051 ± 645	7954 ± 291	8007 ± 217	7902 ± 186
Placebo	10661 ± 118	10827 ± 640	10506 ± 429	9987 ± 365

NS—not significant.
Alpha acceptance value—$p<0.0042$.

TABLE 5
PHYSICAL SCORE

	Day 3	10	21	28
Total Population	NS	$p<0.001$	$p<0.008$	NS
SAAVE	5.18 ± 0.09	5.68 ± 0.06	6.00 ± 0.05	6.10 ± 0.05
Placebo	4.94 ± 0.06	5.35 ± 0.06	5.80 ± 0.05	5.96 ± 0.05

Alpha acceptance value—$p<0.0125$.

ponents of the Physical Score are largely coincident with the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) of Naranjo and Sellers (64,78). The Bess Score is a nonstandardized evaluation tool developed by the staff of CDU in Monroe, LA. It includes key measures of clinically important psychological and behavioral performance as shown in Table 3. During the course of the treatment, changes in these factors were observed daily by the clinical director, two staff physicians and the head nurse, and their observations were discussed and coordinated to arrive at a consensus score.

On admittance each patient was assigned a baseline value of 5. Each day improvement or regression was noted with a range of improvement from 6–10, and a range of regression from 0–4; 5 indicated no change from admittance status.

These subjective measures quantify the clinical judgment of experienced professionals. Averaging the judgements of the four participating professionals provided a profile that the staff agreed accurately represented their response to each individual patient.

Cardiovascular measurements. Standard systolic and diastolic blood pressure measurements and pulse measurements were taken daily throughout the treatment period. Statistical analysis was limited to those persons not using medication for hypertension.

Method of statistical analysis. Effects of SAAVE treatment were analyzed for the Alcohol and Polydrug groups alone and in combination. In addition to highlighting differences in response of these populations, this approach addressed the question of commonality of the neurobiological mechanisms (97). In addition, combining the samples increased the statistical power of the analysis.

Nonrepeated measure analysis. Student *t*-tests were used to compare the mean scores of the SAAVE versus placebo data. The cumulative effects of treatment regimen were seen by analyzing the sum of all prior recordings as windowed on days three [1–3], ten [1–10], twenty-one [1–21], and twenty-eight [1–28]. The consequences of this approach is that the discrete trend differences were emphasized. By this method each recorded measure is treated as a separate entity or "case." This method is statistically more liberal in its analysis than the repeated measure analysis described below. When many *t*-tests are used, the alpha criterion for any test is no longer 0.05 and a smaller value should be employed to avoid Type 1 errors, i.e., imputing significance inappropriately. To compensate for this potential error the *t*-test significance values were adjusted using the Bonferroni protocol which yields an alpha protection level for SCL of 0.0042, the Physical Score of 0.0125 and for BESS Score of 0.0125. An analysis of the *t*-test values indicates a value greater than 1.0 which verifies the significance of the reported differences as shown in Figs. 3 and 4 and Tables 4–6.

TABLE 6
BESS SCORE

	Day			
	3	10	21	28
Total Population	NS	$p<0.001$	$p<0.001$	$p<0.001$
SAAVE	5.19 ± 0.07	5.75 ± 0.06	6.43 ± 0.06	6.61 ± 0.05
Placebo	4.96 ± 0.06	5.35 ± 0.07	5.92 ± 0.06	6.19 ± 0.06

Alpha acceptance value—$p<0.0125$.

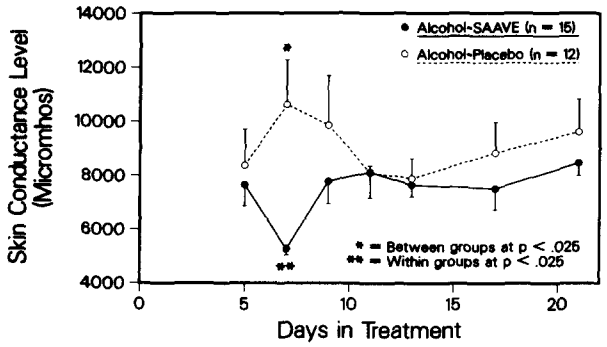

FIG. 1. Analysis of skin conductance level (SCL) for the alcohol-SAAVE and alcohol-placebo groups shows a highly significant difference between the two groups at day seven ($p<0.025$). There are no statistical differences for any specific day within the alcohol-placebo group. However, day seven shows a statistically significant decrease ($p<0.025$) as compared to any other day for the alcohol-SAAVE group, indicating the dramatic changes at the end of detoxification for this group alone.

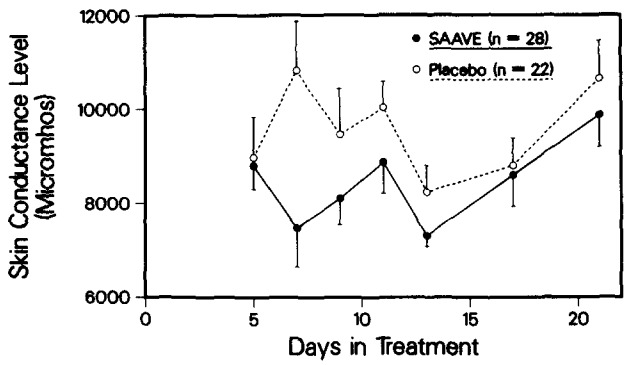

FIG. 2. The SCL value for the total (alcohol and polydrug groups together) SAAVE and placebo groups. After the effect of the first seven days, the striking finding is that the curves for the two groups mirror one another, though the SAAVE groups are lower. This may indicate a commonality in response to the dynamics of the treatment program or it may indicate characteristic changes in the population with recovery groups. In contrast, distinctive changes occur within groups. By day nine the polydrug-SAAVE group shows a marked-time-dependent significant improvement. At day 13 a second significant change occurs with respect to days 11, 17 and 21. In contrast to the alcohol-placebo group, the polydrug-placebo group showed a significant change which occurred later, at day 13 and continued through day 21.

Repeated measure analysis (ANOVA). Analysis was carried out for the first 21 days, the period in which all patients received SAAVE.

We utilized a statistical analysis involving repeated measures to allow for statistical dependency of the subject response over time and to test for differences between groups. The ANOVA compensates for successive case measures by incrementing the value needed for significance. Two factor analysis of variance was used to examine the skin conductance level (SCL), Physical and BESS Scores as well as the blood pressure. By this approach the group status at each of the analysis days is viewed as if frozen in time.

Time factors were analyzed starting on day 5 when the dropout rate plateaued (8 patients left during the first 5 days) and the sample variance was more stable. As the analysis program used is very sensitive to missing observations within subjects, values for postday 5 missing data were substituted by the group average for that day. Analyses were limited to days 5, 7, 9, 11, 13, and 17 since the sample size did not support extensive within group degree of freedom contrasts.

All ANOVA's were calculated on a VAX 8650 computer using the BMDP Bio-Medical Statistical Analysis Programs. For this statistical analysis a total of 50 patients were evaluated. The data are reported in Figs. 1, 2 and 5.

RESULTS

Skin Conductance Level

Nonrepeated Measure Analysis

Table 4 illustrates the differences observed between SAAVE and placebo groups on the SCL stress measurement test at 3, 10, 21 and 28 days of the program. For the alcohol subjects, there is a clear trend to progressively higher scores for both the SAAVE and placebo groups with a peak at day 21. Then, with SAAVE discontinued, the values declined. SCL was consistently lower in the SAAVE group, with the greatest difference between the groups at day 10. Using the stringent alpha acceptance value of 0.0042, significance was not reached.

The pattern for the polydrug groups presents progressive decline in SCL for both the SAAVE and placebo sets but a

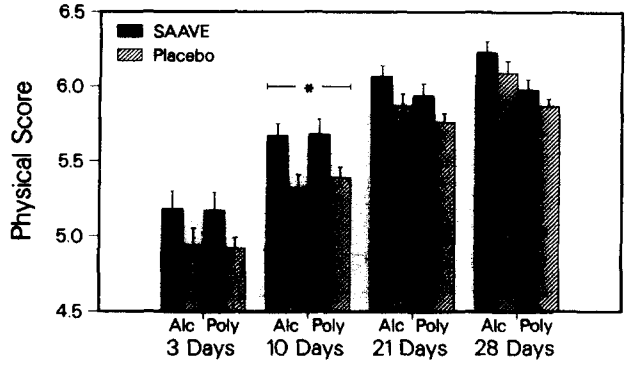

FIG. 3. Graphical representation of the Physical Score values for the experimental (SAAVE) and control (placebo) groups. On all days the SAAVE groups showed fewer physical signs and more rapid recovery than did the control groups. Significant differences were evident for both the alcohol and polydrug groups on day 10—at the end of the detoxification phase.

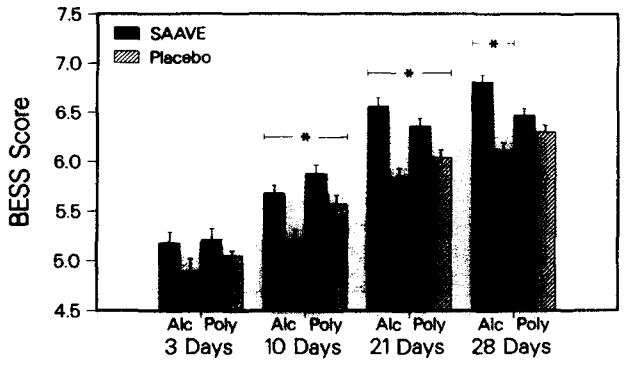

FIG. 4. Graphic representation of the BESS Score values for the experimental (SAAVE) and control (placebo) groups. On all days the SAAVE groups showed a trend to more rapid and more extensive recovery than did the placebo groups. Significant differences were seen for both the alcohol and polydrug groups on days 10 and 21. Additionally, the alcohol-SAAVE group continued to show more dramatic improvement through day 28 (in the absence of SAAVE).

substantial and significant differences between them was evident at day 10 and proceeded to increase with time. These data indicate that use of SAAVE results in clear improvement for the polydrug group early in the program.

When the data from all the patients are combined, significant differences are evident beginning at day 10 and continuing through day 28 despite discontinuance of SAAVE at day 21. The SAAVE effect is evident by a decreasing difference between the groups at day 28 as compared with day 21.

Repeated Measure Analysis

Two factor ANOVA yielded significant differences as a function of time ($p<0.001$), and groups ($p<0.025$) as well as a group-by-time interaction ($p<0.01$). Over the 21-day test period there were significant differences between the four groups. Further, for each group there is a significant change over the treatment period. Single factor ANOVA's within each group over time showed significant time-dependent effects for all but the alcohol-placebo group. The progressive time-dependent effects for the other three groups were examined using multiple paired *t*-tests with the alpha acceptance level adjusted to 0.0042.

Figure 1 illustrates a highly significant difference ($p<0.025$) between the alcohol-SAAVE and placebo groups on day 7. While the placebo group was demonstrating higher SCL measures, the SAAVE group had markedly lower levels. Further, as early as day 7 there is a significant decrease in SCL within the SAAVE group alone. This day is significantly different from all other days. In contrast with the SAAVE group, the placebo group has no time-dependent-within-group significant differences. Thus, early in the program, in what appears to be a detoxification related event, the SAAVE patients showed reduced stress response.

The profile of time-dependent changes in the polydrug population SCL is mirrored in the two groups. Thus, all patients appear to respond similarly to environmental, program-dependent stimuli. With this stringent form of analysis no differences occur between groups.

Examining the total SAAVE versus total placebo population (Fig. 2), we find that the SAAVE group has consistently lower SCL scores. Between-group differences approach significance overall ($p<0.08$), especially for the first 11 days ($p<0.06$).

Physical Score

Nonrepeated measure analysis. Figure 3 and Table 5 illustrate the effect of SAAVE on the Physical Score. For the first three days, SAAVE had an effect which did not reach statistical significance for either the alcohol or polydrug groups. However, by day 10 very significant effects of SAAVE were observed for both the alcohol ($p<0.004$) and polydrug ($p<0.002$) groups. The total drug group is significant for days 10 and 21 with the maximal difference at day 10 (Table 5). SAAVE appears to be of benefit during this peak period of patient stress, when patients may still be experiencing craving and are deciding whether to remain in the program or are preparing to leave.

At days 21 and 28, although the mean values were higher for the Physical Score in both the alcohol and polydrug groups, no statistically significant differences were obtained between SAAVE and placebo groups. This is not surprising since it is known that with time patients generally improve physically in an inpatient treatment center.

Detoxification is typically completed between day 3 and day 7. The symptoms listed in Table 2 are detoxification parameters. Thus by day 10, clearly at the end of detoxification, the SAAVE groups have improved not only more fully but more quickly. Comparison of the Physical Score values for the alcohol-SAAVE and placebo groups show the former to be about seven days further advanced in treatment. In contrast, the polydrug-SAAVE group is only four days in advance of its placebo counterpart. These data indicate that there is a cumulative effect of SAAVE with continued gradual improvement.

Repeated measure analysis. To further evaluate the effects of SAAVE versus placebo with regard to the Physical Score a two-factor ANOVA was employed. Although the nonrepeated measure analysis yielded significant differences on the 10th day between SAAVE and placebo for both the alcohol and polydrug groups, results using the more conser-

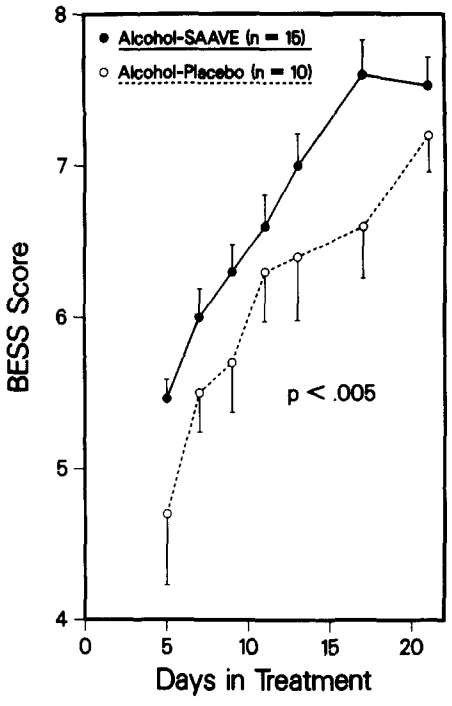

FIG. 5. Nonrepeated measures analysis of differences in the BESS Score for the alcohol-SAAVE and alcohol-placebo groups. As early as day five and continuing throughout the 21-day period shown the SAAVE group was rated as significantly more improved than their placebo counterparts. There is a five to seven day earlier improvement throughout.

vative repeated measure analysis were nonsignificant for the Physical Score. It is quite possible that the higher AMA dropout rate for placebo relative to SAAVE groups biased the sample. Furthermore, inasmuch as all patients in the program are improving and the placebo patients, due to their interaction with the improved SAAVE patients, were improving more rapidly than is normally the case, the overall group effect may be contaminated and the difference not meaningful. Additionally, since evaluation of the Autogen 3000 SCL response proved significantly different for SAAVE versus placebo during the time period of 5 to 11 days, this tends to support the significantly different effects found for SAAVE in both the alcohol and polydrug groups as compared with their placebo counterparts at the 10th day.

BESS Score

Nonrepeated measure analysis. Figure 4 and Table 6 illustrate the statistical evaluation of the clinical, subjective BESS Score measurement. At the 3-day time interval, no statistically significant differences were observed between SAAVE and placebo for either the alcohol or the polydrug groups. However, the mean values were consistently higher (improved) for patients receiving SAAVE compared to patients receiving placebo. At day 10, however, very significant differences between the SAAVE and placebo groups were obtained for the alcohol group ($p<0.001$). A value of $p<0.017$ (barely not significant) was found for the polydrug group at the 10-day time interval. These findings are consistent with what was reported above for both the stress measurement and Physical Score. Additionally, at day 21, we found significant improvement for the alcohol ($p<0.001$) group and the polydrug ($p<0.004$) groups using SAAVE. Similar differences are evident for the combined SAAVE versus placebo groups (Table 6).

Finally, when the patients ceased using SAAVE or placebo for one week, mixed results were obtained for the BESS Score. At day 28 significant differences remained between SAAVE and placebo for the alcohol group alone ($p<0.001$). This observation suggests that the consequences of using SAAVE continue yielding a longer term effect for alcoholics than polydrug abusers. Support for a mechanism of long-term benefits of SAAVE may be derived from the finding that use of DPA in animals and humans results in an analgesic response which continues for days after cessation of use (26). This prolonged response of DPA may be due to the fact that its metabolism is slow in relation to the more commonly occurring L-form amino acids.

Repeated measure analysis. The BESS Scores were significant for each group over time. However, the between groups test was not significant due to the higher variance contributed by the polydrug-SAAVE group.

Analysis of the BESS Score for the two alcohol groups alone demonstrated a significant group difference ($p<0.005$) (Fig. 5), whereby the alcohol-SAAVE group demonstrated greater improvement than the alcohol-placebo group every day in treatment. Further, within the alcohol-SAAVE group, differences occurred between a given day and each subsequent day measured. In contrast, for the placebo group statistical differences occurred only between days 17 and 21 and the remaining days. The endpoints alone were different. This indicates that SAAVE increases the rate of recovery. The data shown in Fig. 5 suggest that improvement begins about one week earlier.

Analysis of the two polydrug groups showed no significant differences within groups but significant differences for within-group time-dependent changes. The most profound differences occur for the polydrug-SAAVE group only with respect to day 21, i.e., progressive changes require a greater number of days before a dramatic change is attained. For the polydrug-placebo group differences are evident between days 5 and 11, 17 and 21.

Treatment with SAAVE, therefore appears more effective for the alcohol than the polydrug groups. This is in agreement with the data obtained from nonrepeated measure analysis. This also suggests that the polydrug group, which is particularly heterogeneous with respect to drugs used, needs longer maintenance on SAAVE than do the alcoholics.

Premature departure (against medical advice—AMA). The detoxification process (clearance of drug and primary metabolites) can take as long as seven days (20). It is well recognized that many chemically-dependent patients enter treatment under pressure from family and job with the sole intention of sobering-up and leaving. Further, although previous data suggested an early effect of SAAVE, we wanted to be certain that there was adequate time for SAAVE to have an effect on all of the patients. For these reasons a detoxification withdrawal time of five days was used as a cut-off point.

Table 7 illustrates the data. In the SAAVE groups only 15% (5 of 33) of the starting population, or 3.3% (1 of 30) of the postday 5 population left AMA. In striking contrast, for the placebo groups 24% (7 of 29) of the starting population, or 21% (6 of 28) of the postday 5 population left AMA. The

TABLE 7
PREMATURE DEPARTURES (AMA)

	Alcohol		Polydrug		Total	
Days	SAAVE	Placebo	SAAVE	Placebo	SAAVE	Placebo
>5	1	2	0	4	1	6

consequence of the dropout pattern is that, following detoxification, compared to the SAAVE population, six times as many patients on placebo failed to complete the 28-day treatment program. Thus, in the preday 5 period SAAVE patients are 1.6 times as likely to remain in the program as placebo patients and this likelihood increases 6.4 fold after detoxification (postday 5). In all, use of SAAVE increases likelihood of program completion almost four-fold. Statistical analysis using Fisher's exact test supports this conclusion by demonstrating a significant ($p<0.05$) difference in favor of the SAAVE patients.

Cardiovascular measurements. Administration of SAAVE had no significant effect on any cardiovascular measure—pulse, systolic or diastolic pressure. ANOVA's for both time and group, as well as for each factor and group alone yielded no significant effect. This is at variance with our earlier findings but in agreement with more detailed studies (18,60).

Side effects and study blindness. Throughout the treatment period there was no observable differences between patients so as to suggest SAAVE-related side effects. Similarly, there was no evidence to suggest that any member of clinical staff had knowledge of patient utilization of SAAVE. Thus, we believe that group blindness was intact.

DISCUSSION

Data are presented for two groups of depressant abusers—alcoholics and polydrug users—in a 28-day inpatient treatment setting. They show, particularly dramatically for the alcoholics, that use of the nutritive supplement SAAVE resulted in significant improvement. The improvement was manifest in both physiological and psychological measures.

The SCL, a measure of autonomic function and a correlate of anxiety level, revealed at day 10 significant improvement for the polydrug group and for the combined polydrug and alcohol groups (Total). The 10-day period is known for peak postdetoxification problems associated with inpatient hospitalization (i.e., higher rates of premature patient departure—AMA). For both the alcoholics and the polydrug abusers the SAAVE groups had lower (improved) scores. These values were statistically significant using the repeated measures but just missed significance for the alcohol group when the strict alpha acceptance value was imposed. The significant improvement for the polydrug and total drug groups continues throughout the remainder of treatment. Thus, these data suggest that SAAVE is a particularly useful adjunct to reduce stress (e.g., as associated with anxiety and craving). It is noteworthy that in each individual situation tested the score was consistently lower for the SAAVE patients than for those receiving placebo.

Seven days after SAAVE and placebo were eliminated from the program (measurements through day 28) the SCL response for all of the groups declined with the greatest decline coming in the alcoholic group. This suggests that the alcoholic would benefit from continued supplementation with SAAVE throughout the recovery period and in aftercare to help maintain effective functioning in a sober state.

Autogen 3000 SCL effects were measured using a single factor ANOVA with a Student-Newman-Keuls test for post hoc analysis of any significant ANOVA. Statistically significant differences were obtained for the different groups on day 7 (for the alcoholics) and day 11 (for the polydrug abusers). In addition, the polydrug groups showed parallel curves with the SAAVE patients exhibiting less stress. These findings suggest that SAAVE reduces response to the situationally induced stresses evident throughout the program and particularly prevalent with the detoxification-transfer-group assimilation events occurring from days 7 to 10. Two clinical observations lend support to this conclusion. First, the patients' disciplinary problems are diminished and, second, the number of calls for the physicians is decreased.

Similarly, for the Physical Score, a significant improvement was most evident at day 10. Later in the program the patient is unlikely to exhibit these detoxification-related physical signs, as patients in treatment generally improve physically over time. For these reasons one cannot expect to obtain a significant difference between groups using the ANOVA analysis.

Naranjo, Sellers and colleagues (60,78) in discussing the dynamics of physical signs associated with detoxification support this last conclusion. The parameters they report are largely coincident with our Physical Score. They find that most of the physical responses appear early in withdrawal, 0–48 hours, peaking at 24–36 hours. The remainder appear between 24 and 150 hours, peaking at 72–96 hours. In their experience, typically working with mild to moderately afflicted alcoholics, only 5% of patients exhibit these later, major and possibly fatal withdrawal signs and symptoms.

In terms of the BESS Score, comparing the absolute values for the SAAVE and placebo groups one sees about a one week advantage to the SAAVE group. The difference between the groups is smaller than one would have expected because there is a "peer calming effect" in operation. In all behavioral groups there is behavior mirroring, i.e., the calmer patients who are rewarded by the counselors serve as role models and thereby moderate the behavior of the placebo patients. This is a phenomenon common to group therapy, i.e., the SAAVE population improves all of the groups by elevating mood and stabilizing patients. The effect is to decrease the differences that would have been evident were the SAAVE and placebo portions carried out separately.

Despite the peer calming effect, the differences between the alcohol-SAAVE and placebo groups were highly significant. The SAAVE-related improvements occur early in the program; thus, they can facilitate the patient's ability to comply with the program demands and thereby benefit more

fully from their inpatient experience. In particular, SAAVE reduces somatic complaints, irritability, acting out and benzodiazepine requirement. Patients exhibited enhanced compliance and reduced resistance to change. They recognize the effects of their drug-taking behavior and more quickly abandon denial. Continued use of SAAVE may sustain recovery and reduce relapse time—a subject currently under investigation.

The absence of cardiovascular responses was not surprising since in earlier studies Shaw *et al.* (70) in developing their CIWA-A scale, found that heart rate, body temperature and blood pressure are covariates which do not significantly affect the CIWA-A factors. The CIWA-A components are similar to those used in our Physical Score. We, along with Naranjo and Sellers, find that these cardiovascular measures tend not to be a significant correlate of physical detoxification parameters. We have shown, in addition, that they are also not a meaningful correlate of behavioral changes. Hypertensive responses are a function of several factors, including resting blood pressure, quantity of alcohol consumed and time since last drink, and extent of noradrenergic response. In other than controlled experimental conditions it is difficult to demonstrate a hypertension protective effect.

There is increasing interest in developing a neurochemical treatment for alcoholism (64). The development of new psychopharmacological treatments is based on the idea that there is one or more CNS physiological mechanisms regulating ethanol intake. These mechanisms are, in our conception, multineuronal, involving opioidergic, serotonergic, catecholaminergic and GABAergic systems. We believe that proper operation of this multineuronal cascade requires that the essential neurotransmitters function cojointly, within a given range. Thus, balancing of several transmitters with special emphasis on the opioid peptides is essential. The nutritional supplement SAAVE was developed to increase the activity of these neurotransmitters by means of precursor amino acid loading and to enhance enkephalins by enzyme inhibition. The clinical effects reported here speak in favor of this multineuronal cascade balance concept (10).

In addition to the views we have put forth, there may be alternative explanations for the effects observed in this investigation. One explanation is that the effects of SAAVE may be due to the individual precursor amino acids acting through single specific neurotransmitters rather than their cojoint action. A variety of experimental data focus on the contribution of specific transmitters. Data currently suggest, for example, that the serotonergic system plays an important, and possibly singular, role. However, similar claims could be made for the opioidergic, catecholaminergic, or GABAergic systems. Myers (58,59) showed that IV or IP injection of the serotonin precursor 5-hydroxytryptophan suppressed voluntary alcohol consumption. Similar effects were seen with intraventricular delivery of serotonin (42). This lead to the notion of enhancing serotonin levels by use of reuptake inhibitors. Naranjo and co-workers (61), among others, report significant alterations of alcohol consumption with several serotonin reuptake inhibitors such as zimelidine and norzimelidine (2, 26, 41), fluoxetine (27), citalopram (27), and indalpine (9) in rodents. Additionally Naranjo *et al.* (62) report that zimelidine significantly attenuates ethanol intake in humans. However, the patients in their outpatient studies would likely be classified as alcohol abusers rather than alcoholics. Finally, zimelidine was never approved for use in the U.S. and was approved only for investigational purposes in Canada. This drug has been withdrawn by the manufacturer because of infrequent but potentially fatal multisystemic reactions and Guillain-Barre syndrome (29).

In contrast, Williams (95) and his associates are strong advocates of the contribution of GABA as influenced by L-glutamine. The protective effect of L-glutamine was first discovered by Rogers and Pelton (69) who found that L-glutamine significantly reduced the inhibitory action of ethanol on the growth of *Streptococus facculis* (69). This finding stimulated Rogers *et al.* (70) to systematically evaluate the role of L-glutamine in alcohol seeking behavior. Rats receiving 100 mg/kg of L-glutamine for 26 days relative to a 55-day control period reduced their intake of 10% ethanol by 35%. Finally, the contribution of amino acids to the treatment of other addictions, notably cocaine, has drawn attention recently (5, 71, 88, 93).

In virtually all clinical uses of single amino acids where daily dosages range from hundreds to thousands of milligrams, only a modest effect has been observed. This contrasts with the fact that the present study shows significant effects at much lower dosage, an observation we believe speaks for a synergistic effect.

An alternate possibility to account for the significant data observed here with modest amounts of amino acids might be that the doses are sufficient to permit subjects to discriminate between an inert placebo and a compound with subtle but still discernible properties. Thus, SAAVE may be producing a "placebo effect" on a more subtle and complex level than might be expected with an inert placebo alone. It would be potent enough to generate psychological effects associated with the subject's ability to discriminate SAAVE from placebo. Expectations, attitudes of staff, prior information about the study, rumors in the treatment center, and so forth may have operated to sensitize placebo control subjects and SAAVE subjects to try to guess the condition (SAAVE or control) to which they had been assigned. And once subjects categorized themselves as SAAVE or placebo, then it is possible that they behaved accordingly.

While plausible, this explanation does have some difficulties among which are that placebo effects tend to be of limited duration (typically well under 28 days) and commonly affect only about one-third of patients. Thus while placebo effects can prevent significant findings, in most cases they are only suggestive and do not present significant differences in their own right. In contrast, we have presented clearly significant results. Nevertheless, in consideration of these alternative explanations, it may be appropriate in future studies to include, in separate control groups, individuals who receive each amino acid alone (i.e., phenylalanine, tryptophan, glutamine).

Considering the desirable characteristics of new agents useful in alcoholism Naranjo *et al.* (64) suggest seven idealized properties which include the following:

1) Application of an active form of the drug should produce a consistent and robust effect in the target population, thereby developing expectations of success. 2) The active form of the drug should not have deleterious interactions with ethanol or accentuate any of the mechanisms by which ethanol induces organic damage (e.g., increase acetaldehyde concentration). 3) The drug should be easily administered (e.g., oral route). 4) The drug should be long-acting to simplify administration and enhance compliance. 5) The agent should preferentially be capable of antagonizing some of the deleterious effects of ethanol (e.g., impairment of memory or psychomotor performance) in addition to at-

tenuating ethanol intake. 6) The drug should have a wide therapeutic margin. 7) It should be reasonably safe, and the side effects should not significantly affect subjects' functioning (e.g., motor skills).

CONCLUSIONS

Prior anecdotal reports indicated that patients using SAAVE became responsive to counseling earlier than non-SAAVE patients; i.e., "the postdetoxification fog" lifted earlier. Other reports indicated that anger, anxiety, sleep disturbances and dysphoria were mitigated by SAAVE, while the impression of a decreased AMA rate was reported by several treatment facilities. This investigation confirms and enlarges upon these anecdotal reports.

The findings of this investigation suggest that SAAVE is efficacious as an adjunct in the detoxification and short-term recovery of both alcohol and polydrug abusers. Preliminary data indicate that SAAVE may also have benefit for continuing recovery in alcohol and polydrug abusers and potentially reduce relapse rates.

Considering both the nonrepeated measure and repeated measure statistical analyses the following conclusions can be made involving potential clinical effects of SAAVE for inpatients:

1) A six-fold improvement is evident for the SAAVE groups in comparing frequency of AMA dropouts.

2) Patients on SAAVE improve their psychological status as measured by the BESS Score. The ANOVA's of BESS Scores were significant for the alcohol group whereby the alcohol-SAAVE group demonstrated a greater improvement than the alcohol-placebo group. Higher BESS Scores were consistently obtained with SAAVE for both groups relative to placebo. In fact, the BESS Score was significantly improved for SAAVE patients seven days after cessation of its use.

3) Patients on SAAVE showed significantly reduced stress manifestations, as measured by the Autogen 3000 SCL, in both the alcohol and polydrug groups. This indicates that SAAVE hastens improvement. Effects for the alcoholics were more dramatic than for the polydrug abusers.

4) Patients on SAAVE improve their physiological condition as measured by the Physical Score at the 10th day for both the alcohol and polydrug groups. This finding is consistent with the clinical observations that patients have most detoxification-related somatic problems until the 10th day and then show improvement thereafter in a consistent fashion.

5) Patients using SAAVE in this inpatient setting improve about one week in advance of their fellows who are not using SAAVE.

In consideration of the seven properties outlined by Naranjo and associates (64) for an ideal pharmacotherapeutic agent for the treatment of chemical dependence, this investigation supports SAAVE as meeting the requirement of having a "consistent and robust effect in the responders." SAAVE appears to satisfy Naranjo's criteria, namely: no deleterious interactions with ethanol; easily administered; attenuating alcohol intake; wide therapeutic margin; and, safety. Studies are in progress to more systematically define the promising features of this nutritional adjunctive agent especially in outpatients where we are investigating relapse rates following long-term use of SAAVE.

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