

REDUCTION OF BOTH DRUG HUNGER AND WITHDRAWAL
AGAINST ADVICE RATE OF COCAINE ABUSERS IN A 30-DAY
INPATIENT TREATMENT PROGRAM BY THE
NEURONUTRIENT TROPAMINE[®]

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ABSTRACT

Tropamine[®], an amino acid and vitamin supplement designed to restore catecholaminergic, serotonergic, opioidergic, and GABAergic deficits observed in stimulant abusers (primarily cocaine), significantly reduces both the withdrawal against medical advice (AMA) rate and drug hunger of inpatients at a 30-day hospital treatment program when compared with patients receiving either the neuronutrient SAAVE[™] or with controls who had no supplement added to treatment regimen. The AMA rate for controls was 37.5% (6/16), and that for the SAAVE[™] group was 28.6% (4/14) yielding no significant differences. In sharp contrast, for the Tropamine[®] group, the AMA rate was significantly ($P < 0.014$) less than for controls, being only 4.2% (1/24)—almost a ninefold improvement. For this study a drug hunger index was devised utilizing various behavioral observations, requests, and/or need for benzodiazepines, threats, or actual leaving AMA. Patients were rated throughout the 30-day program and were found to have significantly reduced drug hunger with Tropamine[®] compared with SAAVE[™] and control groups. These results suggest that Tropamine[®], which contains specific neuronutrients, vitamins, and minerals, accelerates recovery during withdrawal of serious cocaine abusers by facilitating retention in a treatment program and by reducing drug hunger.

INTRODUCTION

Traditional treatment for the cocaine abuser during withdrawal has tended to focus on the acute symptoms of cocaine toxicity, prescribing

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drugs such as propranolol to treat erratic heart rhythms, diazepam to control convulsions, and chlorpromazine to relieve psychoses such as paranoid disorders.¹ These treatment approaches do not relieve the patient's craving for cocaine. With modern realization of the profound effect of cocaine on brain neurotransmitters, interest has grown regarding agents that may have benefits not only during withdrawal, but during the inpatient, outpatient, and aftercare phases of recovery.

The use of several modern therapeutic agents is supported by the dopamine depletion hypothesis of cocaine action.² It is well established that cocaine blocks dopamine re-uptake, acutely increasing synaptic dopamine concentrations.³ In the presence of cocaine, synaptic dopamine is metabolized to 3-methoxytyramine and excreted. This loss of dopamine at the synapses places demands on the body for increased dopamine synthesis, as evidenced by the increase in tyrosine hydroxylase activity after cocaine administration.⁴ When precursor supplies are exhausted, a dopamine deficiency develops.⁵

The dopamine depletion hypothesis² suggests the use of agents that act at dopamine receptor sites or alter dopamine availability. Based on this theoretical model, a number of drugs have been suggested for use in helping cocaine users during withdrawal and possibly later in treatment. Antidepressants, such as lithium and desipramine, were studied by Tennant and Rawson⁶; Dackis et al⁷ tested bromocriptine, a dopamine receptor agonist; Tennant and Sagherian⁸ employed amantadine, a dopamine releaser; and the dopamine precursors L-dopa⁹ and L-tyrosine¹⁰ have also been utilized. Cocaine affects changes in the synthesis, re-uptake, and metabolism of norepinephrine, which parallel those seen with dopamine. Additionally, cocaine interferes with the synthesis, re-uptake, and metabolism of serotonin in the central nervous system¹¹; this is the basis for use of the serotonin precursor L-tryptophan.^{10,12} Finally, certain vitamins and minerals found deficient following chronic cocaine abuse in humans have also been used in treatment.³

The effect of cocaine is not limited to these aminergic transmitters. Chronic utilization of cocaine alters opiate receptor binding¹³; this is supported by the fact that naloxone effectively blocks the threshold-lowering action of cocaine in reward centers of the brain.¹⁴ Opioid peptides, catecholamines, serotonin, and gamma-aminobutyric acid all contribute to a concert of events leading to stimulation of reward circuitry in the brain. Significant deficits in these neurotransmitters either via genetic predisposition or drug use/abuse may lead to excessive compulsivity.¹⁵ In addition, chronic use of cocaine may lead to dangerous adverse drug reactions (eg, convulsive seizures).¹⁶

A number of therapeutic agents currently under study are neurotransmitter releasers. However, we caution that these may be effective only if they have something to release; they will not cure a state of dopa-

mine depletion. Furthermore, in view of the several neurotransmitters involved, an approach limited to one therapeutic agent is unlikely to fully address the multiplicity of brain dysfunctions of the cocaine abuser. Indeed, it is possible that dopamine releasers, or antidepressants used alone, may exacerbate the chronic depletion of dopamine.

As an adjunct to standard psychological, supportive therapy, we believe that the following brain chemistry changes should be pursued in the treatment of long-term recovery from cocaine abuse: (1) recovery of catecholaminergic and serotonergic functions; (2) enhancement of opioidergic activity; (3) reduction of neurotransmitter supersensitivity; (4) normalization of catecholaminergic receptor sites; and, (5) reduction of cocaine-induced sensitization to convulsive seizures.

While there may be a generalized neurochemical mechanism that underlies compulsive disease,¹⁷ it is quite likely that the drug of choice for each individual may be genetically biased and linked to a particular set of mechanisms. For instance, ethanol activates delta opioid receptors via amine condensation products that indirectly activate dopaminergic release in the mesolimbic circuitry. In contrast, cocaine directly activates the same dopaminergic neurons. This distinction is important as it dictates strategies of attack. With this in mind, SAAVE™* was developed for the alcohol or opiate abuser and provides a higher supply of D-phenylalanine as an inhibitor of enkephalinase activity. A full description of the contents of SAAVE™ and its effects in reducing the withdrawal against medical advice (AMA) rate of alcoholics and polydrug abusers as well as stress- and withdrawal-related drug hunger has been published previously.¹⁸ Tropamine™†, targeted to cocaine and stimulant abusers, was designed to provide a higher supply of L-tyrosine as a precursor amino acid for dopamine synthesis as well as provide vitamins and minerals known to be depleted in cocaine abusers.

We now report the results of an open trial of a comparison between the supplements Tropamine™ and SAAVE™ and a control group (no supplementation) of serious cocaine abusers receiving treatment at Charter Forest Hospital in Shreveport, Louisiana.

PATIENTS AND METHODS

In this investigation a total of 54 patients were evaluated. The criterion for acceptance into this prospective study was prolonged evidence of strong cocaine abuse by the intravenous, free-base smoking, or intranasal route(s). All patients signed informed consent forms and were assessed by

* Trademark: SAAVE™ (Matrix Technologies, Inc., Houston, Texas).

† Trademark: Tropamine™ (Matrix Technologies, Inc., Houston, Texas).

means of several clinical and psychological test instruments including the Minnesota Multiphasic Personality Inventory.

The subjects were divided into three groups. The Tropicamine™ group consisted of 24 stimulant abusers who entered the treatment facility from October through December of 1987. The SAAVE™ group, 14 stimulant abusers, were in treatment from June through August of 1987. The control group consisted of 16 stimulant abusers who entered the treatment facility from June through August of 1986.

Patients in the Tropicamine™ and SAAVE™ groups each received six capsules of the respective supplement (two capsules three times per day) one to two hours before meals. Patients in the control group did not receive any amino acid supplementation. The structured program that they received did not differ significantly from that of the two experimental groups.

Table I lists the ingredients of Tropicamine™ as well as their proposed utilization and mechanism of action.

Upon admission each patient was placed in a detoxification ward and blood, urine, blood pressure, respiration, temperature, pulse, weight, and medical and drug history were obtained. Mean weight of all subjects was 145 pounds; mean age, 26.2 years (Table II). Several other parameters are presented in Table III. No significant differences were observed between the groups for any of the covariates—age, weight, sex, race, type of drug use, cardiovascular signs, presence of stimulants upon admission—as tested by utilizing a single factor analysis of variance at an alpha acceptance criterion of 0.05.

To quantify drug hunger we developed a scale, the drug hunger index (DHI), to evaluate the following behaviors: decrease in vivid cocaine-related dreams; number of somatic complaints; requests for medication; drug-related, confrontation-dependent behavioral or physiological responses; program noncompliance; agitation and violent outbreaks; threats of leaving AMA; leaving AMA. These were rated by the medical director (D.A.) on a scale of one to ten. Ten indicated a strong and steady desire for cocaine and other stimulants (eg, amphetamines); a score of five indicated a moderate or intermittent desire for cocaine and other stimulants, and a score of one indicated little or no desire for cocaine or stimulants. If a patient left AMA a score of ten was assigned at the day of departure and carried over to the days remaining for statistical purposes. Therefore, if a patient left AMA on day 19, a score of ten was assigned for days 19 through 30. Each value presented herein is based on an evaluation at three designated time periods, the first period being from days 1 to 10, the second period from days 11 to 20, and the third from days 21 to 30.

To evaluate significant differences between groups, a single-factor analysis of variance was performed at the alpha acceptance criterion of 0.05. The Student-Newman-Keuls multiple comparison test was per-

TROPAMINE AND COCAINE ABUSE

Table I. Tropicamine composition and rationale for use. Amounts are for six capsules (daily dose).

Ingredient	Amount	Restorative Action	Mechanism	Expected Behavioral Change
D-phenylalanine	750 mg	Enkephalins	Enzyme inhibition	Anticraving, antidepressive
L-phenylalanine	750 mg	Dopamine, norepinephrine	Precursor loading	Reward, antidepressive
L-tyrosine	900 mg	Dopamine, norepinephrine	Precursor loading	Reward, antidepressive
L-tryptophan	400 mg	Serotonin	Precursor loading	Anticraving, antidepressive, anti-insomnia
L-glutamine	300 mg	Gamma-aminobutyric acid	Precursor loading	Anticraving, antistress
Vitamin B complex		Neurotransmitter synthesis	Enzyme cofactors in transmitter synthesis	Facilitates action of neurotransmitters
Thiamine (HC1)	100 mg	Vitamin B ₁	Enzyme cofactors in transmitter synthesis	Facilitates action of neurotransmitters
Riboflavin	15 mg	Vitamin B ₂	Enzyme cofactors in transmitter synthesis	Facilitates action of neurotransmitters
Niacinamide	100 mg	Vitamin B _{3a}	Enzyme cofactors in transmitter synthesis	Facilitates action of neurotransmitters
Pantothenic acid	90 mg	Vitamin B ₅	Enzyme cofactors in transmitter synthesis	Facilitates action of neurotransmitters
Pyridoxal-5-phosphate	20 mg	Active metabolite	Promotes gastrointestinal absorption of amino acids	Facilitates action of neurotransmitters
Cyanocobalamin	6 ug	Vitamin B ₁₂	Promotes gastrointestinal absorption of amino acids	Facilitates action of neurotransmitters
Ascorbate (calcium)	600 mg	Neurotransmitter synthesis	Enzyme cofactor	Facilitates action of neurotransmitters
Folic acid	400 ug	Neurotransmitter synthesis	Enzyme cofactor	Facilitates action of neurotransmitters
Zinc (chelate)	30 mg	Neurotransmitter synthesis	Enzyme cofactor	Facilitates action of neurotransmitters
Calcium (chelate)	150 mg	Neurotransmitter promotor	Enzyme cofactor	Facilitates action of neurotransmitters
Magnesium (oxide)	150 mg	Neurotransmitter modulator	Regulates transmitter release	Calmative

formed to determine significant differences between groups during days 1 to 10, 11 to 20, and 21 to 30. Verification of this test was obtained by utilizing other standard statistical tests, including the Duncan multiple range and Tukey's studentized range test. Fischer's Exact Test was used to evaluate the AMA data.

RESULTS

The figure and Table IV illustrate the comparative effects of Tropamine™, SAAVE™, and control on the DHI of the study group. Utilizing the Student-Newman-Keuls multiple comparison statistics, it was found that during the first ten-day period the DHI of the Tropamine™ group was significantly less than controls ($P < 0.015$). At this time the DHI of patients receiving SAAVE™ also differed significantly from the control group ($P < 0.005$) but not from the Tropamine™ group. During the second ten-day period the DHI of the Tropamine™ group continued to be significantly lower than the control group ($P < 0.007$). Again, the DHI of the SAAVE™ group was significantly different from the control group ($P < 0.005$) but

Table II. Vital physiological characteristics.*

Groups(s)	Age	Weight	Pulse	Blood Pressure (mmHg)	
				Systolic	Diastolic
Tropamine™	25.8	146	85	120	78
SAAVE™	25.9	143	85	115	73
Control	27.5	147	87	127	84

* Single factor control analysis of variance yielded no significant differences between groups at alpha acceptance criterion = 0.05.

Table III. Gender, ethnicity, and stimulant abuse demographics.*

Group(s)	Gender		Race		Route of Administration†			Urine Screen Positive‡
	Male	Female	Black	White	IV	FB	IN	
Tropamine™	16	8	4	20	17	5	3	13
%	66.7	33.3	16.7	83.3	70.8	20.8	12.5	54.2
SAAVE™	9	5	5	9	9	5	7	10
%	64.3	35.7	35.7	64.3	64.3	35.7	50.0	71.4
Control	10	6	4	12	8	2	8	5
%	62.5	37.5	25.0	75.0	44.4	11.1	44.4	31.2

* Single factor analysis of variance yielded no significant differences between groups at the alpha acceptance criterion = 0.05.

† IV = intravenous; FB = free base; IN = intranasal.

‡ Urine screen positive = positive for cocaine. The identification of stimulants (ie, cocaine, amphetamines) in the urine was determined using a standard enzyme multiplied immunoassay technique test.

TROPAMINE AND COCAINE ABUSE

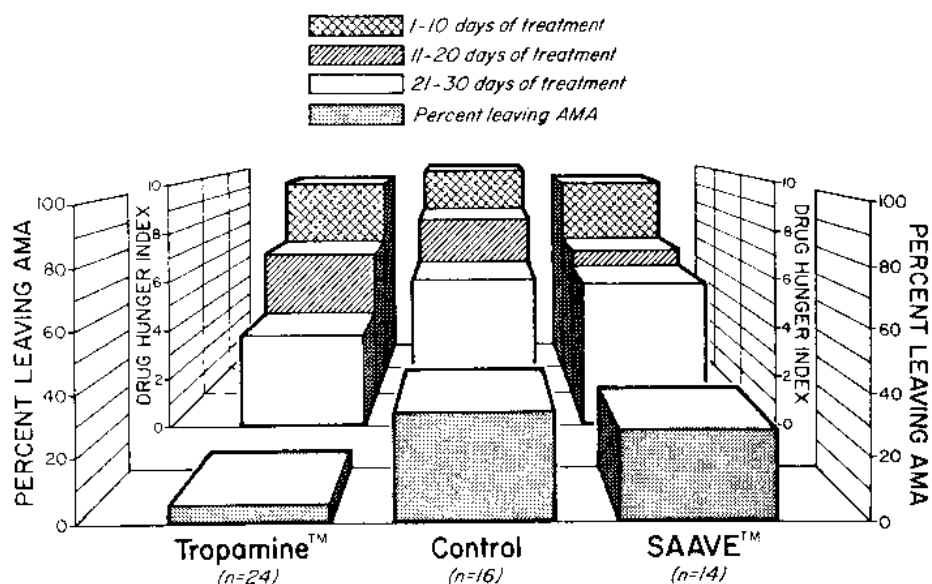


Figure. This three-dimensional graph represents the comparative effects of Tropamine™, SAAVE™, and no treatment (control) on both the number of individuals leaving the program prematurely against medical advice (AMA) and drug hunger. The percent AMA is shown in the foreground while the drug hunger index score for each treatment period is behind. To assist the reader, the control group is positioned in the center so comparisons may be made with Tropamine™ and SAAVE™. N = no. of patients in each group. The drug hunger score was rated for periods 1, 2, and 3 (ie, days 1 to 10, 11 to 20, and 21 to 30, respectively).

not from the Tropamine™ group. In the final period (days 21–30) the DHI of the Tropamine™ group remained significantly lower than that of controls ($P < 0.02$); however, at this point the DHI of the SAAVE™ group did not differ significantly from the control group, but was elevated with regard to the Tropamine™ group ($P < 0.015$).

The figure and Table IV illustrate the comparative AMA rate of inpatients receiving Tropamine™, SAAVE™, or no supplement (control). For

Table IV. Comparative effects of Tropamine™, SAAVE™, and control on drug hunger and withdrawal against medical advice (AMA) rate of inpatient cocaine abusers.

Treatment	No. of Patients	Drug-Hunger Score			Percent AMA
		Days 1–10 (mean ± SE)	Days 11–20 (mean ± SE)	Days 21–30 (mean ± SE)	
Tropamine™	24	9.5 ± 0.13	6.5 ± 0.22	3.8 ± 0.31	4.2
SAAVE™	14	9.5 ± 0.18	6.5 ± 0.21	5.8 ± 0.69	28.6
Control	16	10.0 ± 0.00	8.1 ± 0.38	6.1 ± 0.74	37.5

the Tropamine™ group, one of 24 patients left AMA (4.2%). This remarkably low AMA rate differed significantly from both the SAAVE™ group (4 of 14 [28.6%] individuals left AMA, $P < 0.042$) and the control group (6 of 16 [37.5%] individuals left AMA, $P < 0.014$). The AMA rate of the SAAVE™ group did not differ significantly from that of the control group.

The clinical impression a patient leaves with the physician and staff is essential to establishing the merit of a particular treatment modality. As early as five days of treatment the staff and physicians reported that both the Tropamine™ and SAAVE™ patients exhibited a decrease in agitation, outside focus, and, most importantly, drug hunger. There was much less acting out and less craving. The vital signs were more stable with a reduction in parasympathetic discharge, ie, the severity of the cocaine crash was reduced. Normally, the viewing of street corners associated with drug traffic and drug dealer's houses produces agitation in patients. With the neuronutrient Tropamine™, this was decidedly reduced in frequency and magnitude. These behavioral observations help to explain an overall enhanced program compliance.

DISCUSSION

In this open-trial study of 54 inpatients with evidence of strong cocaine abuse at a 30-day hospital treatment program, use of Tropamine™ as an adjunct to traditional therapy significantly reduced AMA as well as drug hunger. In addition, the staff reported a decided decrease in agitation, outside focus, and drug craving. These positive results are not surprising in view of our knowledge of the neurochemistry of cocaine abuse.

Chronic cocaine use may cause supersensitivity of at least the dopamine, norepinephrine, and serotonin receptors, via increased numbers of receptors or lack of occupied basal receptor-ligands. Many catecholaminergic vesicles are known to contain opioid peptides and other secondary transmitters. In addition, opioid peptides synapse on several important catecholamine-containing cell groups. Empirically, the importance of utilizing a substance that enhances opioid peptide availability via enkephalinase inhibition is supported by the involvement of opioid peptides in the action of cocaine.^{13,14}

Both catecholamine and indolamine transmitters are depleted with chronic cocaine use. Tyrosine and phenylalanine levels in plasma also may be depleted.¹⁹ These two amino acids are the precursors of dopamine and norepinephrine, and tryptophan is a precursor of serotonin. All three amino acids are known to increase the levels of their respective transmitters in nervous tissue. They are believed to allow neurons that utilize these neurotransmitters and fire frequently to synthesize increased amounts of transmitter.²⁰ Similarly, use of the carboxypeptidase-A inhibitor D-phenylalanine²¹ facilitates the availability of enkephalin, which

would function both as a transmitter and to enhance catecholamine transmission. The multiplicity of neurotransmitter deficits underscores the composition of Tropamine™ and helps to explain why use of tyrosine or tryptophan alone has been perceived as providing limited benefit.

The wealth of experimental data indicates a need for transmitter replacement or augmentation. At the very least, the dopamine functioning should be augmented in the nucleus accumbens.²² Increasing transmitter availability would facilitate the efficacy of transmission and could be used advantageously in conjunction with catecholamine releasers such as amantadine.²³ Tropamine™ may also facilitate the action of dopamine agonists that would provide short-term improvement while longer-term improvement is mediated through supplementation.

The first goal of treatment is to retain the patient in the facility so that he/she may be separated from the using environment, may be exposed to information about the disease and disease process, and may begin steps towards sobriety. To do this it is necessary to reduce AMA rates. The significance of the Tropamine™ effect on the AMA rate of cocaine abusers may best be appreciated from Table V where it is seen that the effect of Tropamine™ on this class of abuser is almost identical to that of SAAVE™ for the alcoholic, and both are far better than control. Table V also shows that SAAVE™ alone helps lower the AMA rate in the cocaine population.

Reducing drug hunger facilitates adherence to and participation in the treatment program. During the first two evaluation periods the Tropamine™ and SAAVE™ groups made greater improvement in reduction of drug hunger than did the control group. However, while improvement continued at a significant rate for the Tropamine™ group, it slowed somewhat for the SAAVE™ group. At the end of the 30-day treatment period the Tropamine™ group showed a 60% improvement over controls. Reduction in drug hunger is even more important in aftercare when the patient is now exposed to the street environment that originally fostered the problem.

The observation of the differential improvement in both AMA rate and DHI between Tropamine™ and SAAVE™ is of crucial importance in addressing the issue of specificity of nutritional supplements and in elimi-

Table V. Comparison of nutritional supplement effects on percentage of withdrawal against medical advice rates of cocaine and alcohol abusing populations.

Drug Population	Experimental Group		
	Tropamine™	SAAVE™	Control
Cocaine [this study]	4.2	28.6	37.5
Alcohol ¹⁸	—	3.5	28.5

nating placebo effects. It is not surprising that Tropamine™ was more effective than SAAVE™ in serious cocaine abusers since these individuals, by the dopamine depletion hypothesis, require an augmented dopaminergic function, a special component of Tropamine™.

The performance of Tropamine™ is all the more impressive since almost 92% of the members of the Tropamine™ group were intravenous or free-base users—by far the most addicting route of administration. In contrast only 55.5% of the control group administered cocaine by the intravenous or free-base routes, while 100% of the SAAVE™ group did so. Thus the likelihood of success should have been least for the Tropamine™ and SAAVE™ groups. This result speaks to the strength of their effects.

Our research to date suggests that Tropamine™ is a prototypical nutrient product providing an important adjunct to the recovery process of cocaine abusers. It significantly reduces AMA withdrawals and drug hunger. We feel that it is an exciting new addition to the armamentarium of drug recovery and warrants further investigation in double-blind placebo-controlled studies.

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