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ORIGINAL INVESTIGATION

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Short-term treatment with citicoline (CDP-choline) attenuates some measures of craving in cocaine-dependent subjects: a preliminary report

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Abstract The administration of cytidine-5′-diphosphate choline (CDP-choline, citicoline) to animals increases the rate of membrane phospholipid synthesis and elevates brain dopamine levels. Because cocaine dependence has been associated with increases in brain phospholipid precursors, as well as depletion of dopamine within the central nervous system, the present outpatient study was conducted to assess the safety of citicoline (500 mg bid) and to determine if short-term treatment alters mood states and cocaine craving in subjects with a history of cocaine dependence. In addition, measures of drug craving and mood states after presentation of cocaine-related cues were collected on two occasions: before and after 14 days of double-blind treatment with either citicoline or placebo. Subjects did not experience any side effects and citicoline treatment was associated with decreases in self-reported mood states associated with cocaine craving. These preliminary data are encouraging and suggest that citicoline warrants further study as a promising potential treatment for cocaine abuse and dependence that is devoid of side effects.

Key words Cocaine · Craving · Cytidine · CDP-choline · Human · Medication · Drug dependent · Citicoline

Introduction

Although the scope of cocaine abuse as a clinical syndrome has been well documented, the success rates of various pharmacotherapies have not been very high. Because it is generally believed that the mesolimbic and mesocortical dopamine (DA) circuits (modulated by opiate interneurons) play a pivotal role in brain reward systems, a number of pharmacotherapies for cocaine dependence have been proposed that focus on altering the function of the dopaminergic (Kleber and Gawin 1984; Dackis and Gold 1985; Weiss 1988; Pulvirenti and Koob 1994) and the serotonergic (Batki et al. 1993; Walsh et al. 1994) systems.

There is evidence that chronic cocaine abuse results in focal abnormalities of cerebral perfusion (Kaufman et al. 1998) and single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies have revealed that chronic cocaine abusers demonstrate significant perfusion deficits (Volkow et al. 1988; Tumeh et al. 1990; Strickland et al. 1991; Levin et al. 1994). Cocaine-related ischemic injury results in reduced levels of adenosine triphosphate (ATP) and elevated levels of cerebral phosphomonesters (PME) (Christensen et al. 1996).

The above literature suggest an alternative strategy for treating cocaine dependence. Cytidine-5′-diphosphocholine (CDP-choline, citicoline) is a mononucleotide composed of ribose, cytosine, pyrophosphate and choline, and is an essential intermediate in the biosynthetic pathways of membrane phospholipids, particularly phosphatidylcholine (Kennedy and Weiss 1956; Chida and Shimizu 1973). As a pro-drug, citicoline is almost immediately converted to choline and cytidine after IV or oral administration (Weiss 1995). Once cytidine and choline traverse the blood-brain barrier, they enhance the rate of incorporation of phospholipids into membranes and microsomes. Additionally, citicoline activates biosynthesis of structural phospholipids in neuronal membranes and increases norepinephrine and dopamine levels in the central nervous system (Secades and Frontera 1995).

The rationale for using citicoline to treat cocaine dependence is based, in part, on its efficacy in treating

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a number of central nervous system disorders. For example, citicoline treatment has improved neurological symptoms and level of consciousness in patients with head injury and depressed levels of consciousness (Moriyama et al. 1967), attenuated electroshock-induced memory deficits (Ayuso and Saiz 1977), reduced the morbidity after acute cerebral vascular disease (Goas et al. 1980; Clark et al. 1997), and permitted the dose of levodopa to be reduced in treating patients with Parkinson's disease (Eberhardt et al. 1990), a disorder typified by a significant lack of dopamine in the nigro-striatal pathway (Ruggieri et al. 1976). Because cocaine-induced perfusion deficits appear to be similar to those seen after a stroke or head injury, citicoline might repair the cocaine-related damage to neuronal membranes. Further, the changes in brain ATP and PME associated with chronic cocaine use suggests a pattern of biochemical change which might be reversed, to a degree, using citicoline to increase membrane synthesis (Secades and Frontera 1995).

Interestingly, the potential of citicoline as a novel treatment for cocaine dependence is not limited to its effects on neuronal membranes. Acute treatment with citicoline increases the production of norepinephrine and dopamine levels and decreases serotonin levels in various regions of rat brain (Martinet et al. 1979; Saligaut et al. 1984). This effect on norepinephrine and dopamine is thought to be due to an increase in synthesis of tyrosine in the striatum (Martinet et al. 1979), but it is possible that dopamine reuptake into synaptosomes is reduced, which would have a similar effect (Martinet et al. 1978). If dopamine depletion is a long-term consequence of chronic cocaine abuse (Little et al. 1996; Wilson et al. 1996), then citicoline-induced increases in cerebral dopamine levels may be more beneficial in the treatment of dependence.

The present double-blind, placebo-controlled outpatient study was conducted to assess the safety of citicoline and to test the hypothesis that short-term treatment would improve CNS function and reduce craving in subjects with a history of cocaine dependence.

Materials and methods

Subjects

A total of 14 subjects with a history of cocaine dependence were recruited via newspaper advertisements and provided informed consent to participate in this study, which was approved by the McLean Hospital Institutional Review Board. Subjects were informed that they would be paid for their participation in this study, but payment was withheld until they completed both experimental sessions (see below). In addition, they were told that they would forfeit some of their payments if they had a cocaine-positive urine screen. Before being admitted to the study, all subjects received a physical examination to ensure that they were healthy. Evaluations included full hematology profile and urinalysis analyses as well as an electrocardiogram. In addition, all subjects received a Structured Clinical Interview for the DSM-IV (SCID) (First et al. 1995) in order to identify potential psychiatric disorders. Subjects with diagnoses of psychotic, anxiety or bipolar disorders were excluded from participation. Some subjects did meet criteria for a mood disorder. All subjects met DSM-IV (APA 1994) criteria for current (or within the past year) cocaine dependence. Of the 14 subjects, 13 reported current or lifetime polydrug use, with three reporting information consistent with dependence on two substances, seven meeting criteria for dependence on three substances, and three meeting dependence criteria for four or more substances. Only one subject met dependence criteria for only one substance (cocaine). Subject demographics are depicted in Table 1.

A post-hoc analysis revealed that both the placebo and citicoline groups contained two distinct populations of crack cocaine users. "Active" users were defined as those who had not ceased using for extended periods of time and were currently using cocaine just prior to the study. These reports were confirmed by positive urine drug screens during the screening examination. "Clean" users were those who received a lifetime diagnosis of cocaine dependence, but who had been successful at abstaining for the past 6–12 months (Table 1). Because the number of "clean" users was so small in this preliminary study, and because they represent a very distinct group from the "active" users, they were not included in statistical analyses.

Experimental design

Subjects were randomly assigned to receive either citicoline or placebo. The study design included a baseline assessment of reaction-time performance, mood state, electrophysiological measures and subjective responses to a series of questionnaires, at varying times during the 3.5-h experimental session. A 2-week, double-blind treatment period of either placebo or citicoline ensued followed by a repeat assessment of these measures during a similar 3.5-h experiment. Frequent assessments for adverse effects and urine screens were performed during the 2-week treatment period. The overall research design is depicted in Fig. 1.

On each of the two assessment sessions, subjects were required to report to the laboratory and provide a urine specimen and breath sample prior to completing the psychomotor test battery. They were

Table 1 Demographics, drug use history, and psychiatric diagnoses of the participants in the treatment trial (means ± SD)

Variables	Citicoline[a]	Placebo
Demographics		
No. of subjects	6	8
Race (Caucasian/African/American)	2/4	4/4
Age	38.0 ± 6.1	35.8 ± 8.5
Weight (kg)	70.4 ± 6.5	86.7 ± 12.9
Sex (M/F)	4/2	7/1
Drug use history		
Cocaine use (years)	9.8 ± 4.2	11.6 ± 3.9
Cocaine use (No./week)	10.0 ± 10.0	7.2 ± 1.6
Ethanol use (years)	20.8 ± 6.9	18.4 ± 7.2
Ethanol use (No./week)	13.0 ± 8.5	11.0 ± 4.7
Psychiatric diagnoses		
Cocaine dependence	6	8
Mood disorder	1	3
Antisocial personality disorder	2	5
Cocaine use status		
Active	4	6
Abstinent 6–12 months	2	2

[a]1.0 g/day, PO

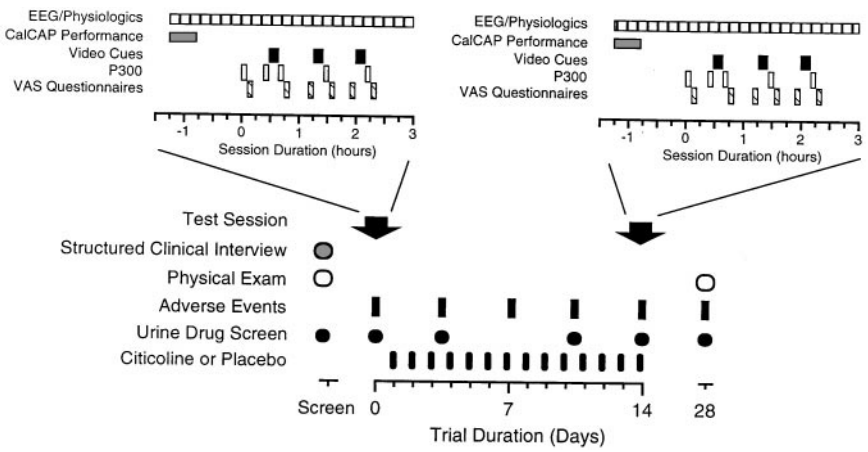

Fig. 1 Experimental protocol of the 2-week citicoline clinical trial. The 3.5-h test sessions on days 1 and 14 included the cue exposure, ERP recording, VAS craving questionnaires and psychomotor performance tasks. The sequence of the test session shown for day 1 was repeated on day 14

told only that the study was being conducted to test the safety of a new medication for cocaine abuse/dependence. Subjects were then escorted to a sound- and light-attenuated room and were prepared for standard EEG/ERP recording and physiological monitoring (see Lukas 1993). Presentation of the videos, recording of mood state and physiological monitoring continued for the duration of the session. Further details of the assessments are provided below.

Performance measures

A psychomotor performance test battery for reaction time and psychomotor function using the California Computerized Assessment Package (CalCAP; Miller et al. 1991) was given. This task has been validated as a sensitive measure of performance changes in patients with sub threshold AIDS-related neurological dysfunction (Miller et al. 1991).

Safety assessments

Subjects came to the laboratory 3 times a week, during which time they were asked whether they noted any changes in their health status. Urine analyses and blood chemistry evaluations as well as vital signs were also collected.

Subjective measures

Subjective effects were assessed using a variety of instruments including the 49-item Addiction Research Center Inventory or ARCI (Martin et al. 1971), numerous questions presented as visual analog scales (VAS) marked on a 100 mm line designed to assess craving and mood states (Table 2) and a cocaine craving questionnaire or CCQ (Tiffany et al. 1993). This latter questionnaire factor loads the answers into five categories: Desire to use cocaine, Intention and planning to use cocaine, Anticipation of positive outcome, Anticipation of relief from withdrawal or dysphoria, and Lack of control over use. All questionnaires were presented on a video monitor and subjects entered their answers via a joystick device. Questionnaires were given at the beginning of the experimental session and then again before and after presentation of the videos during the cue reactivity challenge (see below).

Cue reactivity challenge

As an added measure of the functional status of the subjects during the treatment trial, a cue reactivity challenge was performed.

Table 2 VAS questionnaires presented to subjects

VAS craving
How anxious do you feel right now?
How upset do you feel right now?
How scared do you feel right now?
How happy do you feel right now?
How strong is your desire to use cocaine right now?
How strong is your desire not to use cocaine right now?
How strongly do you desire special good feelings, like a rush or high, right now?
How strongly do you desire to get rid of bad feelings, like withdrawal or anger, right now?
If right now you were in the situation in which you last used cocaine, how likely is it that you would use again?
How strong is your urge for alcohol right now?
How strong is your urge for opiates right now?
How strong is your urge for tranquilizers right now?
How strong is your urge for PCP right now?
How strong is your urge for LSD right now?
How strong is your urge for marihuana right now?
How strong is your urge for stimulants right now?
How strong is your urge for cocaine when your environment reminds you of it?

Measures of physiological activity (EKG and blood pressure), subjective reports of craving, and recordings of brain electrical activity were collected before and after the presentation of three 10-min videos. After a 1-h baseline period, the first of three videos was shown. Subsequent videos were shown at 1-h intervals. Three videos were shown in the following order: (1) "neutral" cues of coral sea life; (2) "emotional" cues of graphic footage from a werewolf movie; (3) "cocaine" cues of two men buying, preparing and smoking crack cocaine. This last video was adapted from one provided by Dr. Anna Rose Childress (Ehrman et al. 1992; Childress et al. 1993).

Citicoline and compliance

Citicoline and identical placebo capsules were provided by Interneuron Pharmaceuticals, Lexington, Mass., USA. Each active capsule contained 500 mg citicoline. Subjects were instructed to take one capsule, twice daily (at 9:00 a.m. and 9:00 p.m.) which is the same dose that has been shown to be effective in treating various neurological disorders (Secades and Frontera 1998). Two measures of compliance were used. (1) Because subjects were required to report to the lab multiple times a week to provide urine specimens,

some of the morning capsules were consumed in the lab. (2) Upon consuming the capsules, subjects were required to call and leave a message on our date- and time-scribing answering machine. Only one subject failed to report on one dose during the 2-week treatment period.

Data analysis

Baseline differences between treatment groups were investigated using one-way analysis of variance (ANOVA) on all dependent variables. For variables on which the treatment groups differed significantly at baseline, change scores were analyzed. Change scores were computed by subtracting baseline scores from the video cue exposure scores. Repeated measures, multivariate analyses of variance were conducted on subjective and physiologic data. When significant interactions were found, simple effects *F* tests were conducted on between-subject variables, and paired *t*-tests were conducted on within-subject variables. Alpha was set at 0.05. All data were analyzed using various subprograms of SPSS 6.1 (SPSS 1994). Due to differences between "active" and "clean" subjects, only data from the larger group of active users were used in the statistical analyses.

Results

The electrophysiology data included raw EEG and ERP measures from 18 electrode sites, and because of the added complexity and multivariate nature of the analyses, these data will be reported elsewhere.

Safety assessments

Subjects who received citicoline reported no side effects and failed to detect that they had received an active dose. No changes in health status or blood/urine chemistry analyses were observed in either treatment group. During the baseline period, three subjects in the placebo group and one in the citicoline group had sinus bradycardia which was not considered clinically significant. One subject who received citicoline developed a mild, non-clinically relevant increase in P-R interval. Finally, there were no changes in heart rate or blood pressure over the course of the clinical trial.

Task performance

The CalCAP Performance Battery consists of ten tasks that become increasingly difficult. There were no significant differences on any of the tasks of this battery.

Effects of citicholine on subjective variables

To investigate the effects of citicoline on spontaneous craving and subjective mood state, 2 (Group: active/placebo) × 2 (Condition: pre-/post-treatment) repeated measures ANOVAs were performed on the indices of cocaine craving and subjective mood states, with condition as the repeated factor. A group × condition interaction on "Lack of control over use" of the CCQ was found to approach significance ($F1,8 = 4.35$, $P = 0.070$). This interaction is depicted in Fig. 2. Simple effects tests indicated that the citicoline treated group reported a significant decrease in feelings of "Lack of control over use" from pre-treatment to post-treatment ($t = 9.77$, $df = 3$, $P = 0.002$). A main effect was found for condition on the measure of "Anxiety" ($F1,8 = 10.20$, $P = 0.013$), with subjects reporting greater anxiety pre-treatment than post-treatment, regardless of treatment presented (data not shown). Finally, there was a trend toward significance for group on the VAS index of "Desire for special good feelings" ($F1,8 = 4.37$, $P = 0.07$), with the placebo group reporting a stronger wish for good feelings ($X = 74.33 \pm 33.66$) than the citicoline group ($X = 32.50 \pm 25.94$), regardless of condition.

There were no other significant differences in VAS or other measures of the CCQ.

Effects of video cues on subjective variables

To investigate the effects of the video cue exposures on subjective indices of mood state and craving, paired *t*-tests were conducted separately for each video. These paired comparisons were made as the low cell sizes precluded repeated measures ANOVAs. Although the Neutral and Emotional cue videotapes did not induce any changes in mood state, following the cocaine cue videotape, scores on the VAS "Anxiety" measure and the "LSD" scale of the ARCI were lower than at baseline ($t = 2.23$, $df = 9$, $P = 0.053$ and $t = 2.81$, $df = 9$, $P = 0.021$, respectively). There were no other significant differences.

Effects of citicholine on responses to crack cocaine cues

As the Neutral and Emotional cue videotapes did not appear to affect responses to mood state measures, only

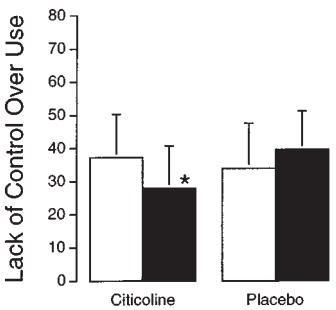

Fig. 2 Changes in CCQ category of "Lack of control over use (of cocaine)" before (□) and after (■) treatment with citicoline ($n = 4$) or placebo ($n = 6$). Data are means ± SEM. *Indicates significance at $P < 0.05$ between citicoline and placebo treatments

data from the crack cocaine cue exposure period was analyzed. To investigate the effects of citicoline on response to crack cocaine cues, 2 (Group) × 2 (Condition) × 2 (Time: pre-post cocaine cue exposure) repeated measures ANOVAs were conducted on the craving and subjective mood state measures, with condition and time as the repeated factors.

A trend was found for group on the VAS measure of "Urge for cocaine" ($F1,8 = 4.96$, $P = 0.057$), with the placebo group reporting a greater urge to use than the citicoline group. These data are presented in Fig. 3. Although the treatment groups did not differ significantly at pre-treatment, they did appear to differ post-treatment. One-way ANOVAs conducted on post-treatment ratings of "Urge for cocaine" indicated that the placebo group reported greater "Urge for cocaine" than the citicoline group at the post-treatment session, both prior to and following presentation of the crack cocaine cue video ($F1,9 = 10.91$, $P = 0.01$, and $F1,9 = 16.62$, $P = 0.002$, respectively). Analyses also revealed a main effect for condition on the VAS measure "Desire to use cocaine right now" ($F1,8 = 5.57$, $P = 0.046$), with subjects reporting a greater desire to use cocaine pre-treatment as compared to post-treatment, regardless of treatment or video presented (data not shown). Finally, results revealed a group × condition interaction on the CCQ category, "Lack of control over use" ($F1,8 = 6.02$, $P = 0.040$). Simple effects tests indicated that the citicoline treatment group reported a decrease in "Lack of control over use" from pre- to post-treatment.

Due to treatment group differences at pre-treatment, the LSD scale of the ARCI was analyzed using change scores as described above. Results revealed a trend for condition ($F1,8 = 5.20$, $P = 0.052$), with all subjects reporting significantly greater decreases in LSD scale scores pre-treatment as compared to post-treatment.

Urine screens

As the primary aim of the study was to assess the safety of citicoline, subjects were instructed to abstain from using cocaine during the 2-week treatment period or risk losing their payment. However, no instructions about the use of other drugs were given. Urine screens were performed twice a week, but the dates were known to the subjects. During the baseline screening period the rates of cocaine positive urines were the same for both the citicoline- and placebo-treated groups (28% of the specimens).

During treatment with either placebo or citicoline, only 7.1% of the urine screens were positive for cocaine indicating that, for the most part, the subjects complied with the instructions. Marihuana was the only other drug that was detected in these screens. During baseline, 7.1% of the urine screens were positive for marihuana. During citicoline treatment, a total of 11.8% of the screens were positive but nearly double (22.7%) of the urines in the placebo-treated group were positive for marihuana.While intriguing and suggestive, a Chi-square analysis indicated that these differences were not statistically significant.

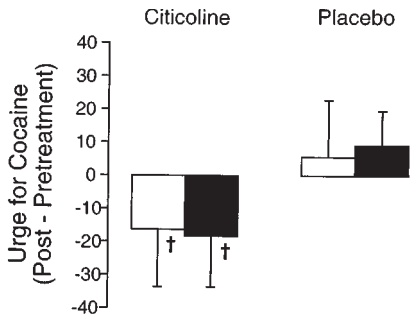

Fig. 3 Changes in "Urge for cocaine" before (□) and after (■) exposure to the Crack video as a function of citicoline ($n = 4$) or placebo ($n = 6$) treatment. Data are means ± SEM of the post-pre-treatment scores. †Indicates a trend ($P = 0.057$) between citicoline and placebo treatments

Discussion

The present study was conducted initially to test the safety of citicoline in cocaine-dependent subjects. As a secondary interest, we measured subjective mood states before and after exposing the subjects to cocaine-related cues in order to obtain some insight as to whether this compound might also be useful in altering cocaine craving. Several preliminary conclusions can be drawn from the results of this pilot clinical trial of citicoline in a group of crack cocaine users. First, a 2-week treatment of 1 g/day citicoline has no side effects in this population. Second, subjects could not distinguish drug from placebo. Third, some measures of cocaine craving and drug use appear to be attenuated by citicoline.

The incidence of citicoline-induced side effects in the younger, generally healthy individuals in the present study appears to be extremely low. This is not entirely unexpected, as, in a dramatic demonstration of the safety and efficacy of citicoline, Carcassone and LeTourneau (1979) treated 43 children with trauma-induced disturbances in consciousness and found that the medication was well tolerated, enhanced recovery of normal states of consciousness, accelerated the disappearance of neuropsychological disorders and disturbances of cerebral electrogenesis and, overall, provided a superior outcome in these young patients.

The membrane repairing effects of citicoline are likely due to an increase in the synthesis of phospholipids (Weiss 1995). An in vivo increase in brain phosphatidylcholine was first suggested in humans by Babb et al. (1996). These authors postulated that it is the cytidine, not the choline, moiety of CDP-choline

that is responsible for the membrane effects they observed.

The reductions in self reports of the CCQ factor "Lack of control over use (of cocaine)", (and the VAS measures of "Urge for cocaine"), and "Desire to use cocaine right now" and trends in other mood states in the citicoline treated subjects are provocative, and suggest that further study with citicoline is warranted. Although animal studies have shown that citicoline increases brain catecholamine levels, similar studies have not been conducted in humans. If citicoline does increase brain dopamine levels, then the reductions in craving for cocaine may be due to a modest replacement of the depleted level of dopamine thought to occur in chronic cocaine abuse. Because the effects of citicoline on dopamine levels are thought to be indirect due to increased synthesis (Martinet et al. 1979), it is unlikely that this compound will have a primary abuse liability. Thus, citicoline may act as a low level "maintenance" drug that restores the neurotransmitter imbalance along with repairing neuronal membranes.

The lack of a differential effect of citicoline and placebo on cocaine use (as evidenced by negative urine screens) is not unexpected because the monetary incentive for cocaine-free urines was a strong motivator for these subjects to avoid using cocaine. However, no stipulation was placed on other drugs of abuse, so the finding that the placebo-treated subjects had twice as many marihuana-positive urines than the citicoline-treated subjects is intriguing. The implication of this finding is that citicoline may affect drug-taking behavior in general, and not be specific for any one drug class. Because of the present protocol limitations, the incidence of cocaine positive urines in a treatment setting needs to be explored empirically in a study that does not impose such a contingency.

The present findings from this pilot study are encouraging because they suggest that citicoline may be a useful adjunct to current therapies for cocaine abuse. The reduction in some measures of cocaine craving might be expected as a consequence of increased dopamine activity. The "dual" action of this medication (repair of membranes and increased dopamine levels) makes it very appealing because it addresses the biological basis of cocaine abuse/dependence by recognizing that chronic abuse can lead to changes in brain function. There also is a single report that citicoline is an effective antidepressant (Salvadorini et al. 1975), suggesting that it may prove to be helpful in treating dually diagnosed patients with cocaine dependence and depression.

These data suggesting that citicoline may be useful in treating cocaine abuse/dependence must also be considered in light of some limitations. First, cocaine-induced perfusion deficits may be repaired naturally over time. However, this process may take months which could increase the risk of other problems and relapse to cocaine use. Thus, a more rapid repair of neuronal membranes may translate into a greater likelihood of treatment success. Second, the effects of citicoline on biogenic amines have only been studied after an acute injection in animals and brain dopamine levels actually returned to baseline a few hours later (Martinet et al. 1979). Therefore, it is unclear whether the effects of citicoline on dopamine persist during chronic administration.

In conclusion, citicoline is not a "magic bullet" for treating cocaine dependence. However, these preliminary results indicate that citicoline represents a new concept in medication development that could, by virtue of its lack of side effects and toxicity, be added to other therapies. Because there are no current treatments for pregnant women and adolescents, citicoline may be a particularly good candidate for these populations. Further, chronic use of other CNS stimulants such as methamphetamine results in neurotoxicity (Villemagne et al. 1998), so citicoline may be useful to treat this rapidly increasing drug abuse problem as well.

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