A Randomized, Double-Blind, Placebo-Controlled Study of the Neurocognitive Efficacy of a Treatment for Methamphetamine Dependence

HAROLD C. URSCHEL III, MD, MMA; LARRY L. HANSELKA, PHD; AND MICHAEL BARON, PHD

ABSTRACT

OBJECTIVE: A proprietary treatment program to reduce drug use and restore cognitive function by reversing methamphetamine-induced changes at the $GABA_A$ benzodiazepine receptor has been developed. This study is a follow-up to an open-label study we conducted of the program's clinical effectiveness. There were 3 objectives of this controlled study: (1) to assess cognitive impairment in a sample of chronic methamphetamine users; (2) to test the potential efficacy of the program's medications in reversing drug-induced neurocognitive deficits; (3) to pilot the use of a computerized neuropsychological test battery in the study of cognitive change in drug treatment research.

METHOD: Following screening and baseline assessment, 135 outpatient subjects were randomized to either (1) an active treatment group receiving flumazenil, 2 mg administered IV on days 1, 2, 3, 21, 22; oral gabapentin 1200 mg/day, and hydroxyzine 50 mg for pre-infusion and PRN for sleep; or (2) a control group receiving inactive formulations of the three medications. Eighty-eight subjects, 44 in each group, who completed the 30-day trial were included in the analysis. Cognitive function was measured with Cogtest® (Newark, DE), a computerized battery of neuropsychological tests, at screening and on days 4, 6, 13, 20, and 30. Drug use was assessed weekly using timeline-followback (TLFB) and urine drug screens (UDS). All subjects received drug abuse counseling and nutritional support.

RESULTS: There was no evidence of significant cognitive impairment at baseline in this sample of methamphetamine users with the exception of 1 reaction time measure for the Go-No-Go test. Cognitive performance improved for reaction time in a set shifting and a sustained attention task during the initial course of flumazenil treatment.

CONCLUSIONS: Participants performed much better than expected on the cognitive tasks at baseline given their chronic and frequent methamphetamine use. Reaction time for two complex attention tasks improved following initial pharmacotherapy, which suggests that this treatment may positively affect capacity to increase focus and reduce distraction.

INTRODUCTION

During the initial phases of abstinence, methamphetamine-dependent patients may experience cognitive impairments which may compromise their ability to engage in and benefit from psychosocial treatment (Meredith, et al., 2005). Cognitive deficits may contribute to the high rates of relapse and treatment failure often observed in this population (Maxwell, 2005). A medical treatment is needed that to address the cognitive deficits associated with chronic methamphetamine use, improve engagement and retention in psychosocial treatment programs, and reduce or discontinue drug use.

Clinical observations from a variety of treatment settings suggest that this proprietary treatment program improves patients' cognitive function. Our recent open-label study of this treatment found that subjects reported improved alertness, attention and short-term memory in the days following completion of the medication component of the program. Chronic methamphetamine administration in animals has been found to produce changes in the $GABA_A$ benzodiazepine receptor that are reversed by flumazenil (Smith, et al., 2007).

PURPOSE

This study was designed to evaluate the short-term neurocognitive efficacy of the medication regimen of a proprietary treatment targeting the $GABA_A$ benzodiazepine receptor in a sample of methamphetamine-dependent patients. This investigation is part of a larger controlled study demonstrating a significant reduction in cravings, and decreased use during initial treatment of methamphetamine dependence.

METHODOLOGY

STUDY DESIGN

The 30-day study used a randomized, double-blind, placebo-controlled, parallel-group design. It was conducted at Research Across America in Dallas, TX. Study procedures, consent form, and media advertising were approved by the Western Institutional Review Board.

SAMPLE

135 participants who met DSM-IV-TR criteria for methamphetamine dependence were randomized to either active treatment or placebo. Eighty-eight participants (ages 18-55) who had completed all 5 flumazenil administrations and completed the last scheduled study visit were included in the analysis. Participants did not have a diagnosis of alcohol or non-methamphetamine dependence (except nicotine); did not have an IQ score < 80 or a blood alcohol level > .08 mg%; did not have renal, hepatic, or gastric disease, uncontrolled hypertension, advanced HIV disease, or other medical or psychiatric diagnosis that might preclude safe participation in the study; and did not use benzodiazepines within 14 days of the study.

Participants received incentives if they completed their appointed sessions ±1 day ($50 voucher for food or gasoline). After the halfway point in the study, subjects were offered the active medication to be given at the conclusion of the trial if once the blind was broken they had been randomized to the placebo group.

MEASUREMENTS

Full-scale WAIS IQ estimates obtained with the Shipley Institute of Living Scale (SILS) (computerized version) were utilized to screen individuals with low general cognitive ability. Cognitive function was measured with Cogtest®, a computerized neuropsychological test battery of well-known conventional paper-and-pencil tests. The Cogtest battery has been shown to be consistent with paper-pencil tests with respect to age effects and also has good test-retest reliability. In repeated testing, 2 weeks apart, the interclass correlation was found to be highly significant (ICC range .51-.78, p-values < .001). The battery selected for this study consisted of seven tests which assessed processing speed, working memory, declarative memory, attention, response inhibition, implicit memory, and executive function (reasoning and problem solving. Figure 1.

RANDOMIZATION

An independent research pharmacist prepared the study medications, assigned subject identification (ID) numbers from a randomly generated list, and maintained the treatment group schedule. The pharmacist was at a different site, not associated with Research Across America, and not in contact with the participants or study staff.

PROCEDURE

The following information concerns a use that has not been approved by the U.S. Food and Drug Administration. The active treatment group intravenously received flumazenil (saline for the placebo) on days 1, 2, 3, 21, and 22. The medication was administered over 30 minutes by incremental IV bolus through an intravenous line kept open with Ringer's Lactate Solution. Up to 1200 mg of gabapentin (4 capsules of fructose for the placebo) was administered daily for 30 days and 50 mg of hydroxyzine (capsules of fructose for the placebo) was administered one hour before the infusions. It was also dispensed as a sleep aid to be taken if needed. Cogtest®, TLFB, and UDS were administered to subjects in both groups at screening and on days 4, 6, 13, 20, and 30.

STATISTICAL ANALYSIS PLAN

Cognitive deficits at screening were calculated using age-specific normative values for the neurocognitive tests provided by Cogtest. To evaluate the effect of the medications on cognition, repeated measurements ANOVA was used to examine within-group, between-group, and interaction effects for the treatment and placebo groups across 3 time points: screening, day 4 (after 3rd flumazenil infusion), and day 30 (after 5th flumazenil infusion). The level of significance was .05 (two-tailed).

RESULTS

At baseline no significant cognitive deficits were found for participants in the active treatment and placebo groups (see Figure 1). In general both groups fell within the range of normal functioning, as baseline scores for all subjects were +/- 1 SD of the normative group. This was found for all 7 tests except for reaction time in the Go-No-Go task.

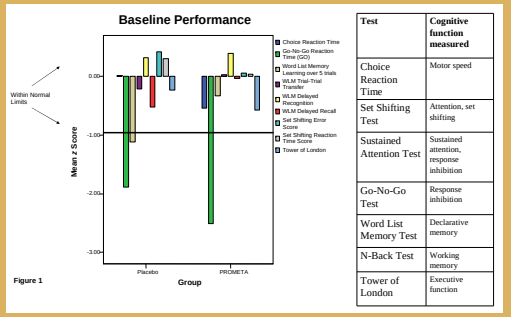


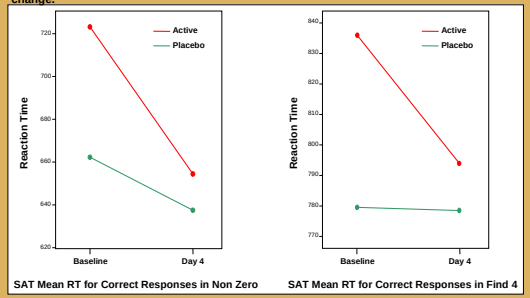
Figure 1

Test	Cognitive function measured
Choice Reaction Time	Motor speed
Set Shifting Test	Attention, set shifting
Sustained Attention Test	Sustained attention, response inhibition
Go-No-Go Test	Response inhibition
Word List Memory Test	Declarative memory
N-Back Test	Working memory
Tower of London	Executive function

Significant results for the active treatment group were found in the change from baseline to day 4, where improvements (decrease) in reaction time were observed in two tests: the Sustained Attention Test and the Set Shifting Test. No significant change was observed for the placebo group.

Sustained Attention:

There was a significant interaction between group and time for the Non-Zero condition: F (1,66) = 4.5, p < .05, and a trend toward significance in the Find 4 condition: F (1,66) = 3.2, p = .07. The active treatment group showed a significant improvement with decreasing reaction times from baseline to day 4, while the placebo group showed no significant change.

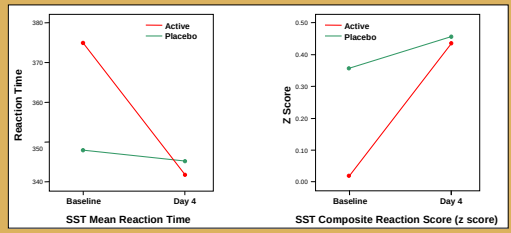


SAT Mean RT for Correct Responses in Non Zero | SAT Mean RT for Correct Responses in Find 4

RESULTS

Set Shifting:

There was a significant interaction between group and time for the reaction time in the Reversal condition: F (1,74) = 9.2, p < .01, and the composite reaction time z score: F (1,74) = 4.1, p < .05. After the 1st infusion, reaction times decreased significantly for the active group but not for the placebo group. The composite reaction score is a combination of z scores which were scaled to show improvement as a positive slope.



SST Mean Reaction Time | SST Composite Reaction Score (z score)

CONCLUSIONS

The results of our analyses found no evidence of significant cognitive deficits at baseline in either the active treatment group or placebo group. In fact, when the sample is viewed as a whole, performance scores were within the normal range of functioning on all but 1 of the 7 neurocognitive tests when compared to age-based norms. This finding is surprising in light of the recent literature documenting drug-induced cognitive deficits in chronic psychostimulant users. Participants did not show cognitive impairment to the degree we expected given the chronicity and frequency of their methamphetamine use. This may be attributable to the types of tasks selected for this study.

With respect to between-group changes in the 7 neuropsychological tests studied, reaction time for two complex attention tasks showed significant changes between the two groups from baseline to day 4. The set shifting task required the subjects to learn a pattern of responses and when that pattern changed (reversal condition) the improvement in reaction time was noted. With respect to the sustained attention task, reaction time improvement were seen whether the stimuli was specific to the condition (find 4) or when the stimuli is specified to be "non zero" (a condition requiring greater attention, focus and inhibition than the specified condition). This may be due to the significant decrease in cravings for the active treatment group and resulting effects on attention and focus. The failure to find significant changes in cognitive function at day 30 may be explained by the high scores obtained by the participants at screening. In addition, subsequent drug use may have influenced performance scores. Although the majority of participants curtailed their drug use during the 30-day trial, a percentage of participants in both groups returned to at least occasional methamphetamine use.

REFERENCES

Maxwell JC. Emerging research on methamphetamine. Addictive disorders. *Current Opinion in Psychiatry*. 2005 May;18(3):235-242.

Meredith CW, Jaffe C, Ang-Lee K, Saxon AJ. Implications of chronic methamphetamine use: a literature review. *Harv Rev Psychiatry*. 2005;13:141-54.

Smith, S.S.; Kemelman, M. & Carpov, A. 2007. Chronic methamphetamine administration increases GABA(A) receptor 4 subunit expression in hippocampus and cortex: Reversal by flumazenil treatment *Neurobiology ofAddiction ZOS3/ 1/2007*. Santa Fe. New Mexico: Abstract Poster Presentation.

Urschel, H.C.; Hanselka, L.L.; Gnomov, I.; White. L. & Baron, M. 2007. Open-label study of a proprietary treatment program targeting type A gamma aminobutyric acid receptor dysregulation in methamphetamine dependence. *Mayo Clin Proc* 82(10): 1170-1178.

Supported by funding from Hythiam, Inc.