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

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INTRODUCTION

During the initial phases of abstinence, methamphetamine-dependent patients may experience cognitive impairments which may compromise their ability to engage in work and benefit from psychosocial treatment (Merendino, et al., 2005). Cognitive deficits may contribute to the high rate 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 discourage 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. The report of the present study has been found to produce changes in the GABA_A/benzodiazepine receptor that are reversed by flumazenil (saline for the placebo).

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 a part of a larger controlled study demonstrating a significant reduction in craving, and decreased use during initial treatment of methamphetamine dependence.

METHODS

STUDY DESIGN

The 38-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.

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 hydroxyurea 50 mg for pre-infusion and PRN for sleep; or (2) a control group receiving identical 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 withCogstate (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 improvement at baseline in the sample of methamphetamine users with the exception of reaction time measure for the Go-No-Go test. Performance improved for reaction time in a set shifting test and a sustained attention task during the initial course of flumazenil treatment.

CONCLUSION

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 sustain attention.

STUDY METHODS

To determine the neurocognitive efficacy of this treatment, the following methods were used:

1. **Baseline Performance**: Baseline data were collected 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.

2. **Randomization**: Participants were assigned to either the active treatment group receiving flumazenil, 2 mg administered IV on days 1, 2, 3, 21, 22; oral gabapentin 1200 mg/day, and hydroxyurea 50 mg for pre-infusion and PRN for sleep; or the control group receiving identical formulations of the three medications.

3. **Outcome Measures**: Cognitive function was measured with Cogstate (Newark, DE), a computerized battery of neuropsychological tests.

4. **Statistical Analyses**: 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 neuropsychological measures when compared to age-matched 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 improvement to the degree expected given the chronicity and frequency of their methamphetamine use.

5. **Statistical Analysis Plan**: The statistical analysis plan included within-group, between-group, and interaction effects for the treatment and placebo groups across 3 time points: screening, day 4 (after 3 days of treatment), and day 30.

6. **Statistical Analysis**: 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 neuropsychological measures when compared to age-matched 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 improvement to the degree expected given the chronicity and frequency of their methamphetamine use.

7. **Statistical Significance**: 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: 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.

8. **Set Shifting**: 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 time from baseline to day 4, while the placebo group showed no significant change.

**REFERENCES**
