

# Safety and Efficacy of $\gamma$ -Vinyl GABA (GVG) for the Treatment of Methamphetamine and/or Cocaine Addiction

JONATHAN D. BRODIE,<sup>1\*</sup> EMILIA FIGUEROA,<sup>2</sup>  
EUGENE M. LASKA,<sup>1,3</sup> AND STEPHEN L. DEWEY<sup>1,4</sup>

<sup>1</sup>Department of Psychiatry, NYU School of Medicine, New York, New York 10016

<sup>2</sup>Clinica Integral de Tratamiento Contra las Adicciones CP21120, Mexicali, B.C., Mexico

<sup>3</sup>Statistical Sciences and Epidemiology Division, Nathan Kline Institute for Psychiatric Research, Orangeburg, New York 10962

<sup>4</sup>Chemistry Department, Brookhaven National Laboratory, Upton, New York 11973

**KEY WORDS** vigabatrin; methamphetamine; cocaine; treatment; addiction

**ABSTRACT** This study examined the safety and efficacy of gamma vinyl-GABA (GVG, vigabatrin) for the treatment of methamphetamine and/or cocaine addiction. A total of 30 subjects, who met DSM-IV criteria for methamphetamine and/or cocaine dependence, were enrolled in an open label 9-week safety study. The protocol was specifically designed to include extensive visual field monitoring as well as outcome measures of therapeutic efficacy. Patients were screened twice weekly for the presence of urinary cocaine, methamphetamine, heroin, alcohol, and marijuana. In total, 18/30 subjects completed the study and 16/18 tested negative for methamphetamine and cocaine during the last 6 weeks of the trial. GVG did not produce any visual field defects or alterations in visual acuity. Furthermore, it did not produce changes in vital signs even with continued use of methamphetamine and cocaine. Thus, under conditions that appear to be appropriate for the successful treatment of methamphetamine and/or cocaine addiction, GVG is safe. **Synapse 55:122–125, 2005.** © 2004 Wiley-Liss, Inc.

## INTRODUCTION

A rapid elevation in nucleus accumbens (NACc) dopamine (DA) characterizes the neurochemical response to cocaine, methamphetamine, and other drugs of abuse (Dewey et al., 1998). Previously, we demonstrated that this response and associated behaviors are attenuated or even blocked by gamma vinyl-GABA (GVG, vigabatrin), an antiepileptic drug (AED) and an irreversible inhibitor of GABA-transaminase (Kushner et al., 1997, 1999; Dewey et al., 1998, 1999; Morgan and Dewey, 1998; 2001; Ashby et al., 1999; Gerasimov et al., 1999, 2000, 2001; Paul et al., 2001; Schiffer et al., 2001, 2003; Stromberg et al., 2001; Gardner et al., 2002; Lee et al., 2004). In addition, GVG does not produce tolerance, withdrawal, or appetitive behavior (Takada and Yanagita, 1997; Kushner et al., 1999). Finally, with respect to treatment, our preclinical dosing data suggest that low sub-chronic exposure is more effective at inhibiting cocaine-induced increases in NACc DA than large acute exposures (Schiffer, et al., 2003).

In an extension of these data, we recently reported the results of an open label clinical trial that demonstrated the efficacy of GVG for the treatment of cocaine dependence (Brodie et al., 2003). Combined with the

knowledge that GVG also blocked methamphetamine-induced increases in NACc DA, (Gerasimov et al., 1999) we recruited a preponderance of methamphetamine abusers for this second clinical trial.

Methamphetamine is a powerful and lethal psychostimulant that is readily synthesized from inexpensive over the counter medications. According to the National Household Survey on Drug Abuse (SAMSA, 2000), an estimated 8.8 million people have tried it. Further, the Drug Abuse Warning Network (DAWN) reported an estimated 30% increase in methamphetamine-related emergency room episodes between 1999

Research for this study was conducted at the Clinica Integral de Tratamiento Contra las Adicciones, Mexicali, B.C., Mexico.

Contract grant sponsor: Biochemical Psychiatry Fund, NYU School of Medicine; Contract grant sponsor: Catalyst Pharmaceutical Partners; Contract grant sponsor: NIH/NIDA; Contract grant numbers: DA015041, DA15082; Contract grant sponsor: U.S. Department of Energy Office of Biological and Environmental Research; Contract grant number: USDOE/OBER DE-AC02-98CH10886.

\*Correspondence to: Jonathan D. Brodie, Ph.D., M.D., Dept. of Psychiatry, NYU School of Medicine, 550 First Avenue, New York, NY 10016. E-mail: brodij01@gcr.med.nyu.edu

Received 5 September 2004; Accepted 17 September 2004

DOI 10.1002/syn.20097

Published online  
in Wiley InterScience (www.interscience.wiley.com).

and 2000. In view of this increased prevalence and lethality, it is striking that no pharmacologic strategies have been developed and that only cognitive behavioral interventions are available for treatment.

Despite the widespread chronic use of GVG in over 250,000 subjects in approximately 65 countries for the treatment of infantile spasms and refractory partial complex seizures, recent reports of a significant prevalence of largely asymptomatic visual field defects (VFDs) (~30–40% in subjects with years of treatment) have caused concerns about its long-term use (Bruni et al., 2000; Nicolson et al., 2002; Schmitz et al., 2002). The mechanisms underlying these VFDs are unknown. However, a recent study suggests that while they do not appear to be related to GABA, they may be due to direct light exposure and reactive oxygen species, which are known to be retinotoxic (Izumi et al., 2004). With this in mind, we specifically designed this study protocol to maximize safety by limiting total cumulative exposure and by including extensive ophthalmic screening and monitoring prior to, throughout, and following the study.

All subjects ( $n = 30$ , 29 M, 1F) were recruited by word-of-mouth or newspaper advertisement, provided signed informed consent, and met DSM-IV criteria for drug dependence. The protocol for this study was reviewed and approved by the Government of Mexico according to the standards of the Helsinki Convention as currently modified. Subjects abused methamphetamine, cocaine, or both on a daily basis and were otherwise in good health. The mean duration of drug dependence for all subjects was  $12.8 \pm 1.1$  years and 27/30 subjects met DSM-IV criteria for methamphetamine dependence, either alone (10/30) or in addition to cocaine dependence (17/30). The other three subjects met DSM-IV criteria for cocaine dependence. A complete preadmission history and physical examination were obtained. The baseline ophthalmologic examination consisted of funduscopy, visual acuity determination, and visual field measurements (automated Humphreys VF60-4 protocol), which were repeated in the middle and end of treatment and again at one to two months following treatment cessation. Ophthalmic measurements were performed at the Codet Eye Institute, Tijuana, B.C. Mexico. In addition, these data were independently evaluated by a Board Certified Ophthalmologist at the University of Medicine and Dentistry, Newark, New Jersey, who was blinded to all subject identifiers (Fechtner et al., unpublished data).

GVG administration was initiated at 500 mg twice daily for three days, then 1.5 g/day for the next 4 days and 2 g/day for the next week. On day 15, subjects were placed on 3 g/day, maintained at that dose for the next 28 days, and then tapered to zero over the next 3 weeks. Completers received a cumulative GVG dose of 137 g, less than 10% of the lifetime exposure where there appears to be an increase in the incidence of

visual field abnormalities (Manuchehri et al., 2000). Twice weekly urine samples were obtained under direct observation and tested for cocaine, methamphetamine, marijuana, heroin, and alcohol. Daily vital signs were obtained while all subjects were encouraged to participate in weekly group therapy.

Of the 30 volunteers, 11 dropped out before completing 4 weeks, 1 completed 8 weeks and 18 (3/3 cocaine, 6/10 methamphetamine, 9/17 mixed) completed all nine weeks. Completers did not differ significantly from non completers in either the pre-study daily usage ( $0.78 \pm 0.12$  g vs.  $0.88 \pm 0.12$  g) or years of dependence ( $11.7 \pm 1.4$  vs.  $14.5 \pm 1.7$ ).

GVG did not change vital signs even with continued use of cocaine and methamphetamine. Further, there were no VFDs, funduscopic changes or changes in visual acuity detected in any subject (regardless of completion). Completers reported increased appetite and showed a significant weight gain over non-completers ( $5.2 \pm 0.8$  vs.  $2.0 \pm 0.6$  kg;  $P = 0.004$ ). Fifteen completers were methamphetamine and cocaine free for >4 consecutive weeks (no slips allowed) while 2 were never drug-free although use was markedly reduced by self report. The mean drug-free interval was  $40.1 \pm 2.4$  consecutive days with an average use of  $0.03 \pm 0.02$  g/day over the last 3 weeks of the study.

In order to characterize time-related parameters connected with abstinence, we fit a nonparametric Kaplan-Meier based “cure model” (Laska and Meisner, 1992) to the entire data set. This model states that:

$$H(t) = (1 - p) + pS(t)$$

where  $H(t)$  is the survival distribution of abstinence onset,  $S(t)$  is the conditional probability of onset, given that onset will occur, and  $p$  is the probability that onset will occur.

The median onset time to the first day drug free regardless of what happens thereafter is 10 days in the entire group and 7 days among those who had at least one day drug free. The probability of being drug free for at least one day was estimated under the cure model to be 0.91. The median onset to the first day drug free, which is followed by 21 days drug free, without any contiguous observations non-drug-free or missing (among those who have 21 days drug free), is 14 days. Of the 30 subjects, 15 had onset followed by 21 days drug free and the cure model estimate of the probability of an individual achieving this status is 0.6. In our study population, whose mean time to relapse is about one day without treatment, 21 days was chosen as a time condition that would be expected reasonably to exceed a placebo effect in the treatment of cocaine or methamphetamine dependence (Kosten et al., 1992; Carroll et al., 1994).

Of the 15 subjects who had the next 21 consecutive days drug free after onset of abstinence, 12 remained drug free to week 9 (the end of the study,) 1 dropped out

at the end of week 7 while still drug free, 1 was drug free for all of the 3 weeks that he was in the study, and the remaining subject had a variable course. Within the 63-day study period, the median number of days drug free in this group was greater than 42 days.

Despite an abundance of data that have demonstrated efficacy of GVG in the treatment of infantile spasms and other forms of epilepsy, the emergence of largely asymptomatic, concentric VFDs following cumulative GVG exposures in excess of 1,500 g (Manuchehri et al., 2000) has delayed its approval by the United States Food and Drug Administration. Therefore, to specifically address the emergence of this side effect, the present study was designed to limit cumulative exposures to less than 10% of this value. We chose a sample population to include individuals who abused methamphetamine, cocaine, or both.

This group of subjects had a mean daily reported use of nearly 1 g of methamphetamine or cocaine for a period of 12 years and no subject acknowledged a history of more than several consecutive days drug-free in the past year. Since animals given methamphetamine required a higher GVG dose than those given cocaine for a similar level of neurochemical and behavioral attenuation (Gerasimov et al., 1999), we did not expect that the reduction of methamphetamine use would approximate our previous cocaine trial (Brodie et al., 2003), due to the lower GVG dose and shorter treatment interval used in the present study. Thus, it is remarkable that half of these predominantly methamphetamine-dependent individuals remained essentially drug free for approximately 6 consecutive weeks despite living in their normal home environment with ready access to drugs. As in our previous study (Brodie et al., 2003), we observed an obvious weight gain that correlated with the conversion to negative urine screens that may be attributed to relief of the appetite suppressant effects of the psychostimulants.

We are unaware of any pharmacologic strategy that successfully treats methamphetamine dependence, making these findings unique with respect to efficacy and critical in terms of safety. Furthermore, these preliminary clinical findings are a striking confirmation of the relevance and validity of our preclinical data using animal models of addiction that ranged from behavioral paradigms (Dewey et al., 1998) to *in vivo* neurochemical and neuroimaging strategies (Schiffer et al., 2001).

Finally, due to the open-label nature of this study, the lack of a control group, and randomized allocation, we have not proved that GVG caused the observed abstinence. In fact, the conclusive demonstration of treatment efficacy must be established by an appropriately blinded randomized trial. Nevertheless, the failure to detect *any* signs of visual pathology or changes in vital signs even with continued use of methamphetamine and cocaine indicates that GVG is safe under these clinically relevant treatment conditions.

## ACKNOWLEDGMENTS

This study would not have been possible without the dedicated efforts of the Mexicali staff of the Clinica Integral de Tratamiento Contra las Adicciones. We acknowledge support from an unrestricted grant from Catalyst Pharmaceutical Partners and the NIH/NIDA (DA015041 and DA15082 to S.L.D.).

## REFERENCES

- Ashby Jr CR, Rohatgi R, Ngosuwan J, Borda T, Gerasimov MR, Morgan AE, Kushner S, Brodie JD, Dewey SL. 1999. Implication of the GABA(B) receptor in gamma vinyl-GABA's inhibition of cocaine-induced increases in nucleus accumbens dopamine. *Synapse* 3:151–153.
- Brodie JD, Figueroa E, Dewey SL. 2003. Treating cocaine addiction: from preclinical to clinical trial experience with gamma-vinyl GABA. *Synapse* 50:261–265.
- Bruni J, Guberman A, Vachon L, Desforges C. 2000. Vigabatrin as add-on therapy for adult complex partial seizures: a double-blind, placebo-controlled multicentre study. *Seizure-Eur J Epilepsy* 9:224–232.
- Carroll K, Rounsaville BJ, Gordon LT, Nich C, Jatlow P, Gawin F. 1994. One-year follow up of psychotherapy and pharmacotherapy for cocaine dependence: delayed emergence of psychotherapy effects. *Arch Gen Psychiatry* 51:989–997.
- Dewey SL, Morgan AE, Ashby CR, Horan B, Kushner SA, Logan J, Volkow ND, Fowler JS, Gardner EL, Brodie JD. 1998. A Novel Strategy for the Treatment of Cocaine Addiction. *Synapse* 30:119–129.
- Dewey SL, Brodie JD, Gerasimov M, Horan B, Gardner EL, Ashby Jr CR. 1999. A pharmacologic strategy for the treatment of nicotine addiction. *Synapse* 31:76–86.
- Gardner EL, Schiffer WK, Horan BA, Highfield D, Dewey SL, Brodie JD, Ashby Jr CR. 2002. Gamma-vinyl GABA, an irreversible inhibitor of GABA transaminase, alters the acquisition and expression of cocaine-induced sensitization in male rats. *Synapse* 46:240–250.
- Gerasimov MR, Ashby CR, Gardner EL, Mills MJ, Brodie JD, Dewey SL. 1999. Gamma-vinyl GABA inhibits methamphetamine, heroin, or ethanol-induced increases in nucleus accumbens dopamine. *Synapse* 34:11–19.
- Gerasimov MR, Schiffer WK, Brodie JD, Lennon IC, Taylor SJ, Dewey SL. 2000. gamma-aminobutyric acid mimetic drugs differentially inhibit the dopaminergic response to cocaine. *Eur J Pharmacol* 395:129–135.
- Gerasimov MR, Schiffer WK, Gardner EL, Marsteller DA, Lennon IC, Taylor SJ, Brodie JD, Ashby Jr CR, Dewey SL. 2001. GABAergic blockade of cocaine-associated cue-induced increases in nucleus accumbens dopamine. *Eur J Pharmacol* 414:205–209.
- Izumi Y, Ishikawa M, Benz AM, Izumi M, Zorumski CF, Thio LL. 2004. Acute vigabatrin retinotoxicity in albino rats depends on light but not GABA. *Epilepsia* 5:1043–1048.
- Kosten T, Gawin FH, Kosten TA, Morgan C, Rounsaville BJ, Schottenfeld R, Kleber HD. 1992. Six-month follow-up of short-term pharmacotherapy for cocaine dependence. *Am J Addict* 1:40–49.
- Kushner SA, Dewey SL, Kornetsky C. 1997. Gamma-vinyl GABA attenuates cocaine-induced lowering of brain stimulation reward thresholds. *Psychopharmacology (Berl)* 133:383–388.
- Kushner SA, Dewey SL, Kornetsky C. 1999. The irreversible gamma-Aminobutyric Acid (GABA) transaminase inhibitor gamma-vinyl-GABA blocks cocaine self-administration in rats. *J Pharmacol Exp Ther* 290:797–808.
- Laska EM, Meisner M. 1992. Nonparametric estimation and testing in a cure model. *Biometrics* 48:1223–1234.
- Lee DE, Schiffer WK, Dewey SL. 2004. Gamma-Vinyl GABA (vigabatrin) blocks the expression of toluene-induced conditioned place preference (CPP). *Synapse* 54:183–185.
- Manuchehri K, Goodman S, Siviter L, Nightingale S. 2000. A controlled study of vigabatrin and visual abnormalities. *Br J Ophthalmol* 84:499–505.
- Morgan AE, Dewey SL. 1998. Effects of pharmacologic increases in brain GABA levels on cocaine-induced changes in extracellular dopamine. *Synapse* 28:60–65.
- Nicolson A, Leach JP, Chadwick DW, Smith DF. 2002. The legacy of vigabatrin in a regional epilepsy clinic. *J Neurol Neurosurg Psychiatry* 73:327–329.

- Paul M, Dewey S, Gardner E, Brodie J, Ashby C. 2001. Gamma-vinyl GABA (GVG) blocks expression of the conditioned place preference response to heroin in rats. *Synapse* 41:219–220.
- SAMSA (Substance Abuse and Mental Health Administration, Office of National Drug Control Policy). 2000. National Survey on Drug Abuse.
- Schiffer WK, Gerasimov M, Hoffman L, Marsteller D, Ashby CR, Brodie JD, Dewey SL. 2001. Gamma vinyl-GABA differentially modulates NMDA antagonist-induced increases in mesocortical versus mesolimbic DA transmission. *Neuropsychopharmacology* 25: 704–712.
- Schiffer WK, Marsteller D, Dewey SL. 2003. Sub-chronic low dose gamma-vinyl GABA (vigabatrin) inhibits cocaine-induced increases in nucleus accumbens dopamine. *Psychopharmacology (Berl)* 168: 339–343.
- Schmitz B, Schmidt T, Jokiel B, Pfeiffer S, Tiel-Wilck K, Ruther K. 2002. Visual field constriction in epilepsy patients treated with vigabatrin and other antiepileptic drugs: a prospective study. *J Neurol* 249:469–475.
- Stromberg MF, Mackler SA, Volpicelli JR, O'Brien CP, Dewey SL. 2001. The effect of gamma-vinyl-GABA on the consumption of concurrently available oral cocaine and ethanol in the rat. *Pharmacol Biochem Behav* 68:291–299.
- Takada K, Yanagita T. 1997. Drug dependence study on vigabatrin in rhesus monkeys and rats. *Arzneimittel-Forschung/Drug Res* 47: 1087–1092.