

*Short Communication*

# Treating Cocaine Addiction: From Preclinical to Clinical Trial Experience With $\gamma$ -Vinyl GABA

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In the present study, we report data from the first human clinical trial using gamma vinyl-GABA (GVG, vigabatrin), as a potential therapeutic drug for the treatment of cocaine addiction. GVG, an irreversible inhibitor of GABA-transaminase, elevates human brain GABA concentrations (Mattson et al., 1995) and is currently available in many countries around the world for the treatment of epilepsy and infantile spasms. Currently, however, GVG is not approved for use in the United States.

In the course of examining potential candidates for the modulation of schizophreniform psychosis by means of modulating a putative hyper-dopaminergic syndrome, we reported that when administered acutely, GVG reduced synaptic and extracellular dopamine (DA) levels (Dewey et al., 1992). Further investigation revealed that these effects were restricted to the (S)-enantiomer (Schiffer et al., 2000) and modulated by the GABA<sub>B</sub> receptor subtype (Ashby et al., 1999). Primate positron emission tomography (PET) studies demonstrated that the pharmacologic profile of <sup>11</sup>C-GVG in the central nervous system was regionally specific and consistent with irreversible enzyme inhibition (Ding et al., 2001). Together, these findings supported our initial objective. Furthermore, they provided the foundation upon which we based our notion that GVG could play an effective role in preventing cue-induced and psychostimulant-induced increases in brain DA as well.

Therefore, in an extensive series of preclinical rodent and primate studies using in vivo microdialysis and PET, respectively, we reported that GVG blocked drug and cue-induced increases in nucleus accumbens and striatal DA (Dewey et al., 1998, 1999; Gerasimov et al., 2001; Morgan et al., 1997; Morgan and Dewey, 1998). Further, we demonstrated that GVG blocked cocaine self-administration (Kushner et al., 1999) and cocaine-induced lowering of brain stimulation reward thresh-

olds (Kushner et al., 1997). In addition, we demonstrated that GVG blocked the expression and acquisition of cocaine-seeking behavior (conditioned place preference, Dewey et al., 1998) as well as sensitization to cocaine (Gardner et al., 2002). We subsequently extended this work to include similar findings with heroin, nicotine, methamphetamine and amphetamine, and alcohol (Gerasimov and Dewey, 1999; Paul et al., 2001a; Dewey et al., 1999).

In an early report, Buckett (1981) demonstrated that GVG decreased voluntary morphine consumption. More recently, Xi and Stein (2000) demonstrated that GVG blocked heroin self-administration while Bevins et al. (2001) demonstrated that it partially blocked the expression of nicotine-induced locomotor activity. Wegelius et al. (1993) demonstrated that GVG decreased voluntary alcohol consumption in alcohol-preferring rats and Stromberg et al. (2001) established that GVG, at doses of 100, 200, and 300 mg/kg, reduced both ethanol and cocaine consumption in a dose-related manner. Taken together, these data are all consistent with anecdotal reports provided by self-medicating cocaine, methamphetamine, and heroin abusers as well as cigarette smokers.

The present clinical trial was conducted in a Mexican government designated addiction treatment center under a drug treatment protocol approved by the state of Baja California and the Mexican federal government.

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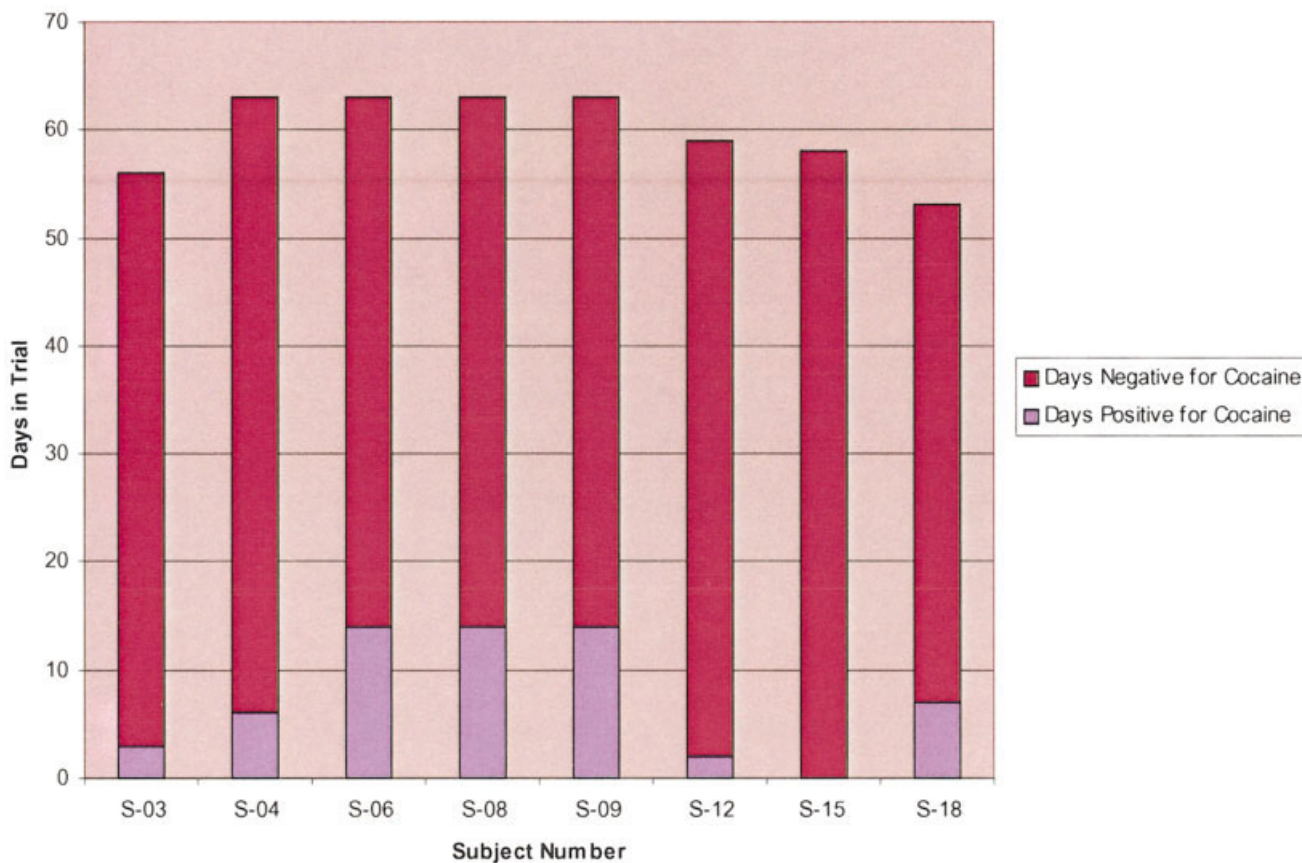


Fig. 1. Treatment completers. Total days in the trial dirty (light shading) and clean (dark shading) for each subject. Note that Subjects 12, 15, and 18 have finished the treatment phase and are completing the taper. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

The protocol was designed as an outpatient, open-label, fixed-dose, time-limited trial in a setting with psychotherapeutic support and intervention.

A total of 20 subjects (19 male and 1 female) who met standard inclusion criteria were enrolled. For the purposes of this study, these were primarily daily cocaine abusers who met DSM-IV criteria for cocaine addiction with a minimum of 3 years of continuous use. Most, however, were polydrug abusers whose cocaine use was often supplemented with methamphetamine, marijuana, and/or alcohol. As a prerequisite for inclusion, all subjects indicated that they were interested in breaking their drug dependence and gave informed, signed consent. Exclusion criteria included intravenous drug use and subjects treated within the past year for substance abuse.

Following an admission physical examination and screening for medical exclusion criteria, all subjects were given a screening urinalysis and a craving questionnaire and were then placed on GVG. The dosing schedule was designed using an escalating strategy. Specifically, GVG was administered on day 1 at 2.0 g (1 g, twice daily). After 3 days, GVG was increased to 1.5 g twice daily and on the seventh day GVG was adminis-

tered at a continuing dose of 2 g twice daily. All dosing was done under observation in the clinic. Subjects who had a negative drug screen for 4 successive weeks (28 days) were then tapered by 1 g of GVG per day per week.

At inception, the mean age of the subjects was 29, with a 12-year history of cocaine abuse and a daily consumption of ~1.7 g. All subjects were encouraged to participate in the normal group and individual programs and were required to twice weekly provide urine samples in addition to a daily questionnaire of drug use and craving. The drug screen included cocaine, heroin, methamphetamine, tetrahydrocannabinol, and phen-cyclidine.

Of the 20 subjects enrolled in the study, eight remained in the program and have been drug-free for periods ranging from 46–58 days (Fig. 1). Only two subjects had a single slip once the craving stopped. For the purpose of this study, a slip restarted the consecutive days clean value. Of the 12 subjects who failed to complete the program, eight requested termination within 10 days, stating that they did not wish to stop their cocaine use (Fig. 2). As shown, the other four subjects stayed in the protocol for periods of 25–43

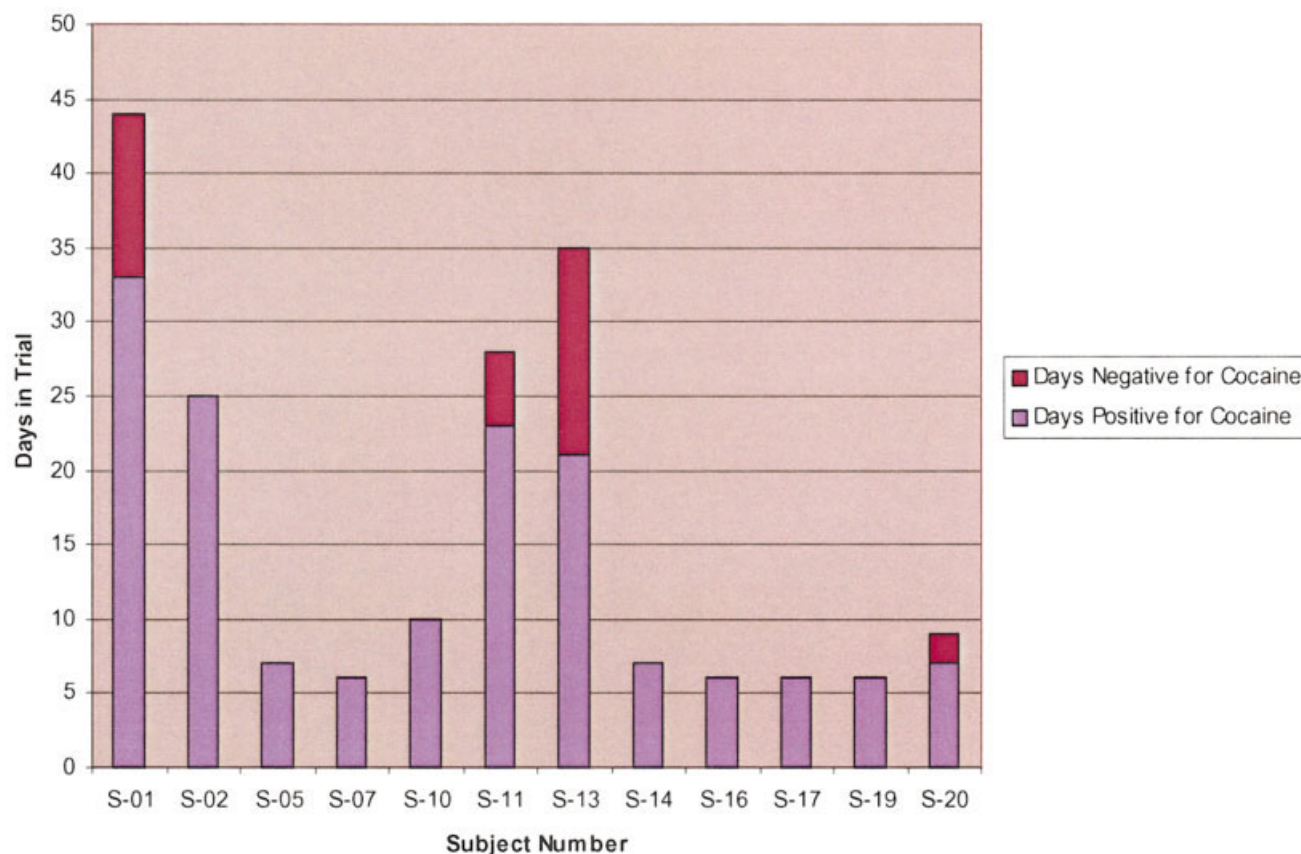


Fig. 2. Treatment noncompleters. Total days in the trial clean (dark shading) and dirty (light shading) for each subject. Note that seven of the eight early dropouts were never clean. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

TABLE I. Results of the clinical trial

	Completers (n = 8)	Non-completers (n = 12)	
Age	28.8 ± 5.7	29.3 ± 6.2	<i>P</i> = 0.73 (ns)
Abuse history (years)	9.5 ± 4.9	11.5 ± 6.7	<i>P</i> = 0.74 (ns)
Mean cocaine use (g/day)	1.8 ± 1.5	1.6 ± 0.8	<i>P</i> = 0.62 (ns)
Consecutive clean days	48.5 ± 5.7	1.9 ± 3.3	<i>P</i> < 0.0001
Weight increase (lbs)	18.2 ± 10.7	0.2 ± 0.6	<i>P</i> < 0.0001

All data are expressed as the mean ± SD. The Mann-Whitney Test was used to determine statistical significance.

days but continued to use cocaine, albeit in greatly reduced amounts (two out four had a >80% reduction, one out of four had a 50% reduction, and the other did not reduce at all, self-reported), despite their claim that the drug did not engender the usual high. Most completers reported that their craving was not eliminated until ~2–3 weeks (17.9 ± 7.1 days) following GVG administration. Craving was never eliminated in the four subjects who continued to use drugs as well as GVG for >3 weeks or in the eight early noncompleters.

As summarized in Table I, the trial completers did not differ significantly from the noncompleters in age, duration of cocaine abuse, or average daily use. However, there was a significant and striking difference in the consecutive days clean (48.5 ± 5.7 vs. 1.9 ± 3.3, *P* <

0.0001) and a clear distinction of the two groups on the basis of weight gained during the trial (18.2 ± 10.7 lbs. vs. 0.2 ± 0.6 lbs.). No subject who continued cocaine use during their participation in the study reported increased appetite or experienced weight gain.

For this to be convincing in the light of concerns about safety and efficacy, we chose an outcome measure of 28 consecutive days clean (negative for cocaine). This is particularly stringent for an outpatient setting and in the field of addiction therapy where statistical significance often exceeds therapeutic reality. Overall, GVG was well tolerated. No subjects reported visual disturbances of any kind throughout their exposure to GVG or admitted to vision changes of any kind upon questioning. The major side effects were transient som-

nolence in the first 10 days (17/20) and an intermittent low-grade headache (9/20) that occasionally persisted for several weeks, although never severe enough for the subject to request termination on that basis.

Subjects in this study were all hard-core cocaine users, who consumed cocaine 5–7 days per week and had been doing so for 3–15 years. Nevertheless, 40% of those who entered the study completed it without relapse. Once cocaine use ceased, six of the eight completers were entirely drug free for the duration of the study (~7 weeks). The others had a single “slip” and were again clean for >4 weeks. On the other hand, the mean time to relapse of all 12 noncompleters was ~2 days. Significantly, all of the trial completers gained weight ( $18 \pm 11$  lbs.), while none of the noncompleters gained any. Weight gain precisely paralleled cessation of cocaine use by self-report as well as by the twice-weekly drug screen and daily observation. This is not surprising in view of the well-known appetite-suppressing effects of cocaine.

The trial completers manifested clear behavioral changes. They showed profound gains in self-esteem, reestablished healthy family relationships, and went to work or actively sought work. It is interesting to note that there were no relapses over an extended period despite their remaining in the same neighborhood environment in which the drug was readily available and with all of the cues and social pressures that supported their addiction for so many years.

The eight noncompleters who voluntarily terminated within the first 10 days of GVG treatment demonstrate the vulnerability of a simple pharmacologic strategy to a phenomenon as psychologically and socially complex as cocaine addiction. Without psychosocial intervention it is likely that the fraction of subjects who complete a program will be lower than observed here. For example, in this study most subjects who continued using cocaine reported an altered and diminished response (reward) but persisted in their use, albeit at reduced amounts. If the outcome measure was a greater than 80% reduction in drug consumption, then that criterion was met by 10 of the 12 subjects who stayed on GVG for more than 10 days.

In addition, all eight subjects who completed the program noted a cessation of craving which persisted during the exit phase (GVG taper). This suggests that elimination of craving might be the single most important factor in achieving successful therapeutic remission. The persistence of drug abstinence and lack of craving, despite lowering the GVG dose during the taper (in all completers), also offers the clinically relevant possibility that the GVG dose during the maintenance phase could be significantly lower than the initial acute treatment phase, thereby markedly lowering lifetime cumulative exposure and the risk of visual field defects (VFDs). Interestingly, these data are consistent with our recent preclinical report that sub-

chronic dosing is equally effective at blocking cocaine-induced increases in extracellular DA as large acute doses (Schiffer et al., 2003).

The United States Food and Drug Administration (FDA) has not approved GVG for the treatment of epilepsy or any other indication due to concerns about the emergence of VFDs, which have long been associated with antiepileptic drugs (AEDs) (Nielsen and Syversen, 1986; Wohlrab et al., 1999). Concerns about AED-induced VFDs must be addressed within the context of risk/benefit for the indication of drug dependence. Cocaine addiction is a life-threatening disease for which there are currently no effective pharmacologic treatments. Therefore, in combination with our recent preclinical report (Schiffer et al., 2003), these human clinical data support the need for a larger double-blind placebo control trial that will more carefully examine the risk/benefit relationship for GVG in the treatment of this life-threatening illness.

VFDs have been reported with other new FDA-approved AEDs. These include tiagabine (Kaufman et al., 2001), progabide (Nordmann et al., 1999; not FDA-approved), and topiramate (Foroozan and Buono, 2003). GVG has been in use around the world for more than a decade with ~250,000 treated patients, mostly children, before the first report of a VFD (Eke et al., 1997). Since then, a series of studies (Nicolson et al., 2002; Schmitz et al., 2002; Bruni et al., 2000) suggests that the prevalence of concentric VFDs is on the order of 30–50% in patients under long-term treatment whose lifetime burden exceeds 1,500 g (Manuchehri et al., 2000). Men appear to be affected more than women (Hardus et al., 2001), while visual function has been reported to remain stable in patients who continue long-term therapy (Paul et al., 2001b). Finally, it remains unclear whether these VFDs are reversible (Vanhatalo et al., 2001) or not (Nousiainen et al., 2001).

These clinical data support our robust preclinical findings. In addition, they emphasize the need for combining biochemical assessments with measurements of the behavioral manifestations of their consequence. For example, many preclinical findings have been verified in this clinical trial. These include the observation that drug-seeking and compliance can likely be managed at a dose that would be safe for months or even years. In view of this marked coherence between our preclinical and clinical findings with cocaine, we suggest, based on our similar preclinical findings with methamphetamine, amphetamine, heroin, nicotine, alcohol, and their combinations (Gerasimov and Dewey, 1999), that GVG may be equally effective for treating dependence to these drugs as well as addictive behaviors (i.e., gambling).

Finally, for the first time there is now compelling human clinical trial data that supports the efficacy of this well-tolerated, nonreceptor-active (Jung et al., 1977), and nonaddicting drug (Takada and Yanagita,

1997) that could be expected to have a salutary outcome in a significant fraction of those individuals suffering from the life-threatening consequences endemic to cocaine addiction. However, while these data suggest that GVG, in combination with psychosocial therapy, offers a potential treatment for cocaine addiction virtually unparalleled by any other drug, they do not obviate the need for a larger double-blind placebo-controlled trial.

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