

Bupropion Reduces Methamphetamine-Induced Subjective Effects and Cue-Induced Craving

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Bupropion is an antidepressant with stimulant properties, which inhibits the reuptake of dopamine (DA) and norepinephrine, and is purported to enhance DA neurotransmission. Bupropion is considered an appealing candidate medication for the treatment of methamphetamine dependence. The current laboratory study was set forth to assess the impact of bupropion treatment on the subjective effects produced by methamphetamine in the laboratory. We also assessed the effects of bupropion treatment on craving elicited by exposure to videotaped methamphetamine cues. A total of 26 participants were enrolled and 20 completed the entire study ($n = 10$ placebo and $n = 10$ bupropion, parallel groups design). Bupropion treatment was associated with reduced ratings of 'any drug effect' ($p < 0.02$), and 'high' ($p < 0.02$) following methamphetamine administration. There was also a significant bupropion-by-cue exposure interaction on General Craving Scale total score ($p < 0.002$), and on the Behavioral Intention subscale ($p < 0.001$). Overall, the data reveal that bupropion reduced acute methamphetamine-induced subjective effects and reduced cue-induced craving. Importantly, these data provide a rationale for the evaluation of bupropion in the treatment of methamphetamine dependence.

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INTRODUCTION

Methamphetamine dependence directly or indirectly affects millions of Americans, and despite the efficacy of current treatments for some patients, relapse remains a significant problem (Huber *et al*, 1997; Rawson *et al*, 1999, 2004; Shoptaw *et al*, 1994). These studies, along with many others, underscore the challenge inherent in providing effective treatment to methamphetamine users.

A number of factors are thought to contribute to relapse, including drug availability and exposure to drug cues. Drug cues ('triggers') include people, places, and things associated with drug use. This has been studied more fully in opiate and cocaine dependence, although similar considera-

tions are likely to apply to dependence on methamphetamine (Ehrman *et al*, 1992; O'Brien *et al*, 1976).

There have been sustained and partly successful efforts to develop medication treatments for drug abuse disorders (de Lima *et al*, 2002; Garbutt *et al*, 1999; Mattick *et al*, 2002; Sofuoglu and Kosten, 2005), although fewer medications have been studied in randomized clinical trials for the treatment of methamphetamine dependence (Galloway *et al*, 1994, 1996; Huber *et al*, 2000).

Bupropion is an attractive candidate medication for the treatment of methamphetamine dependence for several reasons. Bupropion is an antidepressant with stimulant properties (Stahl *et al*, 2004) that is effective for the treatment of nicotine dependence (Richmond and Zwar, 2003). In a clinical trial of bupropion for cocaine dependence (Margolin *et al*, 1995), an exploratory analysis suggested that patients with greater levels of depression may have benefited the most. Clinically, acute abstinence from methamphetamine in chronic users is associated with depression and impaired concentration (Newton *et al*, 2004). These symptoms may be due to methamphetamine-induced neuroadaptations in presynaptic DA neurons manifest as reduced striatal DA availability (McCann *et al*, 1998; Sekine *et al*, 2003; Volkow *et al*, 2001; Wilson *et al*,

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1996). Bupropion inhibits the reuptake of DA and enhances residual DA neurotransmission, effects that may ameliorate methamphetamine abstinence symptoms. The current laboratory study was designed to assess the impact of bupropion treatment on the subjective effects produced by methamphetamine and to assess the effects of bupropion treatment on craving elicited by exposure to methamphetamine cues.

MATERIALS AND METHODS

Subjects

In total, 26 participants were enrolled and 20 completed the entire study ($n = 10$ placebo and $n = 10$ bupropion, parallel groups design). Participants were recruited through advertisements and were paid for their participation. All met DSM-IV-TR criteria for methamphetamine abuse or dependence and were not seeking treatment at the time of study entry. Other inclusion criteria included being between 18 and 45 years of age, a history of using methamphetamine by the smoked or intravenous (i.v.) route, twice-weekly use of methamphetamine in 4 of the 6 weeks prior to screening, and normal laboratory assessment and vital signs. Exclusion criteria included a history of seizure disorder, head trauma, dependence on other drugs aside from nicotine, prior adverse reaction to methamphetamine, or the presence of any other axis I psychiatric disorder. Serious medical conditions such as heart disease, AIDS, asthma, Parkinson's disease, and other serious medical conditions were also exclusionary. Concomitant use of psychotropic medications or medications interacting with bupropion was not allowed. This study was approved by the institutional review boards at both UCLA and the University of Texas Health Sciences Center at San Antonio (UTHSCSA), and all participants gave informed consent after being fully informed about potential risks of participation.

Study Design

The study was conducted using a double-blind design at UCLA and UTHSCSA. Following admission to the clinical research center (CRC), subjects received a baseline series of i.v. doses of methamphetamine (0, 15, and 30 mg). Subjects received a second identical series of methamphetamine doses 6 days after initiation of twice-daily oral placebo or bupropion treatment. The order of the methamphetamine 0 and 15 mg administration sessions was randomly assigned, although the 30 mg methamphetamine dose always followed the lower doses (see Study Scheme: Table 1). Thus, the investigators (but, not the participants) were not blinded to the 30 mg methamphetamine dose. Assignment of placebo and bupropion was random, and stratified by site.

Drugs

Commercially available bupropion tablets (150 mg extended-release) were cut in half (due to the large size of the tablet) and encapsulated in gelatin capsules by research pharmacies at each site. The manufacturer provided documentation that these procedures did not affect

Table 1 Summary of i.v. Doses of Methamphetamine Administered at Baseline and 6 Days after Initiation of Twice-Daily Oral Placebo or Bupropion Treatment

| Study phase | Session | Study day | Methamphetamine challenge (mg) |
|-------------|---------|-----------|--------------------------------|
| Baseline | 1 | 2 | 0 or 15 |
| Baseline | 2 | 3 | 0 or 15 |
| Baseline | 3 | 5 | 30 |
| Treatment | 4 | 18 | 0 or 15 |
| Treatment | 5 | 19 | 0 or 15 |
| Treatment | 6 | 22 | 30 |

bioavailability of the bupropion (personal communication to Dr John Roache). Placebo was prepared in a similar manner. A NIDA contractor provided sterile methamphetamine solution for human use and a saline solution of equal volume and appearance was used as the control. An IND was obtained from the FDA for the use of bupropion and methamphetamine in this study. Methamphetamine was administered over 2 min (between 0900 and 1100 hours on specified infusion days) using an i.v. pump.

Subjective Measures

Subjective effects data were collected using computerized visual analog rating scales (VAS), the Within Session Rating Scale (WSRS, a craving rating scale), the General Craving Scale (GCS) (Merkle, 1999), the Multiple Choice Questionnaire (MCQ), Brief Psychiatric Rating Scale (BPRS), Adjective Scales, and the Addiction Research Center Inventory (ARCI) (Haertzen, 1965, 1966).

VAS data were collected at 15 min before, and 3, 6, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 min following methamphetamine or placebo administration. For the VAS scales, subjects reported the degree to which they feel 'any drug effect', 'high', 'good effects', 'bad effects', 'like methamphetamine', 'desire for methamphetamine', 'depressed', 'anxious', 'stimulated', and 'likely to use' on a continuous scale digitized between 0 and 100. In addition, they were asked to answer the question: 'How much would you pay for this drug?'

Within the first several days of the study, participants rated craving (using the WSRS and the GCS) prior to and following exposure to a neutral cue video consisting of a nature scene. On subsequent days (twice prior to randomization and twice after randomization), participants rated craving prior to and following exposure to a cue video showing actors using drugs. Cueing procedures took place on days that participants could potentially receive 15 mg methamphetamine in order to maintain the salience of the cues. The GCS consists of 59 questions rated on a scale of 1–5, and yields data on several dimensions, including 'behavioral intention', 'physical symptoms', 'positive outcome', 'affect', 'cues affect', and several others.

Participants also completed the MCQ, in which participants complete a series of hypothetical choices between

doses of methamphetamine and varying amounts of money. The crossover point indicated how much participants would pay for a dose of methamphetamine.

The BPRS is a psychiatrist-administered interview that was conducted 60 min after methamphetamine/saline infusion sessions. The BPRS evaluates the severity of subject's psychopathology, including anxiety, depression, and symptoms of schizophrenia. The BPRS total score ratings serve as indicators of psychiatric comorbidity in drug-dependent subjects and as predictors of mental health services utilization.

Adjective Scales consisted rating of 22 adjectives on a scale of 0–4, ranging from 'not at all' to 'extremely', and the ARCI consisted of 49 statements in a true/false format. The BPRS was administered 60 min following methamphetamine administration to detect possible behavioral toxicity (Overall and Gorham, 1962). The Adjective Scales and the ARCI were administered 15 min before and at 30 min after each infusion. The ARCI and Adjective Scale were included to assist interpretation, if needed.

Data Analysis

The primary outcome measures were changes in subjective ratings following administration of i.v. methamphetamine, as compared to placebo. A secondary outcome measure was change in self-reported craving following exposure to a cue video showing actors using drugs. Descriptive statistics for demographic data are presented for all subjects ($n = 26$). However, because of the need to balance the mixed repeated measures design, inferential analyses of the primary outcome data were possible only for the 20 completers. Subjective effects data were analyzed using SAS Proc Mixed (Release 8.2). Fixed effects of Bupropion dose (0 or 150 mg), Period (before vs after initiation of bupropion/placebo treatment), and Methamphetamine dose (0, 15, or 30 mg) were specified in a factorial design (with repeated measures on Period and Methamphetamine dose). In addition, we also examined the effects of Bupropion and Period on the maximum subjective effects reported following methamphetamine administration, using the baseline response immediately prior to dosing as a covariate. The covariance structure was specified as autoregressive and the empirical option was used to maximize validity of this assumption.

RESULTS

Demographics and Drug Use

A total of 26 participants were enrolled and 20 completed the entire study ($n = 10$ placebo and $n = 10$ bupropion, parallel groups design). Data are presented as a comparison of patients who dropped from the study vs those who completed (Table 2), as well as a comparison of all patients who completed and were treated with either bupropion or placebo (Table 3). No significant differences were noted for these comparisons.

Of completers, the majority were non-Hispanic white (55%), male (65%), and had a mean age of 32.8 ± 8.4 years. The majority of completers met criteria for current methamphetamine dependence or current methamphetamine abuse. In addition to methamphetamine use, the

Table 2 Participant Demographics and Drug Use Data for Drops and Completers

| | Drops (N = 6) | Completers (N = 20) | Total (N = 26) | |
|---------------------------------|-------------------------------|----------------------------|----------------------------------|----------------|
| <i>Gender, N (%)</i> | | | | |
| Male | 4 (67) | 13 (65) | 17 (65) | |
| Female | 2 (33) | 7 (35) | 9 (35) | |
| <i>Single major race, N (%)</i> | | | | |
| White, not Hispanic | 4 (67) | 11 (55) | 26 (58) | |
| Hispanic or Latino | 2 (33) | 6 (30) | 8 (31) | |
| African American or Black | 0 (0) | 1 (5) | 1 (4) | |
| Other | 0 (0) | 2 (10) | 2 (8) | |
| <i>Age (years)</i> | | | | |
| Mean \pm SD | 29.7 \pm 6.6 | 32.8 \pm 8.4 | 32 \pm 8 | |
| | | | Drops Completers | |
| | | | Major drug Any use | |
| Drug/alcohol use, N (%) | Major drug^a | Any use^b | Major drug | Any use |
| Alcohol | 0 (0) | 5 (83) | 0 (0) | 17 (85) |
| Heroin | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Barbiturates | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Sedatives/Hypnotics/Tranqs | 0 (0) | 1 (17) | 0 (0) | 1 (5) |
| Cocaine | 0 (0) | 2 (33) | 1 (5) | 4 (20) |
| Amphetamines | 0 (0) | 1 (17) | 0 (0) | 0 (0) |
| Methamphetamine | 6 (100) | 6 (100) | 18 (90) | 20 (100) |
| Cannabis | 0 (0) | 4 (67) | 0 (0) | 11 (55) |
| Inhalants | 0 (0) | 0 (0) | 0 (0) | 1 (5) |
| Nicotine | 0 (0) | 6 (100) | 0 (0) | 15 (75) |
| More than 1 subs/day | 0 (0) | 4 (67) | 1 (5) | 15 (75) |

^aThe number and percent of subjects for whom the drug is the major substance use problem.

^bThe number and percent of subjects who reported any use of the substance in the last 30 days.

completers reported use of several substances, including nicotine (75%), marijuana (55%), and alcohol (85%), in the past 30 days. Participants had significant past histories of abuse of other drugs, including past cocaine dependence, past alcohol abuse or dependence, and past marijuana abuse or dependence.

Subjective Effects

There were significant effects of methamphetamine on all VAS measures other than 'depression'. There were significant interactions between Bupropion (0 vs 150 mg) and Period (before vs after initiation of treatment) for ratings of 'any drug effect' ($p < 0.02$), 'high' ($p < 0.02$), and there was a trend for ratings of 'stimulated' ($p < 0.07$). For 'any drug', there was a trend for a three-way interaction between Methamphetamine, Bupropion, and Period

Table 3 Participant Demographics and Drug Use Data for Completers Only

| | Bupropion (N = 10) | Placebo (N = 10) | Total (N = 20) | |
|---------------------------------|-------------------------------|----------------------------|-------------------|----------------|
| <i>Gender, N (%)</i> | | | | |
| Male | 5 (50) | 8 (80) | 13 (65) | |
| Female | 5 (50) | 2 (20) | 7 (35) | |
| <i>Single major race, N (%)</i> | | | | |
| White, not Hispanic | 6 (60) | 5 (50) | 11 (55) | |
| Hispanic or Latino | 3 (30) | 3 (30) | 6 (30) | |
| African American or Black | 0 (0) | 1 (10) | 1 (5) | |
| Other | 1 (10) | 1 (10) | 2 (10) | |
| <i>Age (years)</i> | | | | |
| Mean ± SD | 32 ± 10.4 | 33.5 ± 6.3 | 32.8 ± 8.4 | |
| | Bupropion | | Placebo | |
| Drug/alcohol use, N (%) | Major drug^a | Any use^b | Major drug | Any use |
| Alcohol | 0 (0) | 8 (80) | 0 (0) | 9 (90) |
| Heroin | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Barbiturates | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Sedatives/Hypnotics/Tranqs | 0 (0) | 0 (0) | 0 (0) | 1 (10) |
| Cocaine | 0 (0) | 0 (0) | 1 (10) | 4 (40) |
| Amphetamines | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Methamphetamine | 9 (90) | 10 (100) | 9 (90) | 10 (100) |
| Cannabis | 0 (0) | 5 (50) | 0 (0) | 6 (60) |
| Inhalants | 0 (0) | 1 (10) | 0 (0) | 0 (0) |
| Nicotine | 0 (0) | 8 (80) | 0 (0) | 7 (70) |
| More than one subs/day | 1 (10) | 6 (60) | 0 (0) | 9 (90) |

^aThe number and percent of subjects for whom the drug is the major substance use problem.

^bThe number and percent of subjects who reported any use of the substance in the last 30 days.

($p < 0.08$). This indicated that during the medication treatment phase of the study, volunteers receiving bupropion reported reduced responses on these measures compared to those receiving placebo. In addition, there was a trend for a Bupropion by Period interaction ($p < 0.10$) for 'likely to use' and 'desire'. There were significant Bupropion by Methamphetamine interactions for both 'desire' and 'likely to use' scores ($p < 0.05$). In both cases, patients receiving placebo showed higher ratings following the 30 mg dose of MA, as compared to the 15 mg dose. Of interest, patients receiving bupropion did not show this dose-related increase, although the effects of Period were not significant. There were no Bupropion effects on 'good effects', 'bad effects', 'liking', 'depression', or 'anxious' scores. In addition, there were no Bupropion effects on the 'pay for the drug' rating following methamphetamine administration. There was no Bupropion effect on responses on the MCQ.

The analyses were repeated using the maximum effect on each rating scale. Very similar results were obtained. Specifically, 'any drug effect' and 'high' remained significant and the three-way interaction for 'any drug effect' became significant, as did the two-way interaction (Bupropion and Period) for 'stimulated'.

For simplicity, and to highlight the most important findings, time-course data from the Treatment phase are shown for 'Any Drug' (Figure 1), 'High' (Figure 2), and 'Stimulated' (Figure 3).

Craving

Exposure to the neutral cue produced minimal, nonsignificant changes in craving ratings. Before initiation of bupropion/placebo treatment, there were no significant Bupropion by cue exposure (before/after) interaction effects. This indicated that the groups did not differ in the magnitude of cue-induced craving at before initiation of active treatment. Following initiation of bupropion/placebo treatment, there were significant Bupropion by cue exposure (before/after) interactions in GCS Total Score ($p < 0.002$) and in the Behavioral Intention subscale of the GCS ($p < 0.001$). This indicated that treatment with bupropion, compared to placebo, was associated with significantly reduced cue-induced craving (Figure 4). Similar results were obtained for WSRS 'likely to use'. There was a significant Bupropion by Period by cue exposure interaction ($p < 0.02$), indicating that during active treatment ratings on this scale were lower. There were no significant effects of bupropion treatment on the WSRS 'feel like using' scores. In general, GCS total scores and scores on each of the subscales were greater prior to randomization, and declined thereafter, possibly indicating that hospitalization, by removing participants from their usual cue-rich environments, reduced cue reactivity.

ARCI, BPRS, and Adjective Scales

Among the ARCI subscales, the pentobarbital-chlorpromazine-alcohol group (PCAG) subscale scores (reflecting sedative effects) decreased with increasing methamphetamine dose, whereas scores on the remaining subscales increased with increasing methamphetamine dose. The only significant Bupropion by Period interaction was seen for the LSD subscale, for which there was a three-way interaction between Bupropion, Period, and Methamphetamine dose ($p < 0.05$). Among the Adjective Scales, significant ($p < 0.05$) Bupropion by Period interactions were found for 'tremor', 'fidgety', and 'nervous'. Mean values for 'tremor' were low in both groups, reducing the implications of the statistical findings. For the 'fidgety' and 'nervous' ratings, bupropion reduced effects of methamphetamine on these measures during the active medication phase.

BPRS ratings were greater than mild on only 25 of approximately 3215 rating events. Ratings other than mild were more common after 30 mg methamphetamine than after 15 or 0 mg. In all, 12 of the 25 ratings of greater than mild occurred following randomization, and there was no effect of Bupropion treatment on the BPRS ratings.

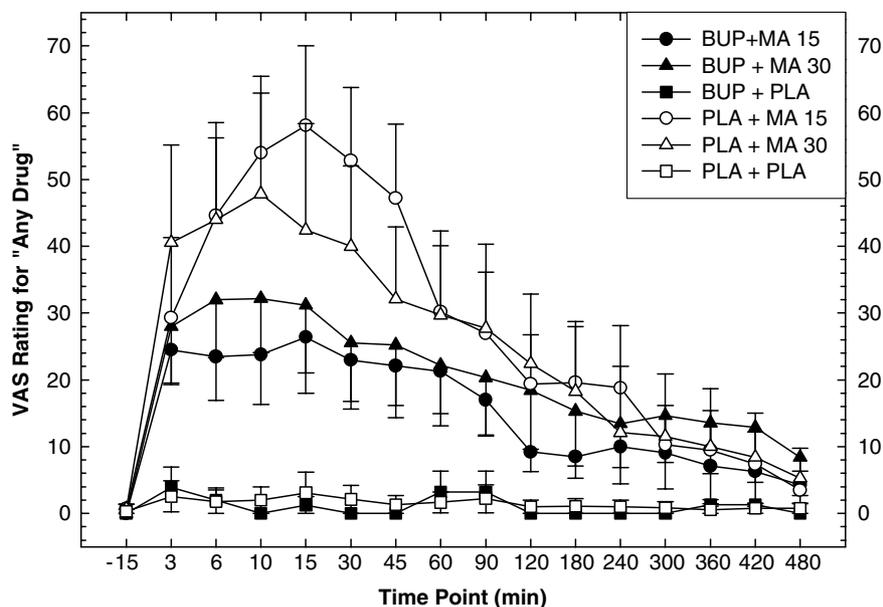


Figure 1 Ratings for 'any drug' Effects (mean \pm SEM). The full time-course is shown following acute administration of placebo (squares), 15 mg (circles), and 30 mg (triangles) methamphetamine 6 days after initiation of twice-daily oral placebo (open symbols) or bupropion (filled symbols).

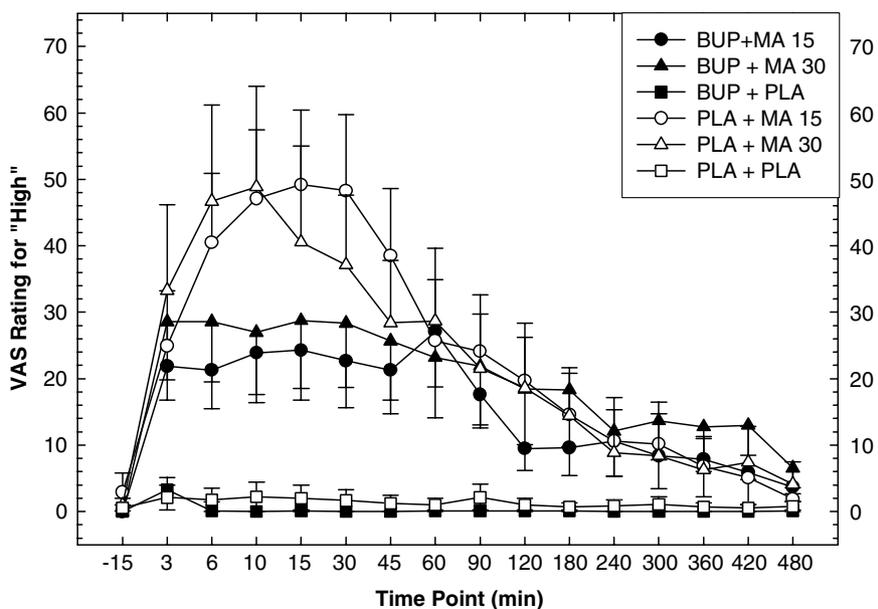


Figure 2 Ratings for 'high' (mean \pm SEM). The full time-course is shown following acute administration of placebo (squares), 15 mg (circles), and 30 mg (triangles) methamphetamine 6 days after initiation of twice-daily oral placebo (open symbols) or bupropion (filled symbols).

DISCUSSION

This group of methamphetamine using volunteers tolerated administration of methamphetamine during treatment with bupropion with no evidence that bupropion enhanced the effects of methamphetamine, or produced behavioral toxicity. Adverse events observed in this study were minor, with both active and placebo groups reporting similar magnitude and severity of events. In fact, bupropion treatment tended to blunt the cardiovascular effects of experimentally administered methamphetamine, with this effect reaching statistical significance for heart rate (Newton *et al*, 2005).

BPRS assessment was included to screen for behavioral toxicity of methamphetamine and to determine if bupropion treatment altered these responses. Very little evidence for behavioral toxicity (eg agitation or psychosis) emerged following administration of methamphetamine, and bupropion treatment did not significantly alter these responses.

Of particular interest, bupropion treatment was associated with reduced 'any drug' and 'high' ratings following methamphetamine administration. Ratings of 'high' and increased scores on ARCI subscales have been associated with abuse liability (Fischman and Foltin, 1991). Bupropion reduced several drug-related subjective effects and did not

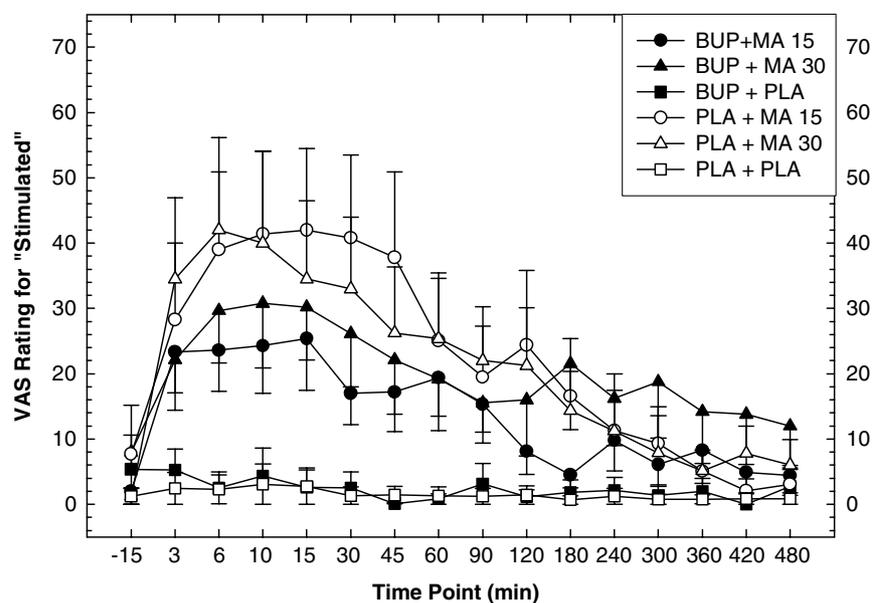


Figure 3 Ratings for 'stimulated' (mean \pm SEM). The full time-course is shown following acute administration of placebo (squares), 15 mg (circles), and 30 mg (triangles) methamphetamine 6 days after initiation of twice-daily oral placebo (open symbols) or bupropion (filled symbols).

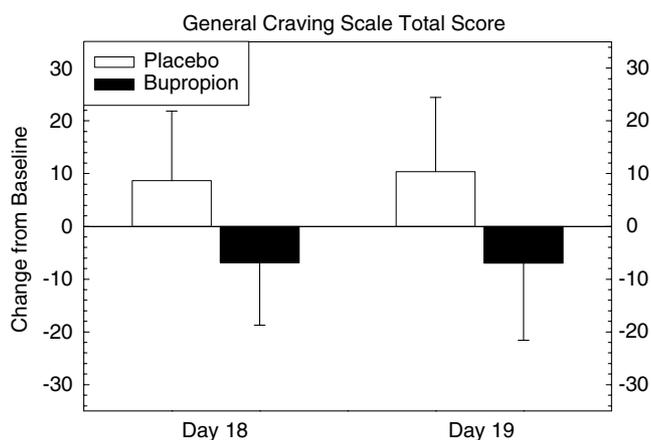


Figure 4 Effects of cue exposure on craving (mean \pm SEM). Bupropion treatment (filled bars) significantly reduced cue-induced changes in craving, as compared to effects observed in patients treated with placebo (open bars).

increase ARCI ratings, suggesting that bupropion treatment did not increase the abuse liability of methamphetamine. Instead, bupropion treatment reduced 'any drug' and 'high' ratings, suggesting that bupropion may reduce the abuse liability of methamphetamine. Confirmatory studies utilizing self-administration approaches would be useful to expand upon these findings. The impact of bupropion treatment on methamphetamine use outside of the laboratory (where much larger doses are used) can only be assessed in an outpatient clinical trial.

Bupropion treatment was associated with reduced cue-induced craving. The GCS was modeled on craving scales developed for craving for cocaine and smoking urges (Merikle, 1999; Tiffany and Drobes, 1991; Tiffany *et al*, 1993). Thus, the GCS captures more dimensions of craving than do visual analogue scales (Tiffany *et al*, 1993). In drug

discrimination tests in pigeons and rats, bupropion substitutes for methamphetamine (Johanson and Barrett, 1993; Munzar and Goldberg, 2000; Sasaki *et al*, 1995). In addition, bupropion is self-administered intravenously (i.v.) by squirrel monkeys and baboons (Bergman *et al*, 1989; Lamb and Griffiths, 1990), indicating that i.v. bupropion produces reinforcing effects in non-human primates similar to that produced by commonly abused stimulants (cocaine, methamphetamine). Differences between the drugs emerge when bupropion and methamphetamine are administered together. Bupropion pretreatment antagonizes methamphetamine-induced stereotypy, but when administered following methamphetamine, bupropion treatment augments methamphetamine-induced stereotypy (Muley *et al*, 1984).

These disparate results can be explained by the known effects of bupropion on the DA transporter (DAT). In an *in vitro* model consisting of immortalized cells transfected with the human DAT, bupropion dose dependently inhibited DA reuptake (Eshleman *et al*, 1994). On the other hand, bupropion pretreatment has been shown to protect against acute methamphetamine-induced decreases in DA uptake in striatal synaptosomes (Kim *et al*, 2000). Similar effects have been reported *in vivo*, as bupropion pretreatment reduced the neurotoxic effects produced by a single large dose (100 mg/kg, s.c.) of methamphetamine in rats (Marek *et al*, 1990). These effects appear to be due to the ability of bupropion to inhibit the inward transport of methamphetamine, thus limiting the ability of methamphetamine to displace DA from vesicular stores. In a recent report (Rau *et al*, 2005), bupropion rapidly, reversibly, and dose dependently increased vesicular DA uptake, an effect associated with vesicular monoamine transporter-2 protein redistribution. Of interest, the bupropion-induced increases in vesicular DA uptake were prevented by pretreatment with eticlopride, a DA D₂ receptor antagonist, but not by SCH 23390, a DA D₁ receptor antagonist.

When administered alone, bupropion increases synaptic DA by inhibiting reuptake. When administered with methamphetamine, bupropion may reduce synaptic DA by reducing the ability of methamphetamine to induce DA release. Bupropion has been reported to produce agonist-like effects in acutely abstinent smokers (Shiffman *et al*, 2000). As such, reduced ratings on subjective effects measures in this study may have been the result of the ability of bupropion to inhibit methamphetamine-induced DA release.

Despite this information, DA may not be the sole neurotransmitter system mediating the effects produced by bupropion. For example, bupropion does not inhibit prolactin, which would be expected if it significantly increases central DA (Whiteman *et al*, 1983). Moreover, therapeutic doses of bupropion have been reported to produce just 25% occupancy of the DA transporter (Learned-Coughlin *et al*, 2003), which may be inadequate to account for alterations to methamphetamine-induced DA release (Dworkin *et al*, 1998). Finally, other data suggest that stimulants (including methamphetamine) release norepinephrine (NE) more potently than DA (Rothman *et al*, 2001), and this neurotransmitter system may be responsible for some of the subjective effects reported in the current study.

We also found that bupropion blocked cue-induced craving. Similar results were reported in smokers, as bupropion treatment was associated with reduced cigarette cue-induced craving (Brody *et al*, 2004). The observed effects may have been the result of inhibition of NE reuptake, resulting in increased extracellular NE, which in turn reduced NE cell firing (Dong and Blier, 2001). Reduced NE output would, in turn, produce reduced cue reactivity and associated changes in cerebral metabolic activity.

The findings in this report are subject to a range of limitations. While bupropion pretreatment reliably reduced some of the subjective effects produced by methamphetamine, the doses of methamphetamine used were small. Methamphetamine-addicted individuals typically use much greater amounts, and may be prone to overcome modest reductions produced by a given medication (eg bupropion). In fact, preclinical models of self-administration demonstrate that reductions in subjective or reinforcing effects are generally accompanied by an increase in the amount of drug administered. Of interest, group differences were not noted between the 15 and 30 mg doses of methamphetamine. A careful analysis of individual responses revealed that this was likely the result of the considerable variability between subjects. Specifically, some patients exhibited moderate to robust responses to methamphetamine exposure, while others show little or no response. When considering only the group means, the impression is that the doses produced equivalent effects (which underestimates the individual responses to the drug). An additional limitation of the current study is the use of low doses of methamphetamine and an equally low dose of bupropion. The doses selected were chosen on the basis of safety information showing that higher doses of bupropion are associated with onset of seizures (Pesola and Avsarala, 2002). In addition, the Physicians Desk Reference website (www.pdr.net) specifies, 'Zyban is contraindicated in patients with a seizure disorder, Zyban is contraindicated in patients treated with

Wellbutrin, Wellbutrin SR, Wellbutrin XL, or any other medications that contain bupropion because the incidence of seizure is dose dependent, and Zyban is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion'. Moreover, the PDR site specifies caution for the interactions of bupropion with stimulants. Specifically, 'Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin'. A final limitation worth noting is the short exposure regimen and small sample size, signaling the need to replicate and extend these findings in a larger cohort (ie in a Phase II clinical trial).

The finding that bupropion reduced cue-induced craving for methamphetamine is especially compelling, although in the absence of other measures of drug seeking behavior (such as self-administration) it is difficult to infer the consequences of reduced craving. Furthermore, based on research with cue exposure in cocaine users (Robbins *et al*, 1997), it is likely that not all methamphetamine users respond to cues with increased craving. Further research in more homogenous populations may facilitate identification of subgroups that would best respond to treatments that alter cue responsiveness.

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