Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence

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Abstract

Objective—To compare bupropion to placebo for reducing methamphetamine (MA) use, increasing retention, and reducing the severity of depressive symptoms and MA cravings. A secondary objective compared bupropion to placebo for reducing cigarette smoking among MA dependent participants.

Methods—Following a 2-week, non-medication baseline screening period, 73 treatment-seeking MA dependent participants were randomly assigned to bupropion sustained release (150 mg twice daily; N=36) or placebo (twice daily; N=37) for 12-weeks under double blind conditions. Participants attended clinic thrice weekly to provide urine samples analyzed for MA-metabolite, to complete research measures and assessments, and to receive contingency management and weekly cognitive behavioral therapy sessions.

Results—There were no statistically significant effects for bupropion relative to placebo on MA use verified by urine drug screens, for reducing the severity of depressive symptoms or MA cravings, or on study retention. In a *post hoc* analysis, there was a statistically significant effect of bupropion treatment on MA use among participants with lighter (0–2 MA-positive urines), but not heavier (3–6 MA-positive urines) MA use during baseline (OR=2.81, 95% CI=1.61–4.93, p<0.001 for MA-free week with bupropion among light users). Bupropion treatment was also associated with significantly reduced cigarette smoking, by almost 5 cigarettes per day (p=0.0002).

Conclusion—Bupropion was no more effective than placebo in reducing MA use in planned analyses, though bupropion did reduce cigarette smoking. *Post hoc* findings of an effect for bupropion among baseline light, but not heavy, MA users suggests further evaluation of bupropion for light MA users is warranted.

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1. Introduction

Methamphetamine (MA) is a psycho-stimulant drug whose addictive characteristics, combined with its longer lasting stimulant effects and a cheaper street price than cocaine (Newton et al., 2005), have led to a surge in its abuse within the United States (US). Once only confined to western and rural areas, MA is becoming increasingly available in most US metropolitan areas (National Drug Intelligence Center, 2006). According to The National Household Survey on Drug Abuse, increased availability of MA has more than doubled the number of individuals who have tried MA in their lifetime from 3.8 million in 1994 to 11.7 million in 2004 (Substance Abuse and Mental Health Service Administration, 2005).

Widespread use of MA has led to numerous health care concerns. MA-related emergency room visits increased 54% in the US between 1995 and 2002 (Drug Abuse Warning Network, 2002). The immediate somatic effects of MA intake include increased blood pressure and heart rate (Newton et al., 2005), raising the risk for fatal cardiac rhythm disturbances and cerebral hemorrhaging (Mokhlesi et al., 2004) as well as acute coronary syndrome and myocardial infarction (Chen, 2007; Turnipseed et al., 2003; Wijetunga et al., 2004). Moreover, MA using populations are at high risk of infection with Hepatitis C virus (Gonzales et al., 2006) and HIV (Peck et al., 2005; Shoptaw et al., 2003) and frequently develop severe dental decay and multiple caries (Donaldson and Goodchild, 2006). MA users also have significant rates of co-morbid mood and anxiety disorders and are at significantly higher risk of developing a psychotic disorder than the general population and may continue to experience psychotic symptoms even years after stopping MA use (Zweben et al., 2004). Finally, although one-time MA use has been shown to improve performance on a variety of cognitive tasks (Silber et al., 2006), prolonged use causes numerous cognitive deficits, including decreased functioning of working memory, executive function, and reaction time (Kalechstein et al., 2003). These multiple health-related complications of MA abuse suggest that effective treatments for MA dependence are needed in order to minimize the negative public health effects of MA abuse.

Acute subjective and reinforcing effects of MA include feelings of euphoria, increased energy, and heightened sense of attentiveness (Hart et al., 2001; Newton et al., 2005; Newton et al., 2006). Withdrawal from MA is characterized by acute symptoms that have the opposite effect of the drug itself; depressive symptoms often including intense feelings of dysphoria (Logan, 2002), anxiety (Zweben et al., 2004), and fatigue (Newton et al., 2004). The acute subjective and reinforcing effects of MA are thought to result from MA-induced release of monoamines, including dopamine (DA) and norepinephrine (NE), via a variety of mechanisms. Like other stimulants, MA inhibits the reuptake of DA by the dopamine transporter (DAT) and causes reverse transport of DA into the synapse via DAT, producing increased extra cellular DA and enhanced stimulation of postsynaptic DA receptors (Khoshbouei et al., 2003). MA has also been shown to inhibit monoamine oxidase and to increase the expression of the DA synthesizing enzyme, tyrosine hydroxylase (Sulzer et al., 2005).

While the neurotoxic effects of MA on the dopaminergic system have yet to be fully understood, there is evidence that the withdrawal symptoms from MA use can be attributed to depletions in extra cellular DA concentrations. For example, studies have shown extensive reductions in the density and activity of DAT in the striatum in the days following

MA use (Chang et al., 2007). Imaging studies have also shown that hypoactivity in the striatum can be correlated with self-reports of depression and anxiety in recovering MA users (Thompson et al., 2004). In addition, cognitive dysfunction and decreased activity of DA receptors caused by prolonged MA use can contribute to poor impulse control and inability to maintain goal-related behavior (Monterosso et al., 2005). Conceptually, restoring levels of DA (by increasing DA release, preventing reuptake, or slowing degradation after release) to pre-dependence levels may help MA abusers to initiate and/or maintain abstinence, may alleviate withdrawal symptoms, and may prevent relapse (Vocci and Appel, 2007).

Bupropion is a DA and NE reuptake inhibitor of the aminoketone class that has been approved both as an antidepressant and as a smoking cessation drug. Bupropion has relatively few antidepressant-associated side effects, such as sexual dysfunction and sedation (Stahl et al., 2004), has a low abuse potential (Nomikos et al., 1989), and is not fatal when taken in large doses (Shepherd et al., 2004). While bupropion's precise mechanism of action is not known, bupropion binds to DAT and has been shown to increase DA transmission in both the nucleus accumbens and the prefrontal cortex (Rau et al., 2005). By restoring depleted levels of monoamines, bupropion may be effective in ameliorating withdrawal symptoms and cognitive deficits in patients recovering from MA abuse, thereby reducing MA use. A randomized, placebo-controlled trial of bupropion for cocaine dependence found a significant effect for bupropion relative to placebo in reducing cocaine use when provided with a contingency management intervention, but not with a non-contingent voucher program (Poling et al., 2006). Two other randomized placebo- controlled trials of bupropion plus cognitive behavioral therapy failed to find an effect for bupropion in cocaine dependence (Margolin et al., 1995; Shoptaw et al., 2008).

To date, no effective pharmacologic treatments for MA addiction have been identified, although results of a recent clinical trial provide preliminary evidence supporting the efficacy of bupropion for reducing MA use among participants with lighter (MA use on 18 or fewer of the past 30 days) but not heavier (MA use on more than 18 of the last 30 days) MA use at baseline (Elkashef et al., 2007). The aim of this study is to evaluate the efficacy of bupropion compared to placebo as a treatment for MA dependence in the presence of evidence-based behavioral therapies, including contingency management and cognitive behavioral therapy. We hypothesized that participants receiving bupropion would demonstrate statistically significant reductions in MA use over participants receiving placebo. We also expected to see greater treatment retention and larger reductions in depressive symptoms and cravings for MA among participants receiving bupropion compared to those receiving placebo. Because bupropion treatment has been shown to reduce cigarette smoking in other populations, we expected to see reductions in cigarette smoking as well.

2. Methods

2.1. Participants

Study participants were 73 MA dependent outpatients seeking treatment in the Los Angeles area. All participants met the following inclusion criteria: (1) 18 years of age or older, (2) current MA dependence verified by the Structured Clinical Interview for the DSM-IV-TR (SCID; (Spitzer et al., 1995), (3) willing and able to comply with study procedures, (4) willing and able to provide written informed consent and (5) if female and of childbearing potential, not pregnant or lactating, and willing to use an acceptable method of birth control.

Participants met none of the following exclusion criteria: (1) a medical condition that would interfere with safe study participation, such as active tuberculosis, unstable cardiac or liver

disease, unstable diabetes, uncontrolled hypertension, symptomatic AIDS diagnosis, or elevated liver enzymes greater than 3 times the upper limit of normal, (2) a current neurologic or major psychiatric disorder not due to substance abuse (e.g., schizophrenia, bipolar or major affective disorder) as assessed by the SCID, (3) current serious suicidal intention or plan, (4) taking a prescription medication that is known to interact with the study medication, (5) current dependence on cocaine, opiates, alcohol, or benzodiazepines, as assessed by the SCID, (6) a history of alcohol dependence within the past 3 years, (7) any history of seizures or a closed head injury, (8) a history of anorexia or bulimia, and (9) a history of sensitivity to bupropion.

2.2. Procedures

Study activities occurred at three clinical research sites in the Los Angeles area (Rancho Cucamonga, Hollywood, and UCLA). All study protocols were approved by two local IRBs (UCLA and Friends Research Institute, Inc.).

2.2.1. Recruitment—Potential study participants were recruited from the community using advertisements for a study of experimental medications for MA dependence. Interested individuals telephoned a toll-free number and if appropriate would schedule an intake visit with a study investigator to discuss the study risks and procedures and initiate the informed consent process.

2.2.2. Design—The study used a randomized, double-blind, placebo-controlled clinical trial design with an active medication condition (bupropion sustained release 150 mg twice daily) and a matching placebo and a psychosocial/behavioral platform of cognitive behavioral therapy (CBT) and contingency management (CM). After completing a two week baseline/screening period for eligibility assessment, including a complete physical exam with blood work and an EKG, eligible participants were randomly assigned to receive either bupropion or placebo, in conjunction with CBT and CM, for 12 weeks. Participants visited the study clinic three times per week (Monday, Wednesday, and Friday) to provide urine samples, to conduct medication exchanges and monitor participant safety, to complete study assessments, and to receive psychosocial/behavioral treatments. At termination, participants underwent a repeat physical examination, including blood work and an EKG, with the study physician, followed by a brief health visit at 30 days after terminating study participation. All study activities were provided free of charge. Other than non-cash vouchers earned as part of the CM intervention, participants were not compensated for participation but did receive $20 both for completing the baseline assessments and the study completion/ termination assessments.

2.2.3. Assessments—A battery of measures determined study eligibility, assessed participant safety and documented treatment efficacy. The SCID was used to identify past and current psychiatric and substance use diagnoses and to verify inclusion and exclusion criteria. The ASI-Lite (McLellan et al., 1992) was used to measure the severity of participants' reported addiction- related problems in seven areas of functioning: medical, employment, drug use, alcohol use, legal, family/social, and psychiatric. The Beck Depression Inventory (BDI), a 21-item questionnaire concerning symptoms of depression (Beck, 1967), was used to measure participants' depressive symptoms at baseline and weekly during the medication period. Participants' reports of MA craving over the past 24 hours was measured at baseline and weekly during the trial using a visual analogue scale that ranges from 0 (no craving) to 100 (most intense craving possible). The quantity of participants' self-reported alcohol and drug use, as well as average number of cigarettes smoked per day, were assessed at baseline and weekly during treatment using the Substance Use Inventory (Sobell et al., 1986).

Medication adherence was measured using weekly pill counts justified against reports of medication-taking to calculate the proportion of dispensed medication doses that were taken. Participants met with the study physician each week to receive a one-week supply of medication in blister packaging in exchange for the previous week's blister package with any unused medication and to complete the pill count. Urine samples were collected thrice weekly throughout the study period. All samples between 93–100° F at the time of collection were considered valid. Urine samples were analyzed immediately onsite using radioimmunoassay (Phamatech, Inc, San Diego, CA) for qualitative tests of MA metabolite.

2.2.4. Psychosocial counseling—All participants received a standard counseling program, consisting of weekly individual CBT sessions during the medication phase of the study. Counseling was delivered by a masters-level therapist who received training in the use of the 12-week CBT program and familiarity with its manualized format (Carroll, 1998). To maintain the integrity of the counseling program, counselors met once weekly with the principal investigator (S.S.) to receive corrective feedback and individual clinical supervision.

2.2.5. Contingency Management—To increase the likelihood of initiating abstinence from MA use, a contingency management (behavioral reinforcement) intervention was provided (Roll et al., 2006). Non-cash vouchers for goods and services promoting a healthy drug-free lifestyle were earned for MA metabolite-free urine samples, on an escalating schedule for the first 4 weeks after signing consent, then remaining at this level for the remaining 10 weeks prior to discontinuation. The voucher for the initial MA-free sample was worth $3.00. Vouchers increased in value by $1.00 for each consecutive MA-free sample to a maximum of $15.00 at the end of the 4th week and remained at $15.00 for the remainder of the 12 week treatment period. Participants who provided a sample positive for MA-metabolite, or who failed to submit a urine sample, did not receive a voucher for that visit and their subsequent voucher value was reduced to the initial $3.00, with a reset after three consecutive MA-free urine specimens. The behavioral technician provided supportive feedback for samples indicating abstinence and informed the subject of the value of the voucher earned that day and their total voucher balance. The maximum that could be earned for providing MA-metabolite free urine samples at all visits throughout the entire study was $537 in vouchers. Participants who terminated study participation early received vouchers reflecting what they earned to date.

2.2.6. Medication procedures—Bupropion sustained release (SR) 150mg tablets were purchased from the manufacturer (GlaxoSmithKline, Middlesex, UK) and over-encapsulated active medication tablets and matching placebo capsules were prepared by a compounding pharmacy (Inland Compounding Pharmacy, Loma Linda, CA). Doses of study medication were as follows: bupropion SR 150 mg per day for days 1–3 of the first week followed by an increase to 300 mg per day (one 150 mg capsule taken twice daily) until week 12 when the dose was decreased to 150 mg of bupropion SR for the last 3 days. Participants ingested the first dose of study medication under the supervision of the study physician and then were dispensed a 2 week supply of medication in blister packages and instructed in how to self-administer the medication at home. Participants were required to bring the experimental drug packets to the site each visit for pill counts to monitor drug adherence.

2.2.7. Safety—Participants underwent a medical history and physical examination, EKG, and routine laboratory studies during screening and at study termination. Participants' vital signs were measured weekly and study research assistants interviewed participants concerning any adverse events and the use of concomitant medications weekly at clinic visits. Participant suicidal intention was closely monitored using data from the BDI, verbal

reports, and during counseling sessions. Participants who showed any signs of suicidal behavior were evaluated by study staff trained to respond with the appropriate steps needed, including other treatment referrals and study discontinuation.

2.3. Data analysis

All analyses used an "intention-to-treat" approach. The primary study outcome was MA use as assessed via urine drug screens and secondary outcomes were treatment retention, depressive symptoms, MA cravings, and adverse events. The following aggregate measures of urine drug screen results were calculated: the Joint Probability Index at six and twelve weeks of treatment (the number of MA-metabolite free urine specimens submitted by participants in each treatment group at that time divided by the number of participants randomized to the treatment group) and the Treatment Effectiveness Score (the sum of the number of MA-free urine samples submitted per participant (Ling et al., 1997), the percentage of samples negative for MA overall, the longest consecutive period of MA abstinence, and the percentage of participants with at least 2 and at least 3 consecutive weeks of MA abstinence. Univariate comparisons of baseline demographic, drug use, and psychiatric characteristics of participants as well as comparisons of missing data rates, aggregate measures of urine drug screen results, medication adherence, and MA craving by treatment group assignment were performed using analysis of variance (ANOVA) for continuous variables and chi square for categorical variables (Tabachnick and Fidell, 2000). The proportion of participants who completed the trial, defined as at least one study visit during week 12 (the final week of the medication treatment period), in each treatment condition was compared using chi square analysis. Study retention was measured as the number of days from the first dose of study medication at the time of randomization to the participant's last study visit during the 12 week medication treatment period. Differences in retention by treatment condition were evaluated using a Kaplan–Meier survival function (Allison and SAS Institute, 1995).

Primary study hypotheses concerning the effect of bupropion versus placebo on treatment outcomes were tested using generalized estimating equation (GEE) models (Zeger and Liang, 1986). The effect of treatment condition on urine drug screen results was examined using a GEE logistic regression model with the dependent variable being a MA-free week, defined as all available urine specimens during the week are MA-metabolite free. A *post hoc* analysis compared treatment outcomes separately among baseline light MA users, defined as 0–2 of the 6 urine drug screens during the two week baseline/screening period positive for MA-metabolites, and baseline heavy MA users, defined as 3–6 of the 6 urine drug screens during the two week baseline/screening period positive for MA-metabolites. The post hoc analysis comparing potential effects of treatment on urine drug screen results in separate GEE models among baseline heavy versus light MA users was also repeated using self-reported past 30 days MA use to stratify the sample as heavy (MA use on >18 days) versus light (MA use on 18 days) MA users, as done previously by Elkashef et al. (2007). Effect of treatment condition on continuous measures such as the BDI and MA-craving VAS scale were evaluated using a mixed model approach (Singer, 1998). All analyses were run in SPSS 14.0 (SPSS Incorporated, 2005) and SAS for Windows 9.0 (SAS Institute Incorporated, 2004).

3. Results

A total of 191 treatment-seeking individuals provided informed consent and entered the 2-week screening period, of which 73 met all inclusion and no exclusion criteria and were randomized into the study (Figure 1). Thirty one percent of participants randomized to the bupropion condition completed the 12-week medication period, defined as at least one study visit during week 12, compared to 38% of participants randomized to placebo ($\chi^2 = 0.43$,

df=1, p=0.512). Reasons for termination prior to study completion in each group are shown in Figure 1. Study completion rates were significantly higher among baseline light MA users (51% versus 17% among baseline heavy MA users, χ^2= 9.75, df=1, p=0.002) and males (43% versus 19% among females, χ^2= 4.04, df=1, p=0.044), but there were no significant associations between study completion and age, ethnicity, or baseline lifetime MA use or route of MA administration (data not shown). In a *post hoc* analysis, there were no significant differences in the proportion of participants completing the trial by treatment condition among baseline light MA users (41% for bupropion versus 60% for placebo, χ^2= 1.30, df=1, p=0.254) or baseline heavy MA users (21% for bupropion versus 12% for placebo, χ^2= 0.56, df=1, p=0.455).

3.1. Baseline demographic, drug use, and psychiatric characteristics

The baseline characteristics of participants randomized to the bupropion and placebo conditions are shown in Table 1. Participants in the bupropion condition reported more days of cannabis use in the past 30 days than participants in the placebo group, otherwise there were no significant differences.

3.2 Missing data

There was no statistically significant difference between the mean proportion of missing urine drug screen specimens in the bupropion versus the placebo conditions (t= −0.45, df=71, p=0.65). On average, of the 36 possible urine samples during the 12 week treatment period, 52% were missing in the bupropion condition compared to 56% in the placebo condition.

3.3 Medication adherence

Pill count data were missing for 5 participants (2 in the bupropion condition and 3 in the placebo condition) who dropped out of the study prior to returning any medication blister packages for pill counts. Among the remaining participants with pill count data available, participants in the bupropion condition reported taking 85% of the pills dispensed to them compared to 92% in the placebo group, which was not a statistically significant difference (t=−1.41, df=49, p=0.16).

3.4 Retention

Survival analysis results showed that there were no statistically significant differences in retention between participants assigned to receive bupropion versus those assigned to receive placebo as tested via log rank (χ^2=0.34, df=1, p=0.56, Figure 2). Participants in the bupropion condition were retained in the study for a mean of 52.6 days (SD=28.1) compared to 50.7 days (SD=31.3) for participants in the placebo condition (t=0.28, df= 71, p=0.783). In a *post hoc* survival analysis, there were no statistically significant differences in retention between treatment groups among baseline heavy or baseline light MA users (χ^2=3.18, df=1, p=0.07 for heavy users and χ^2=0.05, df=1, p=0.83 for light users, plots not shown).

3.5 Urine drug screen results

There were no statistically significant differences between participants receiving bupropion and those receiving placebo in planned univariate analyses of aggregate urine drug screen results (Table 2, Full Sample). The proportion of participants with a MA-free week throughout the trial in the bupropion condition was similar to that in the placebo condition (Figure 3, panel a) and there was no significant difference between treatment conditions in the probability of achieving a MA-free week in a GEE model (χ^2=0.004, df=71, p=0.95). In a *post hoc* analysis, there were no significant differences between bupropion and placebo in aggregate urine measures with the sample stratified by baseline heavy- MA use, defined as

3–6 urine drug screens positive for MA-metabolites during the two week baseline period positive (N=36; Table 2, Heavy MA Users) versus light-MA use, defined as 0–2 MA-positive urine drug screens during the two week baseline period (N=37; Table 2, Light MA Users). There was a statistically significant effect for bupropion relative to placebo in a GEE model adjusting for gender and ethnicity with the sample stratified by baseline light versus heavy MA users. Among baseline light MA users, the probability of achieving a MA-free week was significantly higher in the bupropion condition relative to the placebo condition (OR=2.81, 95% CI=1.61–4.93, p<0.001; Figure 3, panel b), while there was no significant difference between conditions among baseline heavy MA users (OR=0.93, 95% CI=0.24–3.53, p=0.91 for bupropion relative to placebo; Figure 3, panel c). In an additional *post hoc* analysis replicating the analysis of Elkashef et al. (2007), there was no statistically significant effect for bupropion relative to placebo in separate GEE models among participants with baseline heavy MA use (MA use on >18 of the last 30 days) or baseline light MA use (MA use on 18 of the last 30 days), although the effect for bupropion on a MA-free week among light users was in the predicted direction (OR=1.26, 95%CI 0.77–2.09, p=0.36). The heavy/light user variables defined via baseline urine sample results and baseline self-reported MA use were significantly correlated using Pearson's correlation coefficient (r =0.562, p=0.01).

3.6 Depressive symptoms

Depressive symptoms, as measured via the BDI, decreased among participants in both conditions during the treatment period (Table 2, Full Sample). But there was no statistically significant difference in BDI scores during the treatment period between participants in the two treatment conditions in a mixed effects model (t=0.22, df=71, p=0.82). In a *post hoc* analysis, BDI scores decreased during the treatment period among both heavy and light MA users (Table 2), but there were no statistically significant differences in BDI scores between the two treatment conditions in mixed effects models among heavy (t= −0.86, df=1, p=0.40) or light (t=1.01, df=1, p=0.32) MA users.

3.7 MA craving

Cravings for MA, as measured on a 0 to 100 visual analog scale, decreased among participants in both conditions during the treatment period (Table 2). But there was no statistically significant difference in MA cravings between participants in the two treatment conditions throughout the trial in a mixed effects model (t=0.38, df=71, p=0.70). In a *post hoc* analysis, MA cravings decreased during the treatment period among both heavy and light MA users (Table 2), but there were no statistically significant differences in MA cravings between the two treatment conditions in mixed effects models among heavy (t=0.67, df=1, p=0.51) or light (t= −0.16, df=1, p=0.88) MA users.

3.8 Results of Psychosocial and Behavioral Interventions

Participants in the bupropion condition attended an average of 5 of the 12 weekly CBT counseling sessions (SD=3.8) compared to an average of 4 sessions (SD=3.7) for the placebo condition, which is a non-significant difference (t=0.17, df=71, p=0.87). Out of a total possible $537 in vouchers that could be earned contingent on providing MA-metabolite free urine specimens throughout the trial, participants receiving bupropion earned on average $134 (SD=$175) in vouchers, compared to $110 (SD=$153) among participants in the placebo group, which was not a statistically significant difference (t=0.66, df=71, p=0.51).

3.9 Cigarette smoking

Analyses of cigarette smoking were limited to participants who reported cigarette smoking during the trial (48 (65.8%) of the 73 participants randomized). There were no statistically significant differences in the mean number of cigarettes smoked per day between cigarette smokers in the two treatment conditions at baseline. In a mixed effects model, the reduction in the number of cigarettes smoked per day during the trial was significantly greater in the bupropion condition compared to the placebo condition, with participants in the bupropion condition smoking on average almost 5 fewer cigarettes per day compared to participants in the placebo condition (estimate= −4.85, t=−3.26, df=46, p=0.002 for bupropion relative to placebo).

3.10 Adverse events

Three serious adverse events requiring hospitalization occurred during the trial; none were determined to be treatment related. Two HIV positive participants in the bupropion condition were hospitalized for infections (perirectal abscess and cellulitis), which resolved without sequelae allowing them to continue to participate. One participant in the placebo condition was hospitalized for depressive symptoms and suicidal ideation in the setting of continued MA use and was discontinued from study participation and referred to a higher level of care. Experimental medication was also discontinued in one participant in the bupropion condition who developed chest pain requiring treatment in the emergency room but not hospitalization and one participant in the placebo group who became pregnant. The most commonly reported adverse events were headache and nasal congestion/upper respiratory infection symptoms, which occurred in similar rates in the two treatment conditions (Table 3).

4. Discussion

In this randomized, double-blind, placebo-controlled trial of bupropion for the treatment of MA dependence, there were no significant effects for bupropion relative to placebo in planned analyses of MA use, retention, depressive symptoms, and MA-cravings. In a *post hoc* analysis, bupropion reduced MA use significantly more than placebo among participants with light- but not heavy-MA use as defined by the frequency of MA positive urine drug screens during the baseline period. These findings are consistent with those of a previous trial that found bupropion to be more effective in reducing MA use among male participants with low-to-moderate self-reported MA use at baseline (Elkashef et al., 2007), although we were unable to directly replicate the previous study's findings due to the small sample size in our study. Bupropion also significantly reduced *ad libitum* cigarette smoking relative to placebo despite the lack of any psychosocial/behavioral treatment targeting cigarette smoking cessation, which is consistent with bupropion's efficacy for smoking cessation (Hughes et al., 2007) and suggests that the failure to detect a main effect for bupropion on MA use was not due to problems with internal validity. Together, results of the two trials of bupropion for MA dependence suggest that larger studies to determine the effectiveness of bupropion in reducing MA use among baseline light-MA users are warranted.

Chronic high-dose MA use produces neurotoxic effects that may be responsible for bupropion's lack of efficacy among heavy- MA users. In preclinical studies, high-dose MA produces neurotoxic changes in striatal dopaminergic cells as well as deficits in striatal tyrosine hydroxylase activity, DA concentrations, and DAT levels (Davidson et al., 2001; Harvey et al., 2000; Robinson et al., 1990; Sabol et al., 2001; Wagner et al., 1980). Clinical imaging studies have also found significant deficits in dopaminergic function among chronic MA users, including reductions in DAT density (Volkow et al., 2001b) and DA receptor occupancy (Volkow et al., 2001a; Volkow et al., 2001c), which are thought to contribute to

the dysphoric symptoms that accompany MA dependence and withdrawal. Chronic high-dose MA exposure is thought to produce these neurotoxic effects by impairing the ability of synaptic vesicles to take up DA via disruption of the vesicular proton gradient necessary for VMAT-2 functioning (Sulzer et al., 1995; Sulzer and Rayport, 1990), resulting in accumulation of cytoplasmic DA and the subsequent production of harmful reactive oxygen species (Cubells et al., 1994; Fleckenstein et al., 1997). DA reuptake blockers such as bupropion increase vesicular dopamine uptake via enhancement of VMAT-2 function (Brown et al., 2001; Rau et al., 2005) suggesting that treatment with bupropion may counteract the MA-induced accumulation of cytosolic DA and reactive oxygen species thereby reducing the neurotoxic effects of MA. Yet, while preclinical studies have shown that treatment with the reuptake blockers methylphenidate and bupropion reversed MA-induced reductions in VMAT-2 activity, bupropion did not prevent the long-term deficits in dopaminergic function produced by repeated high-dose MA administration (Rau et al., 2005; Sandoval et al., 2003), which may explain the lack of clinical effect for bupropion among heavy-MA users. Alternatively, bupropion's relatively weak effect in blocking DA reuptake (Argyelan et al., 2005; Meyer et al., 2002) may simply be overwhelmed by chronic high-dose MA use.

While this trial did not address cigarette smoking directly, bupropion significantly reduced self-reported cigarette smoking as compared to placebo among MA dependent cigarette smokers in a pre-planned analysis of a secondary outcome. Interestingly, the previous study of bupropion for MA dependence failed to find an effect for bupropion on cigarette smoking relative to placebo (Elkashef et al., 2007), and the reason for this discrepancy between the two studies is not clear. Considering that the prevalence of cigarette smoking among illicit drug users, including MA users, is as high as 70%–90% (Budney et al., 1993; Grant et al., 2004; Kalman et al., 2005; Richter et al., 2002) and that cigarette smoking is associated with poor health outcomes among illicit drug users, above and beyond those found in non-smoking drug users (Hser et al., 1994; Hurt et al., 1996), the identification of smoking cessation treatments effective in MA users is an important public health priority. Our results provide preliminary support for bupropion as a smoking cessation medication among MA users and provide evidence for continued evaluation of bupropion as a medication for co-morbid stimulant abusers who smoke cigarettes.

In contrast to our findings with cigarette smoking, there were no significant effects for bupropion over placebo in reducing depressive symptoms or MA-cravings common to MA-withdrawal despite bupropion's efficacy as an antidepressant (Hansen et al., 2005). This may imply the putative mechanism of action for bupropion as a medication for MA dependence is likely to be independent of reductions in withdrawal symptoms shared by both MA- and nicotine withdrawal, including depressive symptoms, irritability, and difficulty concentrating (Shiffman et al., 2000). Studies suggest that antidepressant treatment is effective among substance abusers for depressive symptoms that persist despite abstinence or in patients with a history of depressive symptoms that pre-date substance use, as compared to transient depressive symptoms related to substance use or withdrawal (Nunes and Levin, 2004). The lack of an effect for bupropion relative to placebo on depressive symptoms may be due to exclusion of participants with non-substance use-related depressive symptoms or to reductions in depressive symptoms in the placebo group as a result of the cognitive behavioral therapy platform.

Findings from this study are limited by the relatively small sample size of this preliminary clinical trial of bupropion for MA dependence and the attrition of participants during the trial, which limit the study's power. But the failure to find a significant effect for bupropion relative to placebo in any of the pre-planned analyses of treatment outcomes suggests that the negative result is likely not due to inadequate power. An additional limitation is that the

finding of an effect for bupropion among light-MA users was in a *post hoc* analysis, although our *post hoc* findings are similar to those of a previous study that included pre-planned analyses among participants with baseline heavy versus light MA use (Elkashef et al., 2007). There is a strong, but incomplete association between using results of baseline urine drug screens to define heavy/light MA users (0–2 urine samples positive for MA-metabolite versus 3–6 positive samples) and Elkashef et al. who used self-reported past 30 day MA use to define heavy/light users (18 days MA use versus >18 days MA use). Coupled with the small sample size and lowered power in the present trial, the differing definitions likely explain the similar, but not identical findings for baseline MA use levels and response to bupropion.

In conclusion, bupropion was no more effective than placebo in reducing MA use in planned analyses of this randomized, double-blind clinical trial, though the medication did reduce cigarette smoking. Bupropion did reduce MA use more than placebo among baseline light-MA users in a *post hoc* analysis. Further evaluation of bupropion as a treatment for MA dependence among light-MA users is warranted.

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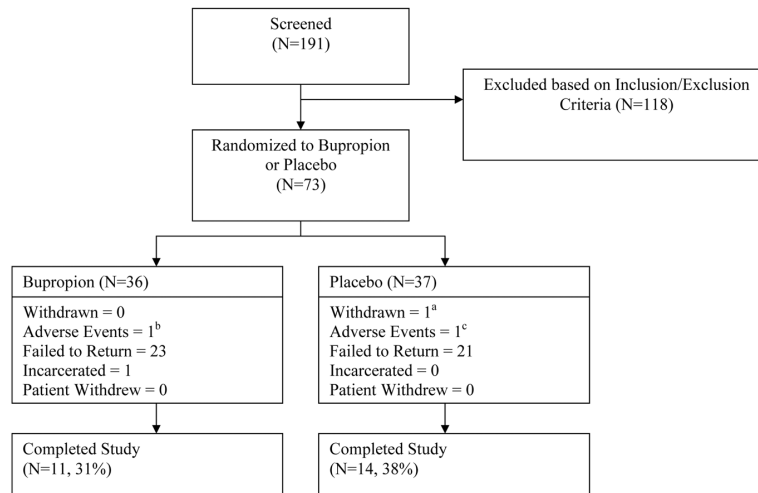
Figure 1.
Study design flow chart. [a]withdrawal due to participant becoming pregnant during medication phase; [b]medication discontinued after participant developed chest pain; [c] treatment discontinued and participant referred to higher level of care after hospitalized for suicidality
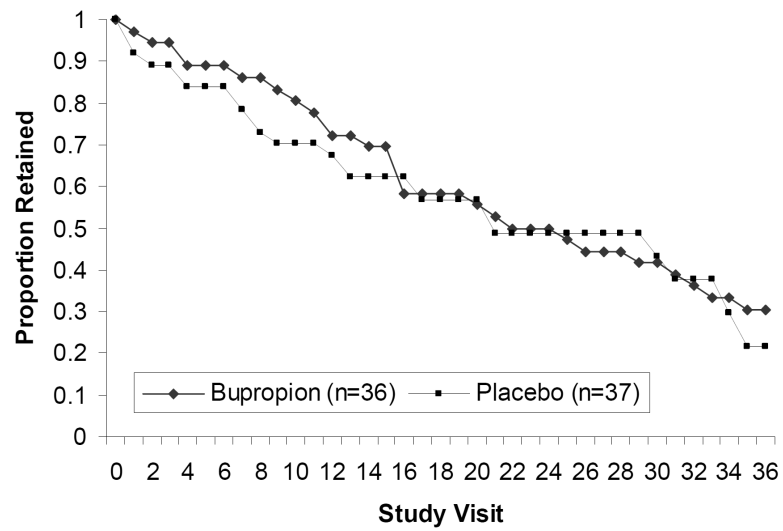
Figure 2.
Survival analysis depicting the proportion of participants retained in each treatment condition (bupropion and placebo) throughout the 36 study visits (12 weeks).
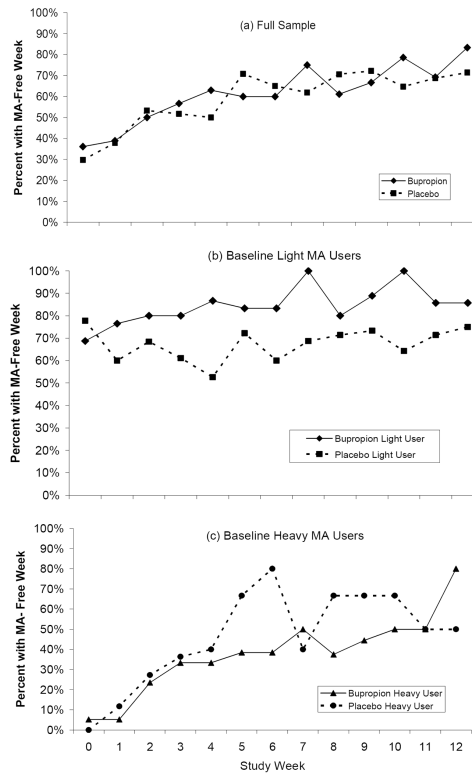
Figure 3.
Percentage of participants with a methamphetamine (MA)- free week by treatment condition for (a) the full sample and among baseline (b) light-MA users (0–2 MA positive urines during the baseline period) and (c) heavy- MA users (3–6 MA positive urines during the baseline period).

Table 1

Participant baseline demographic, drug use, and psychiatric characteristics by treatment condition (bupropion or placebo)

Measures	Condition	
	Bupropion (n=36) mean (sd) or %	Placebo (n=37) mean (sd) or %
Age (in years)	34.6 (10.6)	34.6 (10)
Ethnicity		
White	55.6%	56.8%
Hispanic	38.9%	35.1%
Black	2.8%	2.7%
Asian	0%	2.7%
Other	2.8%	2.7%
Gender		
Male	61.1%	67.6%
Female	38.9%	32.4%
Martial Status		
Married	25.0%	32.4%
Never married	47.2%	45.9%
Divorced/separated	27.8%	21.6%
Education (in years)	13.1 (2.1)	12.8 (2.3)
Employment		
Full time	50.0%	62.2%
Part time	25.0%	18.9%
Unemployed	19.4%	18.9%
Student/retired/military	5.6%	0.0%
Income in past 30 days (US$)	6,181 (13,565)	2,092 (2,197)
Days MA use (in past 30 days)	15.1 (10.4)	16.2 (10.8)
Years MA use	11 (9.6)	8.3 (5.8)
Route of MA administration		
Smoking	58.3%	70.3%
Nasal	25.0%	18.9%
Injection	13.9%	10.8%
Oral	2.8%	0%
Days cocaine use (in past 30 days)	0.1 (0.4)	0.1 (0.4)
Days cannabis use (in past 30 days) [*]	8.8 (11.1)	2.4 (4.7)
Days alcohol use (in past 30 days)	4.4 (6.5)	3.6 (5.5)
Current cigarette smoker	81%	51%
Baseline ASI composite scores		
Medical	0.18 (0.24)	0.22 (0.29)
Employment	0.38 (0.34)	0.37 (0.31)
Alcohol	0.10 (0.18)	0.06 (0.09)
Drug	0.21 (0.10)	0.20 (0.11)

Measures	Condition	
	Bupropion (n=36) mean (sd) or %	**Placebo (n=37) mean (sd) or %**
Legal	0.19 (0.20)	0.14 (0.22)
Family/social	0.24 (0.23)	0.20 (0.27)
Psychiatric	0.15 (0.18)	0.19 (0.21)
Beck Depression Inventory score	17.3 (10.3)	16.8 (11.3)

*
t=3.21, df=71, p=0.002

Table 2

Aggregate measures of urine drug screen results, depressive symptoms (BDI score), and methamphetamine (MA) cravings (visual analog scale) by treatment condition in the full sample and among baseline heavy (3 or more MA-positive urine drug screens during lead-in) and light (0–2 MA-positive urine drug screens during lead-in) MA users

	Full Sample		Heavy MA Users		Light MA Users	
	Bupropion (N=36)	Placebo (N=37)	Bupropion (N=19)	Placebo (N=17)	Bupropion (N=17)	Placebo (N=20)
Urine Aggregates						
Joint Probability Index[a]						
Treatment Week 6	0.33	0.22	0.21	0.12	0.47	0.30
Treatment Week 12	0.25	0.16	0.16	0.06	0.35	0.25
Treatment Effectiveness Score[b]	12.5	11.3	7.2	4.0	18.5	17.6
MA-negative urine samples, mean, %	35%	31%	20%	11%	51%	49%
Longest MA abstinence, mean, days	18	16	10	5	27	25
Two consecutive weeks of MA abstinence, %	39%	38%	16%	18%	65%	55%
Three consecutive weeks of MA abstinence, %	28%	27%	16%	6%	41%	45%
BDI Scores, mean						
Baseline	17.5	16.8	18.5	19.9	16.3	14.3
Treatment Week 12	4.2	3.5	3.8	5.7	4.4	2.9
MA craving, mean, visual analog scale						
Baseline	53.1	45.9	66.8	60.6	37.6	33.5
Treatment Week 12	22.5	27.1	22	33.3	22.9	25.5

[a] The number of MA-free urine specimens submitted at the final visit in the week divided by the number of participants randomized to the treatment condition.

[b] The average of the sum of MA-free urine specimens provided during the treatment period by participants in each treatment condition.

Table 3

Frequency of adverse events reported by treatment condition (bupropion, N=36 and placebo, N=37)

	Bupropion	Placebo	Total
Headache	14	14	28
Nasal congestion/URI	4	10	14
Musculoskeletal pain	6	7	13
Insomnia	5	6	11
Dizziness/Lightheaded	4	1	5
Injury	2	3	5
Chest Pain	2	1	3
Dysphoria	1	2	3
Ear pain	3	0	3
Flu Symptoms	1	2	3
Toothache	2	1	3
Diarrhea	1	1	2
Fever	0	2	2
Heart palpitations	1	1	2
Nausea/vomiting	2	0	2
Rash/itching	2	0	2
Stomach pain	1	1	2
Blurry vision	0	1	1
Cellulitis	1	0	1
Dental pain	1	0	1
Dry mouth	0	1	1
Eye infection	0	1	1
Grogginess	0	1	1
Hepatitis	1	0	1
Menstrual pain	0	1	1
Nausea/vomiting	1	0	1
Nausea/vomiting	1	0	1
Nosebleed	1	0	1
Perirectal abscess	1	0	1
Polyuria	0	1	1
Pregnancy	0	1	1
Total	58	59	117