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Bupropion for the Treatment of Methamphetamine Dependence

Ahmed M Elkashef*[,1], Richard A Rawson[2], Ann L Anderson[1], Shou-Hua Li[1], Tyson Holmes[3], Edwina V Smith[1], Nora Chiang[1], Roberta Kahn[1], Frank Vocci[1], Walter Ling[2], Valerie J Pearce[2], Michael McCann[4], Jan Campbell[5], Charles Gorodetzky[6], William Haning[7], Barry Carlton[7], Joseph Mawhinney[8] and Dennis Weis[9]

[1]Clinical Medical Branch, Division of Pharmacotherapies and Medical Consequences, National Institutes of Health, National Institute on Drug Abuse, Bethesda, MD, USA; [2]Department of Psychiatry, Integrated Substance Abuse Programs, University of California, Los Angeles, Los Angeles, CA, USA; [3]Division of Biostatistics, Department of Health Research and Policy, School of Medicine, Stanford University, Stanford, CA, USA; [4]Department of Psychiatry, Matrix Institute on Addictions, Costa Mesa, CA, USA; [5]Department of Psychiatry, University of Missouri, Kansas City, MO, USA; [6]Department of Psychiatry, Quintiles Inc., Kansas City, MO, USA; [7]John A. Burns School of Medicine, Department of Psychiatry, University of Hawaii, Honolulu, HI, USA; [8]South Bay Treatment Center, San Diego, CA, USA; [9]Department of Addiction Medicine, Lutheran Hospital, Powell Addiction Research Center, Des Moines, IA, USA

Bupropion was tested for efficacy in increasing weeks of abstinence in methamphetamine-dependent patients, compared to placebo. This was a double-blind placebo-controlled study, with 12 weeks of treatment and a 30-day follow-up. Five outpatient substance abuse treatment clinics located west of the Mississippi participated in the study. One hundred and fifty-one treatment-seekers with DSM-IV diagnosis of methamphetamine dependence were consented and enrolled. Seventy-two participants were randomized to placebo and 79 to sustained-release bupropion 150 mg twice daily. Patients were asked to come to the clinic three times per week for assessments, urine drug screens, and 90-min group psychotherapy. The primary outcome was the change in proportion of participants having a methamphetamine-free week. Secondary outcomes included: urine for quantitative methamphetamine, self-report of methamphetamine use, subgroup analyses of balancing factors and comorbid conditions, addiction severity, craving, risk behaviors for HIV, and use of other substances. The generalized estimating equation regression analysis showed that, overall, the difference between bupropion and placebo groups in the probability of a non-use week over the 12-week treatment period was not statistically significant ($p = 0.09$). Mixed model regression was used to allow adjustment for baseline factors in addition to those measured (site, gender, level of baseline use, and level of symptoms of depression). This subgroup analysis showed that bupropion had a significant effect compared to placebo, among male patients who had a lower level of methamphetamine use at baseline ($p < 0.0001$). Comorbid depression and attention-deficit/hyperactivity disorder did not change the outcome. These data suggest that bupropion, in combination with behavioral group therapy, was effective for increasing the number of weeks of abstinence in participants with low-to-moderate methamphetamine dependence, mainly male patients, regardless of their comorbid condition.
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INTRODUCTION

Methamphetamine dependence is a major public health problem, with serious medical, social, and economic consequences. Methamphetamine abuse indicators continue to be high in the United States and globally (CEWG, 2005; UNODC, 2005). The need to find effective medication treatment is urgent, as currently there is no Food and Drug Administration (FDA)-approved pharmacological treatment for stimulant dependence. Psychotherapeutic interventions remain the mainstay of treatment, with some proven efficacy; however, relapse rates remain high (Rawson *et al*, 2004).

The rationale for testing bupropion for methamphetamine dependence is based on several lines of preclinical and clinical data. Bupropion is approved for the treatment of depression and nicotine dependence, with a monoamine uptake inhibition effect (GlaxoSmithKline, 2004; Richmond and Zwar, 2003). Similar to stimulants such as cocaine, it

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*Correspondence: Dr AM Elkashef, NIH, Medications Development Division, National Institute on Drug Abuse, DPMC, Neuroscience Bldg, 6001 Executive Blvd., Rm-4151, Bethesda, MD, USA, Tel: +1 301 443 5055, Fax: +1 301 443 2599, E-mail: ae8a@nih.gov
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can occupy the dopamine (DA) transporter to inhibit reuptake and increase DA concentration in the synaptic cleft (Stahl *et al*, 2004). It has been shown to be effective in improving symptoms of attention-deficit/hyperactivity disorder (ADHD) in adults (Wilens *et al*, 2005). These effects may help alleviate some of the symptoms of withdrawal from methamphetamine, which mimic some vegetative symptoms of depression (Newton *et al*, 2004), and could help reduce methamphetamine dependence in participants who have comorbid depression or ADHD. In a clinical trial of bupropion for cocaine dependence (Margolin *et al*, 1995), an exploratory analysis suggested participants with greater levels of depression might have benefited the most.

On a molecular level, chronic methamphetamine use has been shown to result in low dopaminergic tone, as evidenced by reduced striatal DA availability and decreased DA receptor binding (Volkow *et al*, 2001; Wilson *et al*, 1996). Bupropion's ability to block the DA transporter (Meyer *et al*, 2002) may help restore dopaminergic homeostasis by increasing intrasynaptic DA. Bupropion pretreatment has been shown to protect against acute methamphetamine-induced decreases in DA uptake in striatal synaptosomes (Kim *et al*, 2000), and *in vivo*, to reduce the neurotoxic effects produced in rats by a single large dose (100 mg/kg, s.c.) of methamphetamine (Marek *et al*, 1990).

Before conducting this outpatient trial, we conducted a phase I safety study of the interactions between bupropion and methamphetamine (Newton *et al*, 2005). That study showed bupropion did not exacerbate the cardiovascular or behavioral effects induced by methamphetamine. Furthermore, bupropion significantly attenuated some of the subjective effects of methamphetamine, including the 'high' on visual analogue scale, and the craving for methamphetamine that was elicited by video cues (Newton *et al*, 2006). Based on the clinical data from the cocaine study and the phase I study, we expected bupropion to be efficacious in the depressed subgroup, and/or to reduce craving. Since baseline use is the variable most predictive of outcome (Reiber *et al*, 2002), we also expected bupropion to be efficacious in the subgroup with lower methamphetamine use.

METHODS

Study Design

This was a double-blind, placebo-controlled, two-arm study with parallel groups. After screening and a 2-week baseline period, participants were randomly assigned to treatment with either placebo or bupropion for 12 weeks, with a final follow-up assessment at 4 weeks after completion of treatment. Adaptive 'urn' randomization was used to balance treatment groups within sites (Wei and Lachin, 1988) on factors of gender, baseline severity of depression symptoms (Hamilton Depression Scale (HAM-D) score $\leqslant 12$ *vs* >12), and self-report of methamphetamine use at baseline, determined by timeline follow-back ($\leqslant 18$ days in the last 30, *vs* >18 days). 'Urn' is a method of randomization used to balance a relatively large number of prognostic factors, when the sample size is not large enough to stratify on all of them. After each participant satisfies eligibility criteria and has a baseline assessment on the chosen balancing factors, the factor that is most unbalanced at that point in the trial is used to adjust the probability for that treatment assignment (Stout *et al*, 1994).

The study was reviewed and approved by Investigational Review Boards at the five sites, and by a central Data and Safety Monitoring Board.

Participants

A total of 151 treatment-seeking participants aged 18–65 years, who gave informed consent, met DSM-IV criteria for methamphetamine dependence and were randomized, then took the first dose of study medication (Figure 1). Exclusion criteria included: serious medical illness, seizure disorder, pregnancy or lactation, psychiatric disorder that required ongoing medication (as assessed by SCID interview; First *et al*, 1997), and court-mandated drug abuse treatment. They participated at five sites: Costa Mesa, CA ($n=32$); San Diego, CA ($n=25$); Honolulu, HI ($n=31$); Kansas City, MO ($n=33$); and Des Moines, IA ($n=30$).

During treatment, participants made thrice-weekly visits to provide urine for methamphetamine and creatinine assessments, completed the timeline follow-back Substance Use Report, and described any adverse events. Weekly assessments included the Brief Substance Craving Scale (BSCS) (Somoza *et al*, 2000), medication compliance, and vital signs. HAM-D (Williams, 1988) was obtained biweekly, and the Addiction Severity Index (ASI-Lite, 2000 version) (McLellan *et al*, 1992) at baseline and end of treatment. Current attention deficit/hyperactivity symptoms were assessed at baseline, using a checklist of DSM-IV criteria.

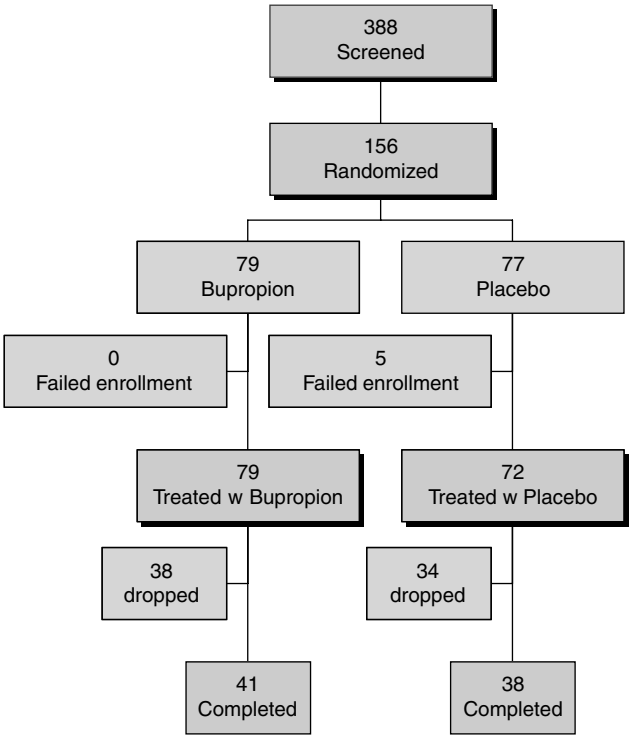

Figure 1 Participant flow chart for clinical trial of bupropion for the treatment of methamphetamine dependence.

Participants were compensated in retail scrip or vouchers for their time, travel, and for providing research specimens and data, at $10/visit.

Study Agent, Psychosocial Treatment, and Methamphetamine Urinalysis

Commercially available, sustained-release bupropion 150 mg (Zyban SR®, GlaxoSmithKline) and matched placebo were film-coated (to mask information on the tablet surface), and provided to sites. Participants received doses of bupropion 150 mg SR or placebo, once daily for 3 days, then increased to 300 mg daily (one tablet twice a day) for about 11 weeks of treatment, until the final dose taper. The dose was reduced to 150 mg daily on the last 3 days of the 12-week treatment period. Compliance was assessed by weekly tablet count.

Throughout the 12 weeks, all participants received standardized, cognitive-behavioral therapy in a 90-min, three times-a-week group session. This manual-driven treatment was derived from the relapse prevention group component of the Matrix Model (Rawson *et al*, 2006).

Urine samples were screened for methamphetamine/amphetamine by immunoassay method with a cutoff level of 300 ng/ml. Positive samples were assayed for methamphetamine level by gas chromatography/mass spectrometry with a quantification limit of 78 ng/ml.

Data Analysis

The primary outcome assessment was the percentage of participants who abstained from methamphetamine use during each week of treatment, according to urine analysis. For this study, a methamphetamine-free urine was defined as a negative qualitative screen (cutoff of 300 ng/ml) or, if the qualitative screen was positive, a quantitative methamphetamine/amphetamine assay of less than 300 ng/ml. A methamphetamine-free week was defined as a week in which all non-missing urine samples in the week (3 samples/week) were methamphetamine-free.

The weekly proportion of participants with methamphetamine-free urine was compared between treatment groups, using generalized estimating equations (GEE) (McCullagh, 1980), with a logistic link. GEE provides a model-based regression method for the analysis of correlated data, of which the repeated measures in this longitudinal study are an example (Zeger and Liang, 1986). Other planned (*a priori*) analyses included testing for significant treatment effects on the primary outcome, using each stratum of the randomization factors as a subgroup: male and female patients, lower and higher level of methamphetamine use at baseline (self-reported no. of days using in the past 30 days: $\leqslant 18$ *vs* >18 days), lower and higher level of symptoms of depression at baseline (HAM-D score $\leqslant 12$ *vs* >12), and site. GEE assumes that missing data are missing 'completely at random' (Little and Rubin, 2002); this assumption was partly tested by analyzing retention, by treatment group, and by study subgroups.

To further test the combined effect of the balancing factors and correct for multiple comparisons, we fitted the primary outcome data with a nonlinear (logistic) mixed effect model (NLMM). This method will adjust for baseline differences while estimating the subject-specific effects of treatment. NLMM can perform regression on longitudinal data, using the less-stringent assumption of 'missing at random' rather than 'missing completely at random.' This model's estimate of the difference in slopes for the two treatment groups represents the per week increment in odds of a non-use week for bupropion relative to placebo.

Subgroups with and without comorbid adult ADHD were analyzed as separate strata using GEE, for a treatment effect on the primary outcome. Secondary outcome measurements included quantitative methamphetamine in urine, self-report of daily methamphetamine use (by timeline follow-back at each visit), changes in addiction severity determined by the ASI-Lite, changes in craving determined by BSCS, and changes in depression determined by HAM-D scores. Other outcomes were the use of other substances of abuse (marijuana, cigarette smoking, and alcohol, as determined by self-report of daily use), and the safety of bupropion in this study population.

All of the secondary analyses were on repeated measures. For ASI and HAM-D, the first (baseline) and last observations for each participant were used. Each domain of ASI was assessed for a significant difference between treatment groups over the 12-week period, using GEE. For BSCS, a total methamphetamine craving score was calculated for each week by adding responses for intensity, frequency, and length of craving, and these weekly total scores were averaged for each treatment group. GEE was used to test for a difference between groups in the change in averages over the treatment period. Regression analyses for BSCS were also stratified by baseline level of methamphetamine use.

Type I error rate was controlled at 5% across the multiple tests of the NLMM analysis, using sequential Bonferroni adjustment (Aickin and Gensler, 1996). All analyses were conducted in version 9 of SAS (SAS Institute, Cary, NC).

RESULTS

Baseline Demographics

Altogether, 151 participants started the study; 79 received bupropion and 72 received placebo (Figure 1). There were five participants from three different clinics who were randomized but did not return for the first dose of study medication. One of them transferred to a treatment program and the others were lost to follow-up. Individuals in the bupropion and placebo groups had similar baseline demographic characteristics (Table 1). Average age was about 36 years, with 67% of participants being male. White Americans accounted for approximately 75% of those participating, while 14% were Asian, 7% were Hispanic, and 3% were African American. The only difference detected between treatment groups on the measured baseline characteristics was in the proportion having threshold symptoms of adult ADHD (8% bupropion *vs* 19% placebo, $p = 0.03$).

Treatment Retention

Of the 151 participants enrolled, 79 (52%) completed the study, where completion was defined as provision of at least

Table 1 Baseline Characteristics of Randomized Participants for the Bupropion-Methamphetamine Study

	Bupropion N = 79		Placebo N = 72		p-values
Age (years)	36.2	(9.2)[a]	35.7	(8.4)	0.72
Gender					0.33
Male	50	(63%)	51	(71%)	
Female	29	(37%)	21	(29%)	
Race					0.93
White, not Hispanic	59	(75%)	53	(74%)	
Hispanic or Latino	5	(6%)	5	(7%)	
African American or Black	2	(3%)	2	(3%)	
Asian or Pacific Islander	11	(14%)	10	(14%)	
American Indian or Alaska	1	(1%)	0	(0%)	
Other	1	(1%)	2	(3%)	
Years of education	12.6	(1.9)[a]	12.4	(1.7)	0.48
Days of methamphetamine use in last 30 days					0.66
⩽18	36	(46%)	35	(49%)	
>18	43	(54%)	37	(51%)	
Lifetime years of methamphetamine use	10.42	(7.59)[a]	9.97	(6.10)	0.69
Route of lifetime methamphetamine use					0.66
Nasal	15	(19%)	10	(14%)	
Smoking	49	(62%)	49	(68%)	
Injection	15	(19%)	13	(18%)	
Baseline period urine methamphetamine screens (% positive)		82.9%		80.3%	
Depression (HAM-D score)					0.78
⩽12	64	(81%)	57	(79%)	
>12	15	(19%)	15	(21%)	
Adult ADHD					0.03
No	73	(92%)	58	(81%)	
Yes	6	(8%)	14	(19%)	

[a]Standard deviation.

one urine sample during the 12th week of treatment (Figure 1). Completion percentages for placebo and bupropion groups were similar, at 52.8 and 51.9%, respectively. Also, no difference was detected in retention (time to last urine sample) between the two groups (log-rank test, $p = 0.56$). In addition, there was no difference in retention between treatment groups within the subgroups having lower or higher baseline use of methamphetamine (log-rank tests, $p = 0.65$ and 0.66). In this regard, the assumption of data missing 'completely at random' was considered acceptable for this analysis. Medication compliance was averaged across the 12-week treatment period. The number of tablets taken was 1.73/day for both groups (SD = 0.31, expected = 2.0/day).

Efficacy as Assessed by Urine Analysis

Figure 2 plots the percentage of participants with a methamphetamine-free study week, along with fitted regression lines obtained with GEE. This regression analysis tested for a significant difference between treatment groups at baseline (intercepts), as well as between their rates

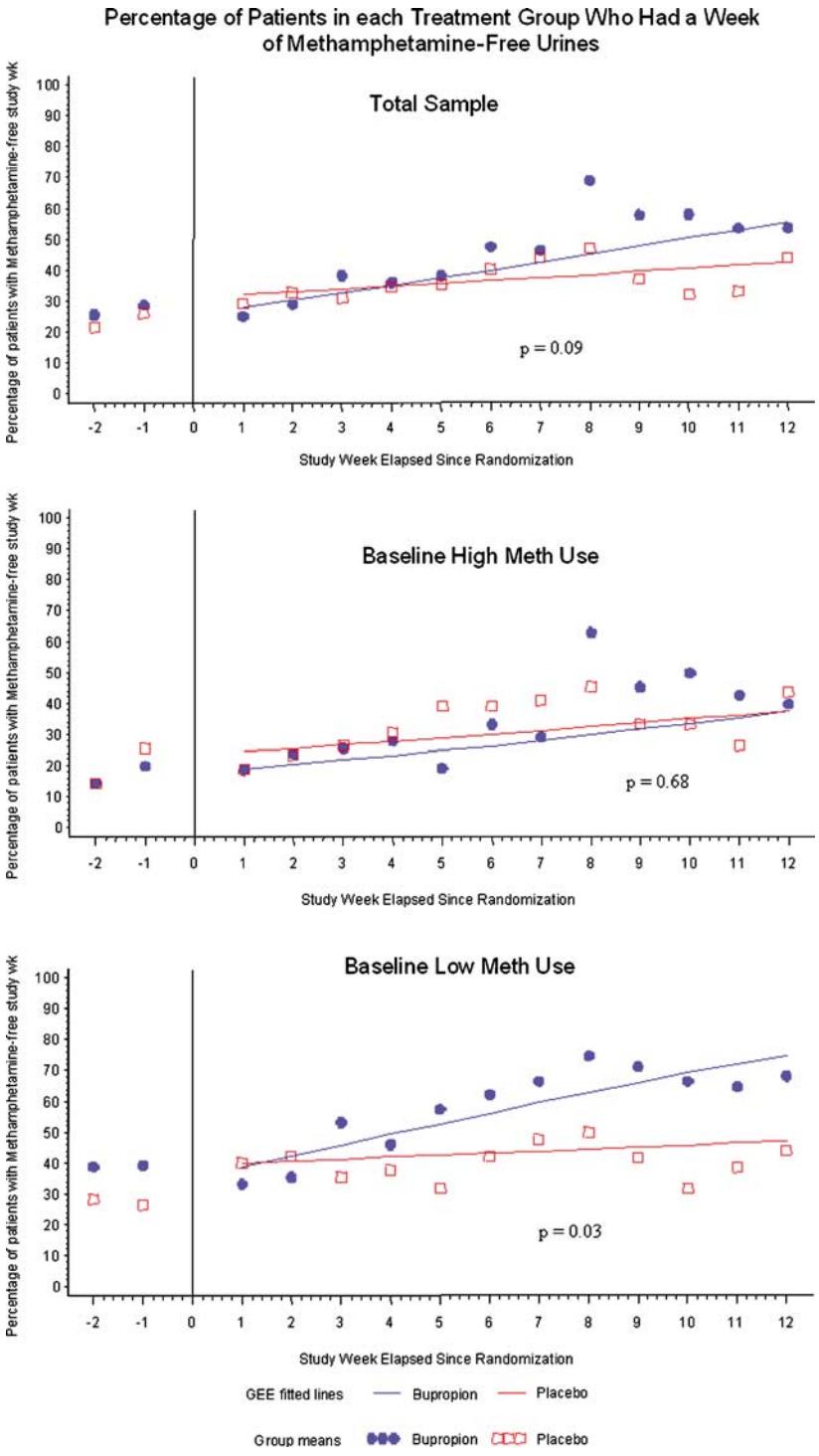

Figure 2 Weekly percentage of participants with methamphetamine-free urine, bupropion *vs* placebo, for total sample, and by subgroups of low and high methamphetamine use at baseline ($\leqslant$18 days in the last 30, and $>$18 days). The group means and the GEE-fitted lines are shown.

of change over the study period (slopes). At week 1, the bupropion group had a lower percentage with a methamphetamine-free study week (25%) than the placebo group (29%), and at week 12, the bupropion group had 10% more participants with a methamphetamine-free study week (54% bupropion *vs* 44% placebo). There was a modest trend for improvement over the treatment period in the bupropion group compared to placebo group (GEE, $p = 0.09$, Figure 2).

Secondary Outcomes

Quantitative urine methamphetamine. Quantitative urine methamphetamine levels were compared between groups.

For each participant in each week, the median methamphetamine concentration was selected and transformed to its logarithm base 10 value. GEE was used to fit a regression line to these data for each treatment group, and to produce a mean value for each week for each group. The rate of reduction in the amount of methamphetamine used by the bupropion group, although estimated to be greater than placebo's, was not significantly different ($p = 0.15$).

Self-report of daily methamphetamine use. The change in percentage of participants having a methamphetamine-free study week, according to self-report alone, was compared between treatment groups using GEE regression analysis. There was no significant difference in the rate of change over the treatment period between bupropion and placebo ($p = 0.28$).

Subgroup analyses. At randomization, the treatment groups were balanced within sites using gender, self-report of methamphetamine use before screening ($\leqslant 18$ days in the last 30, *vs* >18 days), and severity of depression symptoms (HAM-D score $\leqslant 12$ *vs* >12). To assess whether response to treatment depended upon these 'stratification' factors, subgroup analyses of the primary outcome were conducted for male and female patients, for lower and higher baseline methamphetamine use, and for lower and higher severity of depression symptoms.

In the subgroup that had lower use of methamphetamine at baseline ($\leqslant 18$ days in last 30 days), bupropion treatment increased weekly periods of abstinence compared to placebo (Figure 2). Without correcting for multiple comparisons, the increase in proportion of lower baseline use, for bupropion group participants who had a non-use week, was significant (GEE, $p = 0.03$, Figure 2). At the end of treatment, the bupropion group had 16% more participants with a methamphetamine-free study week than placebo (56 *vs* 40%). No significant difference was detected between bupropion and placebo treatment in the rate of change (slope) in non-use weeks, for participants whose baseline methamphetamine use was higher (>18 days in last 30 days) (GEE, $p = 0.68$, Figure 2). In addition, in the subgroup that had a lower baseline use of methamphetamine, the rate of decrease in the urine quantitative methamphetamine was apparently significantly greater for bupropion than for placebo (GEE, $p = 0.04$, data not shown).

Among male patients, the bupropion group demonstrated an apparently significantly greater rate of increase in the proportion of participants with a methamphetamine-free week than placebo (GEE, $p = 0.04$, $n = 101$), while no difference in slopes was detected among female patients (GEE, $p = 0.71$, $n = 50$, data not shown).

Only 30 participants scored >12 on the HAM-D (15 in the bupropion group and 15 in the placebo group). There was no significant difference detected in the primary outcome between bupropion and placebo treatment in the more-depressed subgroup (GEE, $p = 0.58$). The comparison in the less-depressed subgroup nearly attained statistical significance, with bupropion-treated participants having a greater rate of increase in methamphetamine-free study weeks (GEE, $p = 0.08$, data not shown).

To test the combined effect of the balancing factors and to correct for multiple comparisons, we used an NLMM (logistic) to estimate the per-week change in the odds ratio (OR) of having a non-use week, for bupropion compared to placebo. Estimates were obtained for each of the eight subgroups formed by all combinations of gender, level of baseline use, and level of baseline depression (Table 2). To control the overall type I error rate at the level of $\alpha = 0.05$, we used the sequential Bonferroni adjustment method of Holm (1979). The smallest p-value was compared to $\alpha/8 = 0.00625$, the next smallest to $\alpha/7 = 0.00714$, the next to $\alpha/6 = 0.008$, etc. Three of the subgroups had p-values less than 0.05, for a significant effect with bupropion, and two of these remained significant after correction for multiple comparisons. The two subgroups that were significantly more likely to have a methamphetamine-free week on bupropion were depressed, or non-depressed, male patients

Table 2 NLMM Estimates for Per-Week Increment in Odds of a Non-Use Week, Bupropion *vs* Placebo, for 'Stratification' Subgroups

n	Subgroup	Odds of non-use week	*p*-value	Bonferroni-adjusted α
47	Males, non-depressed, lower baseline use	1.39	7.7×10^{-8}	0.00625
10	Males, some depression, lower baseline use	1.34	0.000094	0.00714
13	Females, non-depressed, lower baseline use	1.27	0.020	0.00833
1	Females, some depression, lower baseline use	1.23	0.113	0.01000
34	Males, non-depressed, higher baseline use	1.08	0.396	0.01250
10	Males, some depression, higher baseline use	1.05	0.935	0.01667
9	Females some depression, higher baseline use	0.96	0.967	0.02500
27	Females, non-depressed, higher baseline use	0.99	0.994	0.05000

with low baseline use (OR = 1.39 and 1.34, respectively, NLMM, both $p < 0.0001$). For non-depressed female patients with low baseline use, the estimate was OR = 1.27 ($p = 0.02$; Table 2).

Comorbid ADHD. Only 20 participants met criteria for ADHD as adults (6 in the bupropion group and 14 in the placebo group). The primary outcome was also analyzed using GEE and controlling for ADHD diagnosis, with no change in the results.

Addiction Severity Index. No significant differences were detected between groups for any of the seven ASI domains in the difference in means from baseline to last observation (all $p > 0.28$).

Brief Substance Craving Scale. The slopes over time on the BSCS were not different for bupropion compared to placebo, for the total sample (GEE, $p = 0.35$), and for subgroups with low and high use at baseline (both $p > 0.44$).

Hamilton Depression Scale. HAM-D scores over the treatment period showed a small reduction for the total sample and both baseline methamphetamine-use subgroups; however, bupropion treatment was not significantly different from placebo.

Other substances of abuse. For nicotine, the bupropion group had a lower number of reported days of cigarette smoking during the baseline period and throughout treatment, but the rate of decrease in smoking across the trial was not significantly different from placebo ($p = 0.44$). No treatment group effect was seen for alcohol or marijuana use.

HIV Risk Behavior Scale. There was no significant difference between groups in the change from baseline to last observation in mean HIV Risk Behavior Scale scores, for either domain (needle use or risky sex).

Safety

Bupropion was not associated with any significant changes to vital signs or ECG intervals over the course of the study. Adverse events that were 'definitely or possibly related' were reported by 30% of bupropion and 31% of placebo participants. The most frequently encountered complaints were headache and insomnia. Slightly more participants complained of headache in the placebo group than in the bupropion group, 17 *vs* 11%, while insomnia was experienced by 9% of participants taking bupropion compared to 5% taking placebo. Neither of these differences was statistically significant (Fisher's exact test). Depressed mood was reported in 5% of placebo participants and no bupropion participants, a difference which approached significance ($p = 0.057$). Out of a total of 475 adverse events, 13 were rated as severe (5 bupropion, 8 placebo). Also, there were three serious adverse events, all psychiatric in nature, two occurring on placebo, and one in a participant who stated he did not take his bupropion throughout the trial.

DISCUSSION

Although the overall effect for bupropion was not significant, the main finding of the study is that bupropion reduced methamphetamine use in male participants having low-to-moderate use at baseline. Based on the mixed model analysis, the effect size for the male low users was about 35%, which is clinically meaningful, and comparable to that of medications marketed for the treatment of alcohol dependence, such as naltrexone, and of bupropion for nicotine dependence (Richmond and Zwar, 2003). This is akin to the 'relative success rate' (active/placebo ratio) of other psychotropic medications, such as aripiprazole 20 mg for schizophrenia, 57% (Potkin *et al*, 2003), and divalproex ER for acute mania, 41% (Bowden *et al*, 2006).

Our results raise important questions and validate some of the clinical insight that has developed over the years of conducting clinical trials in stimulant addiction. One of these insights is that baseline use is highly predictive of treatment response (Reiber *et al*, 2002; Elkashef *et al*, 2005; Hillhouse *et al*, 2007). Our study is the first to report a differential medication response by baseline use in methamphetamine-dependent patients, as predicted. The notion that the amount of exposure to methamphetamine could predict a different outcome in response to medication is supported by preclinical data that describes contrasting effects of low and high concentrations of methamphetamine on neuropeptide-containing striato-nigral and nucleus accumbens efferent projections having DA D-1 receptor activity (Hanson *et al*, 2002). The relevance to clinical work is to show that light *vs* heavy use of methamphetamine can be expected to have different consequences on brain monaminergic systems, which could result in different responses to a medication.

Our data give credence to an experience with which clinicians are quite familiar: there is not one treatment that will fit all, and different patients may respond to the same medication differently, based on their gender, biology, and use pattern (Elkashef and Vocci, 2003; Kampman *et al*, 2004). The failure of bupropion to have a significant impact on heavy users raises the important question of what pharmacological treatment might be effective for them. Heavy methamphetamine use may contribute to neurotoxicity (Chang *et al*, 2005), which may manifest clinically as cognitive impairment, and require a different therapeutic strategy, such as a cognitive enhancer. Preclinical data suggest that methylphenidate is capable of attenuating the effects of high doses of methamphetamine on the DA transporter (Sandoval *et al*, 2003). Indeed, early pilot clinical data on methylphenidate in heavy users of intravenous amphetamines showed promising results in reducing their amphetamine use (Tiihonen *et al*, 2007). Data from the interim analysis of a trial of D-amphetamine in Australia suggest that it may be beneficial for methamphetamine-dependent patients (Wickes *et al*, 2007). This study is still ongoing. Earlier data from a trial of D-amphetamine for methadone-maintained cocaine users (Grabowski *et al*, 2004) suggested a possible role for the 30–60 mg dose of D-amphetamine in yielding fewer cocaine-positive urines.

The gender issue is also an important one. In our cocaine trials, we have observed a differential response based on gender, in that female patients aged 40 years or more who used cocaine for 10 years or longer tended to show poor

outcome in medication trials, compared to male patients with the same use pattern and duration (Elkashef *et al*, 2005). However, similar findings have not been reported in other studies, at least for cocaine dependence (Reiber *et al*, 2002; Wong *et al*, 2002; Westhuis *et al*, 2001). The poor response in female patients in this study might be explained by the fact that almost two-thirds of female patients were in the high baseline use group ($n = 36$) and only one-third ($n = 14$) were in the low baseline use group.

With quite a small and unbalanced number who showed the presence of adult ADHD ($n = 6 + 14$), we did not detect an association with bupropion treatment. Neither did we detect differences between the bupropion and placebo groups in any of the addiction severity domains. Contrary to what we expected, there was no difference between treatment groups in the change in weekly craving scores over the treatment period. The small decrease in the usage of nicotine across the treatment period was not different between treatment groups.

A weakness of our study is the imbalance between groups on the presence of ADHD. There are practical limits on the number of factors that can be balanced in randomization, and data in the literature on the prevalence of ADHD in methamphetamine-dependent participants did not match our experience (Jaffe *et al*, 2005). In this study, we found 15% of participants to have comorbid symptoms of adult ADHD. Our raters used a DSM-IV checklist, but lacked training for inter-rater reliability. Even though the imbalance in this study did not change the outcome, we recommend that future studies testing a medication that has an effect on ADHD symptoms should account for the distribution among participants at randomization. Also, we would use a more standardized and validated method of assessment for ADHD (Adler *et al*, 2005).

Similar to the phase I safety study findings, bupropion was safe to administer in this outpatient trial. Medication compliance was high in both treatment groups and would suggest the acceptance of bupropion by this population. The findings from this proof-of-concept study are encouraging, and warrant further study of bupropion for the treatment of methamphetamine-dependent patients who exhibit low-to-moderate ($\leqslant 18$ days per month) use of methamphetamine.

DISCLOSURE/CONFLICT OF INTEREST

No pharmaceutical company supported this study. One of the co-investigators owns stock in GlaxoSmithKline. Dr Gorodetzky has received compensation for professional services from: US World Meds, Catalyst Pharmaceutical Partners, Neurorecovery, Pinney Associates, Quintiles, Sheldon Bernstein, Attorney, Morris and Partners, Ovation Pharmaceuticals, Ashurst (Attorneys for Sanofi-Aventis), Johns Hopkins University, Valeria Pharmaceuticals, Shire Pharmaceuticals, Reckitt Benckiser Pharmaceuticals, and Elsevier.

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