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Short communication

Bupropion for the treatment of methamphetamine dependence in non-daily users: A randomized, double-blind, placebo-controlled trial☆

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ABSTRACT

Aim: Bupropion was tested for efficacy to achieve methamphetamine (MA) abstinence in dependent, non-daily users.
Methods: A randomized, double-blind, placebo-controlled trial, with 12-week treatment and 4-week follow-up, was conducted with 204 treatment-seeking participants having MA dependence per DSM-IV, who used MA on a less-than-daily basis. 104 were randomized to matched placebo and 100 to bupropion, sustained-release 150 mg, twice daily. Participants were seen three times weekly to obtain urine for MA and bupropion assays, study assessments, and thrice weekly, 90-min, group psychotherapy. There was no biomarker for placebo adherence. The primary outcome was achievement of abstinence throughout the last two weeks of treatment; 'success' requiring at least two urine samples during each of Weeks 11 and 12, and all samples MA-negative (<300 ng/mL).
Results: Bupropion and placebo groups did not differ significantly in the percentage achieving abstinence for the last 2 weeks of treatment (chi-square, $p = 0.32$). Subgroup analysis of participants with lower baseline MA use (≤18 of last 30 days before consent) also revealed no difference in success between groups ($p = 0.73$). Medication adherence per protocol (detectable bupropion, >5 ng/mL, in ≥50% of urine samples from Study Weeks 1–10 and ≥66% of urine samples from Weeks 11 to 12) was achieved by 47% of participants taking bupropion.
Conclusions: These data indicate that bupropion did not increase abstinence in dependent participants who were using MA less-than-daily. Medication non-adherence was a limitation in this trial. Psychosocial therapy remains the mainstay of treatment for MA dependence. Further research on subgroups who may respond to bupropion may be warranted.

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1. Introduction

Methamphetamine dependence is a complex and severe health problem for individuals and their communities (Berman et al., 2008; Gonzales et al., 2010). Although 'past month' methamphetamine (MA) use declined slightly in the US from 2006 to 2012, from 0.3 to 0.2% of the population aged 12 years or older (SAMHSA, 2013a), emergency department visits for both illicit and prescribed stimulants increased (up 61% and 85% from 2009 to 2011; SAMHSA, 2013b). In spite of numerous trials of psychoactive medications approved for other indications, and a few phase I trials of new entities (Brackins et al., 2011; Karila et al., 2010), the need to find an effective medication persists.

Bupropion, a weak inhibitor of norepinephrine and dopamine uptake, is approved for the treatment of depression and nicotine dependence (GlaxoSmithKline, 2012), and has been shown to improve symptoms of adult attention-deficit/hyperactivity disorder (ADHD; Wilens et al., 2005).

Previous clinical data suggested that bupropion might be effective in a subgroup with lower baseline MA use (Elkashef et al., 2008). In that trial, males using MA less frequently at baseline achieved more 'non-use weeks' with bupropion compared to placebo. That subgroup was also more likely to achieve abstinence throughout the last 2 weeks of the trial, according to a reanalysis of the data using the outcome of 'terminal abstinence' (McCann and Li, 2012). Other medication trials have also shown greater treatment effects in participants with less frequent baseline cocaine use (Elkashef et al., 2005). The primary objective of this study was to assess the efficacy of bupropion to increase abstinence in MA-dependent participants who used MA on 29 or fewer days in the month prior to signing consent.

2. Methods

The protocol and informed consent were approved by the Investigational Review Board at each site. The study was monitored by a central Data and Safety Monitoring Board. The bupropion was purchased commercially.

2.1. Study design

This was a randomized, double-blind, placebo-controlled, multi-site study, that provided 12 weeks of treatment with either bupropion SR 150 mg twice daily or matched placebo, and had a four week follow-up.

The methods were nearly identical to our previous study (Elkashef et al., 2008), except we attempted to replicate our finding of bupropion's reduction in MA use among lower frequency users. To enrich the study population with lower frequency users, we excluded those with daily MA use, only including those who used on ≤29 of the 30 days prior to consent. Randomization was balanced on factors of: MA use in the 30 days prior to consent (19–29 days), symptoms of depression (HAM-D >12, Williams, 1988), and (instead of gender) symptoms diagnostic of adult ADHD (Adler et al., 2005). Telephone randomization software incorporated the adaptive "urn" method to balance treatment groups within sites on these three factors (Stout et al., 1994).

2.2. Participants

Treatment-seeking participants were assessed for MA dependence by MINI interview (Sheehan et al., 1998). Participants were required to provide at least one MA-positive urine during screening, but because of slow recruitment the protocol was modified to allow inclusion of those who had no MA-positive urine but "corroboration" of baseline use by a family, medical, or judicial source (see Discussion). Exclusion criteria were described in Elkashef et al. (2008), and we also excluded: uncontrolled hypertension (≥Stage 2); history of loss of consciousness greater than 5 min; unstable diabetes with hypoglycemia in the past year; and some antiretroviral medications. Twelve outpatient clinic sites recruited participants in cities across the country.

2.3. Psychosocial treatment, bupropion assays, and MA urinalysis

Clinic visits occurred three times per week. At each visit, urine samples were obtained for MA and bupropion assays. Also, research assessments were performed and participants received cognitive-behavioral, relapse-prevention, manual-driven therapy in 90-min group sessions (Rawson et al., 1995).

Medication adherence in the active group was determined by assay of urine samples for bupropion, with a lower limit of quantification of 5 ng/mL. Adherence was defined as having detectable bupropion in at least 50% of urine samples obtained during Study Weeks 1 through 10 and at least 66% of urine samples obtained during Weeks 11 and 12.

The primary outcome was determined by immunoassay of urine samples for MA and its major metabolite, amphetamine, using a cut-off level of 300 ng/mL for either or both. Only positive immunoassay results were confirmed by gas chromatography/mass spectrometry, with a quantification limit of 78 ng/mL for MA.

2.4. Data analysis

In the analysis plan, a significant treatment advantage would be demonstrated by using chi-square to compare 'successful' proportions of the bupropion vs. placebo groups. Our sample size estimate was obtained by using the last two weeks' abstinence rates from our earlier trial of bupropion for MA dependence. Those proportions of successful participants who used ≤18 days of 30 at baseline were 0.238 for bupropion and 0.057 for placebo. To obtain a power of 95% at a type I error rate of 5%, using a two-tailed Fisher's exact test, would require a total sample size of 200 (100 per group).

The primary efficacy outcome measure was success or failure of each individual to achieve abstinence throughout Study Weeks 11 and 12. Success at abstinence required that, (1) at least two urines samples were provided during each of Weeks 11 and 12 and (2) all urine samples in the last two treatment weeks were negative for MA (negative immunoassay or GC/MS quantitative result <300 ng/mL). Any participant who dropped out before the last two weeks of treatment was scored as a failure on the primary outcome.

Interaction effects on the primary outcome were also evaluated, using Cochran–Mantel–Haenszel regression, for the randomization balancing factors as subgroups: i.e., categories of baseline frequency of MA use, HAM-D score, presence of adult ADHD, and gender. Two-sided, type I error rate was controlled at 5%. All analyses were conducted in versions 9.2 and/or 9.3 of SAS (SAS Institute, Cary, NC).

Safety outcomes included vital signs, electrocardiograms, and weekly logs of adverse events.

3. Results

3.1. Screening and treatment retention

Among 592 participants screened, 388 did not enroll (screen failure = 66%). The main reasons for screen failure are shown in Fig. 1, and include: inability to comply/did not return (n = 179 (46%)) and too frequent MA use (n = 40 (10%)).

The intent-to-treat analysis utilized 204 randomized participants who took the first dose; 104 participants received placebo,

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