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Varenicline treatment for methamphetamine dependence: A randomized, double-blind phase II clinical trial

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ABSTRACT

Background: Previous studies have suggested that varenicline, an α4β2 nicotinic receptor partial agonist, and α7 nicotinic receptor full agonist, may be effective for the treatment of methamphetamine (MA) dependence due to dopaminergic effects, relief of glutamatergic and cognitive dysfunction, and activation of nicotinic cholinergic systems. This study aimed to determine if varenicline (1 mg BID) resulted in reduced methamphetamine use compared to placebo among treatment-seeking MA-dependent volunteers.

Methods: Treatment-seeking MA-dependent volunteers were randomized to varenicline 1 mg twice daily (n = 27) or placebo (n = 25) and cognitive behavioral therapy for 9 weeks. The primary outcomes were the proportion of participants achieving end-of-treatment-abstinence (EOTA, MA-negative urine specimens during weeks 8 and 9) and the treatment effectiveness score (TES, number of MA-negative urine specimens) for varenicline versus placebo.

Results: There was no significant difference in EOTA between varenicline (15%, 4/27) and placebo (20%, 5/25; $p = 0.9$). There was some suggestion that urinary confirmed medication compliance corresponded with EOTA in the varenicline condition, though it did not reach statistical significance, OR = 1.57 for a 100 ng/ml increase in urine varenicline, $p = 0.10$, 95% CI (0.99, 3.02). There was no significant difference in mean TES in the varenicline condition (8.6) compared to the placebo condition (8.1), and treatment condition was not a statistically significant predictor of TES, IRR = 1.01, $p = 0.9$, 95% CI (0.39, 2.70).

Conclusions: The results of this study indicate that 1 mg varenicline BID was not an effective treatment for MA dependence among treatment-seeking MA-dependent volunteers.

1. Introduction

Methamphetamine (MA) dependence is a significant source of deleterious consequences to individual and public health (Cruickshank and Dyer, 2009). Approximately 469,000 people aged 12 and older in the U.S. meet the DSM-IV criteria for MA dependence, and the economic burden of MA use in the U.S. is approximately $23.4 billion per year (Nicosia et al., 2009; Substance Abuse and Mental Health Services Administration, 2014). Available behavioral treatments, including cognitive behavioral therapy (CBT) and contingency management (CM), are only modestly effective (Lee and Rawson, 2008; Roll, 2007). Potential pharmacotherapies have been investigated in randomized, placebo-controlled trials for MA dependence, but results have failed to identify a medication with a robust effect in generalized populations of MA users (Anderson et al., 2015; Courtney and Ray, 2014; Heinzerling et al., 2014; Miles et al., 2013; Pérez-Mañá et al., 2013), instead only efficacious in subpopulations defined by baseline MA use (Elkashef et al., 2008; Ling et al., 2014; Shoptaw et al., 2008) or among men who have sex with men (Colfax et al., 2011).

Cholinergic mechanisms are important in the neurobiology of MA dependence (Hiranita et al., 2008; Williams and Adinoff, 2008). Varenicline is an α4β2 nicotinic receptor partial agonist and α7 nicotinic receptor full agonist that is approved for cigarette smoking cessation (Gonzales et al., 2006) and shows promise for treating alcohol

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dependence (de Bejczy et al., 2015; Litten et al., 2013; McKee et al., 2009). The rationale for varenicline as a treatment for MA dependence includes: (1) restoration of MA-related dopaminergic deficits via binding to α4β2 receptors in striatal DA neurons, (2) reductions in cigarette smoking and associated nicotine-mediated potentiation of MA effects, (3) activation of nicotinic cholinergic systems that mediate reductions in reinstatement of MA seeking, (4) relief of MA-related glutamatergic deficits via α7 nicotinic ACh receptor activation, and (5) reduction in MA-related cognitive dysfunction via the cognitive enhancing effects of cholinergic agonists.

While none of these putative mechanisms raise questions of safety of varenicline for methamphetamine dependence, the U.S. Food and Drug Administration (FDA) issued a "black box" warning regarding increased risks of neuropsychiatric and cardiovascular adverse effects with varenicline for cigarette smoking cessation (U.S. Food and Drug Administration, 2009). Our group found varenicline to be safe and without any psychiatric adverse events in a phase 1 safety study (n = 8) among MA-dependent cigarette smokers (Zorick et al., 2010). Another phase I trial (n = 17) by Verrico et al. (2014) showed that varenicline was safe and reduced subjective positive effects of MA compared to placebo.

Building upon this, we conducted a randomized, double-blind Phase II clinical trial of varenicline (1 mg) versus placebo BID for MA dependence. We hypothesized that MA-dependent participants randomized to varenicline would be more likely to achieve end-of-treatment abstinence (EOTA), reduce MA use during active treatment, and delay time-to-relapse as compared to placebo. In addition, we hypothesized that varenicline would reduce cigarette smoking more than placebo among cigarette-smoking participants. We also explored whether varenicline compliance would be associated with treatment outcomes in the varenicline group and whether an inpatient detoxification period would be associated with better outcomes. Finally, we describe safety and tolerability data for varenicline among MA-dependent participants.

2. Methods

Prior to study initiation, ethical approval was obtained from the Institutional Review Boards at UCLA and LA Biomed and an independent data safety monitoring board and is registered with ClinicalTrials.gov, NCT01365819. A CONSORT study flowchart is presented in Fig. 1.

2.1. Design

This randomized, double-blind, placebo-controlled Phase II clinical trial recruited participants from February 2012 through May 2015 and compared outcomes for varenicline and placebo conditions. Following randomization, participants underwent dose escalation to varenicline 1 mg/placebo BID over one week while completing thrice-weekly outpatient visits. On day 8 of the trial (steady state), participants were admitted to the Harbor-UCLA Clinical and Translational Research Center for 4-night inpatient detoxification and methamphetamine-abstinence initiation. Participants were discharged and returned to the UCLA outpatient clinic on a thrice-weekly basis to complete a nine-week medication phase. Participants then completed four additional weeks of medical and safety assessments; the full duration of the trial was 13 weeks. Due to funding constraints, the inpatient stay was discontinued approximately one-third of the way through the trial (n = 18 of 52 participants underwent inpatient stays), with subsequent participants visiting the outpatient clinic daily instead during week 2 to complete daily required assessments. Prior to study initiation, power calculations were based on 29 repeated measures of the binary outcome variable (MA-negative urine) for each subject (thrice weekly collected samples during study weeks 1, 3–9 and daily samples collected during week 2) with an average within-subject autocorrelation of 0.5 and a two-sided test with alpha = 0.05. The design provided adequate power to detect a medium effect size (Cohen's f = 0.21) with a target enrollment of 90 participants. Due to lack of accrual, enrollment was halted at n = 52.

Participants were reimbursed in gift cards, up to $595, for time spent completing study assessments and transportation to/from the clinic.

2.2. Screening and inclusion/exclusion criteria

In total, 277 participants opened informed consent; 225 screen failed, and 52 were randomized and received varenicline or placebo. Of the 52 randomized, 26 completed and 26 dropped (Fig. 1). Participants were recruited via websites, newspapers, radio, and referrals. Interested individuals called a toll-free number, completed telephone prescreening, were provided study information, and the opportunity to schedule a consent appointment.

Inclusion criteria were: 1) at least 18 years of age, 2) met DSM-IV criteria for MA dependence verified by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (American Psychiatric Association, 2000; First et al., 2002), 3) had an MA-positive urine drug screen at any time during screening, 4) seeking treatment for MA problems, 5) willing and able to comply with study procedures, 6) willing and able to provide written informed consent and 7) if female, not pregnant or lactating and willing to use a medically reliable method of birth control during the trial. Exclusion criteria were: 1) a medical condition that, in the study physician's judgment, might interfere with safe study participation, 2) a current or past history of cardiovascular disease, 3) systolic blood pressure > 160 or diastolic blood pressure > 100 at two or more screening visits, 4) a history of angioedema, 5) renal impairment, 6) a current neurological disorder (e.g., organic brain disease, dementia) or a medical history which would make study agent compliance difficult or which would compromise informed consent, 7) a current major psychiatric disorder (SCID-verified) not due to substance abuse (e.g., schizophrenia, bipolar disorder) 8) a history of attempted suicide in the past 10 years and/or active suicidal ideation in the past year, 9) current dependence on cocaine, opiates, alcohol, or benzodiazepines (SCID-verified), or 10) a history of sensitivity to varenicline or taking any medications that were contraindicated for use with varenicline or nicotine replacement therapy.

2.3. Randomization

Participants deemed eligible by the study physician, were randomized to varenicline or placebo utilizing an urn randomization procedure (Stout et al., 1994) that provided balance across conditions by gender, ethnicity, baseline frequency of MA use (≤18 versus > 18 of the past 30 days), cigarette smoking status (smoker versus non-smoker), and baseline cognitive function (score of ≥26 versus < 26) as assessed by the Montreal Cognitive Assessment (MOCA) tool to determine cognitive impairment (Nasreddine et al., 2005). The analysis is modified intent-to-treat in that two individuals were randomized but failed to present for randomization, did not receive study medication, did not contribute data and were considered part of n = 225 excluded participants (Fig. 1). A staff member not directly involved in the research maintained the randomization key and program off-site. Participants and study staff who had any participant contact were blind to treatment assignment.

2.4. Treatments

Varenicline 0.5 mg and 1.0 mg tablets were obtained from the manufacturer (Pfizer). Varenicline or matching placebo tablets were over-encapsulated in a #1 size capsule with 25 mg riboflavin (daily total). Varenicline dosing was titrated, starting at 0.5 mg daily for days 1–3, then 0.5 mg twice daily for days 4–7, and 1 mg twice daily from day 8 until completion of the medication phase. Urine specimens were