Safety and efficacy of varenicline to reduce positive subjective effects produced by methamphetamine in methamphetamine-dependent volunteers

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Abstract

Methamphetamine use is increasing in the US. Although there are no Food and Drug Administration (FDA)-approved medications for methamphetamine dependence, preclinical and clinical studies suggest that methamphetamine users may benefit from treatments that enhance cholinergic neurotransmission. Consequently, we determined the safety and the efficacy of varenicline treatment, a partial agonist at α4β2 and a full agonist at α7 nicotinic acetylcholine receptors, to reduce positive subjective effects produced by smoked methamphetamine. Additionally, the effects of treatment with varenicline on the cardiovascular and reinforcing effects of methamphetamine were determined. We conducted a double-blind, placebo-controlled, within-subjects trial of varenicline vs. placebo in methamphetamine-dependent volunteers who were not seeking treatment. Participants were randomly assigned to receive one dose of varenicline (0, 1, or 2 mg) po BID, titrated up to the target dose over days 1–7, during each of three separate inpatient phases. Safety measures included the frequency, duration, severity, and relatedness of adverse events reported. Positive subjective effects included ‘Any drug effect’, ‘High’, ‘Good effects’, ‘Stimulated’, and ‘Drug liking’, which were rated by participants before and for 1 h after smoking methamphetamine (0, 10, and 30 mg). There were no serious adverse events and no differences in adverse events reported during the three phases. Varenicline (2 mg) significantly reduced ratings of ‘Any drug effect’ and ‘Stimulated’, as well as attenuated ratings of ‘High’, ‘Drug liking’, and ‘Good effects’, produced by methamphetamine (30 mg). The ability of varenicline to attenuate the positive subjective effects of methamphetamine in the laboratory suggests that varenicline should continue to be explored as a treatment for methamphetamine dependence.

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Introduction

The United States Department of Health and Human Services estimated that there were 439000 current (past month) and 133000 new methamphetamine (METH) users in 2011, representing increases from 2010 of ∼24 and ∼26%, respectively (Substance Abuse and Mental Health Services Administration, 2012). This trend is troublesome because METH dependence is a significant source of deleterious consequences to individuals and public health (Cruickshank and Dyer, 2009).

Stimulant-induced dopamine (DA) release in human striatum correlates with self-reported craving (Volkow et al., 2005), whereas dopaminergic hypofunction, which occurs during abstinence, contributes to withdrawal (Volkow et al., 2001); both of these likely account for the development and maintenance of METH dependence. Several medications that directly affect the DA system reduce METH-induced subjective effects, an excellent predictor of drug-taking in humans (Fischman and Foltin, 1991). For example, modafinil (Volkow et al., 2009), bupropion (Rau et al., 2005), methylphenidate, and amphetamine reduce withdrawal symptoms (McGregor et al., 2008) and/or subjective effects (Newton et al., 2006; De La Garza et al., 2010) produced by METH; each of these medications also reduce METH use to some degree (Tiihonen et al., 2007; Elkashef et al., 2008; McElhinney et al., 2009; Longo et al., 2010). However, the efficacy of modafinil (Shearer et al., 2009) and bupropion (Shoptaw et al., 2008) is marginal and the therapeutic potential of methylphenidate and amphetamine is limited by possible abuse liability.
Medications that act on acetylcholine (ACh) indirectly affect the mesolimbic DA system and thus provide alternative approaches for modulating the effects of METH. For example in humans, treatment with the acetylcholinesterase (AChE) inhibitor rivastigmine reduces the positive subjective effects produced by METH (De La Garza et al., 2008a,b, 2012). In rodents, both the AChE inhibitor donepezil and the nicotinic ACh (nACh) receptor agonist nicotine, but not the nonselective nACh receptor antagonist mecamylamine, attenuate METH-primed reinstatement (Hiranita et al., 2006), whereas the muscarinic receptor antagonist scopolamine prevents the development of sensitization (Ohmori et al., 1995). Interestingly, ACh-induced activation of nACh receptors increases DA release (Dobbs and Mark, 2012). In fact, nACh receptor β2 subunit knockout mice exhibit a global decrease in the excitability of midbrain DA neurons (Mameli-Engvall et al., 2006) and α4β2 nACh receptors are specifically implicated in reinstatement of METH-seeking behavior in rats (Hiranita et al., 2008). Thus the ability of varenicline to elicit a moderate increase of mesolimbic DA, by acting as a partial agonist at α4β2 nACh receptors, may underlie its ability to attenuate the positive subjective effects of METH.

We previously demonstrated that the α4β2 nACh receptor partial agonist varenicline was well-tolerated by METH users (Zorick et al., 2009). However, in 1992 only 12% of the METH-abusing population smoked METH (Substance Abuse and Mental Health Services Administration, 2005); more recently, smoking has become the preferred route of administration with almost two-thirds (64%) of users smoking METH in 2010 (Substance Abuse and Mental Health Services Administration, 2011). Therefore, we evaluated the safety and efficacy of varenicline to reduce the positive subjective effects produced by smoked METH in METH-dependent volunteers. Additionally, the effects of varenicline treatment on cardiovascular and reinforcing effects produced by METH were determined. We hypothesized that varenicline would dose-dependently attenuate the positive subjective effects of smoked METH.

Methods
This study was registered with www.clinicaltrials.gov (NCT01571167) and approved by both the Baylor College of Medicine and the Michael E. DeBakey Veteran Affairs Medical Center (MEDVAMC) institutional review boards.

Participants
Participants were recruited through advertisements and paid for participating. After complete description and potential risks associated with the study were fully explained to potential participants, written informed consent was obtained. Potential participants were excluded if they had previous adverse reactions to METH, dependence on other drugs (except nicotine), other Axis I psychiatric disorders, or any potentially serious medical conditions. Eligible participants met DSM-IV criteria for METH dependence, provided a METH-positive urine sample during screening, had previously smoked and/or used METH via the intravenous route, were not seeking treatment, and had normal laboratory tests, electrocardiogram results, resting heart rates (HR), and blood pressures (BP).

Procedures
This double-blind, placebo-controlled, within-subjects study was conducted at the Research Commons of the MEDVAMC. Enrolled participants were admitted after a thorough search of their belongings for illicit drugs. While residing at the MEDVAMC during each of the three 8-d phases of the study, participants were closely monitored 24 h/d to ensure that no illicit drug use occurred. Nicotine use was permitted at scheduled intervals.

Table 1 provides the dosing schedules of varenicline and METH. During each phase, participants randomly received one dose of varenicline (0, 1, and 2 mg) po BID over days 1–7; were discharged on day 8, and returned 2–4 wk after completing a phase until they completed the identical procedures for all three phases (Table 1). On day 6 of each phase, participants smoked 0 mg METH at 8:30 AM, and smoked 10 and 30 mg (randomized) at either 10:30 AM or 2:30 PM (Table 1). On day 7 of each phase, two self-administration (choice) sessions were conducted (10:30 AM and 2:30 PM). At the start of each session participants were provided with $5 (five $1 bills, one for each choice opportunity) before smoking a non-contingent sample METH dose (0 or 10 mg; randomized) that was available for purchase during that session. Following the non-contingent sample, participants were given five opportunities, at 13-min intervals, to either purchase the same amount of METH as the sample dose or keep $1 for that choice opportunity.

Smoking sessions took place in a negative pressure room in which participants sat across from a research coordinator. The research coordinator placed the stem of either an empty pipe (0 mg, placebo) or a pipe containing METH (10 or 30 mg) through a small circular opening (slightly larger than the stem) in an opaque partition (≈12×24"), taking caution to maintain the single-blind. The coordinator held a flame to the base of the pipe’s bowl, vaporizing the METH, and instructed participants to ‘take one large inhalation and hold it as you normally would’. Because there is no Food and Drug administration (FDA)-approved placebo for METH, 0 mg was delivered by holding the flame at the base of an empty pipe and instructing participants to inhale.

Safety measures
Safety measures included the frequency, duration, severity, and relatedness of adverse events (AEs) reported.
Subjective effect measures

On day 6, visual analog scale (VAS) forms were completed to measure subjective effects before (time = −15 min), 5, 15, 30, 45, and 60 min after each dose of METH was smoked. Similarly, VAS forms were completed on day 7 during both non-contingent infusion plus self-administration sessions, before (time = −15 min) the non-contingent sample dose, 5, and 10 min after smoking each dose. VAS ratings were recorded on a scale from 0 to 100 and included: (1) Positive ratings of ‘Any drug effect’, ‘High’, ‘Good effects’, ‘Stimulated’, and ‘Drug liking’, which is also considered a ‘Quality’ rating (Hart et al., 2008); (2) Craving ratings of ‘Desire’ and ‘Likely to use if given access’; and (3) Negative ratings of ‘Bad effects’, ‘Depressed’, and ‘Anxious’.

Cardiovascular effect measures

During all three smoking sessions on day 6 and both choice sessions on day 7, cardiovascular effects were measured at the same time points subjective effects were determined with a GE Dash-3000 blood pressure monitor with a pulse oximetry attachment (GE Medical Systems, USA) and included: (1) BP (systolic and diastolic) and (2) HR.

Reinforcing effect measures

Reinforcement measures included: (1) a VAS rating on days 6 and 7, which asked participants ‘How much would you ‘pay’ for the dose you just received?’ and, (2) the number of ‘Choices’ made to smoke METH during the sessions on day 7.

Study medication

An IND was obtained from the FDA for the use of varenicline in this study. Varenicline and a matched placebo were obtained from Greenpark Compounding Pharmacy (USA). Varenicline was titrated and participants took two tablets twice daily on days 1–7 during all phases (Table 1). For the placebo phase, participants took placebo twice daily. For the 1 mg phase on days 1–3 and 7, participants took both 0.5 mg varenicline and placebo once daily and 0.5 mg twice daily on days 4–6. The 2 mg phase was similar except participants took 1 mg twice daily on days 5–6 and both 1 mg and placebo once daily on day 7. Sterile METH for human use was provided by a contractor for NIDA’s Drug Supply Program (RTI International, USA).

Table 1. Dosing Schedules

(a) Varenicline – Double Blinded & Randomized

<table>
<thead>
<tr>
<th>Varenicline (mg)</th>
<th>Days 1–3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
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<td>0 bid</td>
<td>0 bid</td>
</tr>
<tr>
<td>1</td>
<td>0 &amp; 0.5 qd</td>
<td>0.5 bid</td>
<td>0.5 bid</td>
<td>0.5 bid</td>
<td>0 &amp; 0.5 qd</td>
</tr>
<tr>
<td>2</td>
<td>0 &amp; 0.5 qd</td>
<td>0.5 bid</td>
<td>1 bid</td>
<td>1 bid</td>
<td>0 &amp; 1 qd</td>
</tr>
</tbody>
</table>

(b) METH – Single Blinded & Randomized (Day 6: 10 & 30 mg)

<table>
<thead>
<tr>
<th>METH (mg)</th>
<th>Day 6</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 10, &amp; 30</td>
<td>8:30</td>
<td>10:30</td>
</tr>
<tr>
<td>0 &amp; 10</td>
<td>0</td>
<td>10:30</td>
</tr>
<tr>
<td>0 &amp; 10</td>
<td>10:30</td>
<td>2:30</td>
</tr>
</tbody>
</table>

Statistical methods

The safety of varenicline was determined by comparing the proportion of participants who reported an AE during the three treatment phases by one-factor analysis of variance (ANOVA).

The most rigorous statistical tests for determining the effects of varenicline on the subjective and cardiovascular effects produced by METH are three-factor repeated measures ANOVAs with varenicline (0, 1, and 2 mg) and METH (0, 10, and 30 mg) doses as factors and time (0, 5, 15, 30, and 60) as the repeated factor. However, poor distribution of single-item VAS ratings at individual time points resulted in the majority failing normality and/or equivalence tests ($p < 0.05$). Collapsing data across time and comparing area under the curve (AUC) via two-factor ANOVAs (varenicline and METH) also resulted in the majority of the subjective and cardiovascular measures failing normality and/or equivalence tests. In contrast, comparing maximum absolute changes from baseline resulted in the majority of analyses passing normality and equivalence of two-factor ANOVAs. Consequently, we analyzed the maximum change from baseline. Additionally, because the most relevant contrasts identified a priori were the effects of...
varenicline within the 30 mg METH dose, we compared the effects of varenicline within the 30 mg METH dose with Bonferroni t tests for each ANOVA. Notwithstanding the analytical approach utilized herein, results from other analytical approaches are available upon request.

The effects of medication on reinforcement measures recorded on day 6 and during self-administration procedures on day 7 were determined using two-factor ANOVAs with varenicline (0, 1, and 2 mg) and METH (day 6: 0, 10, and 30 mg; day 7: 0 and 10 mg) doses as factors. Analysis of ‘pay’ data collected during day 7 only included the ratings collected after the non-contingent sample dose of METH was smoked.

Data were analyzed using SigmaPlot version 12.0. Significant findings were followed with Bonferroni t test method of pairwise multiple comparisons. To correct for multiple comparisons the significance level was set at $p<0.01$ for the five positive subjective measures, $p<0.025$ for the two craving subjective measures, and $p<0.017$ for the three negative subjective measures.

Results
Participants
Figure 1 shows the flow of participants through screening, randomization, and analyses. Twenty-six subjects were enrolled and 17 subjects completed all three phases. Eight of the non-completers withdrew of their own volition. The ninth non-completer was discharged on day 6 during his third (1 mg) phase because he did not meet preset cardiovascular criteria for METH to be administered. The 17 individuals who completed the study were predominantly Caucasian (71%) and male (71%). On average, participants used METH for 14 yr, and 88% currently used nicotine, 59% currently used alcohol, and 47% currently used cannabis (Table 2).

Safety
Table 3 indicates the AEs reported by participants during the three treatment phases. An ANOVA revealed that the proportion of participants who reported an AE during the 1 mg (53.3%) phase was significantly lower ($F_{1,28}=4.27; p=0.0482$) than the proportion who reported an AE during the placebo (86.7%) phase, but not the 2 mg (66.7%) phase. Headache was the most common AE reported by participants during the placebo (73.3%), 1 (33.3%), and 2 mg (53.3%) phases. Significantly fewer participants reported headaches during 1 mg vs. placebo ($F_{1,28}=5.36; p=0.0281$), although the average severity of headaches was not significantly different between placebo (1.20±0.32), 1 (1.50±0.50), and/or 2 mg (1.65±0.40) phases. There were no significant differences between any of the treatments on the frequency, severity, duration, or relatedness of any other AE. Importantly, no serious AEs were reported by participants during any of the treatment conditions.

Subjective effects
Positive measures
For ‘Any drug effect’ (Fig. 2a), although the effect of varenicline was not significant ($F_{2,32}=1.72; p=0.196$), there was a significant effect of METH ($F_{2,32}=27.83; p<0.001$) and a significant METH×varenicline interaction ($F_{4,152}=2.53; p=0.049$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 mg within 0, 1, and 2 mg varenicline ($p<0.001$), between 10 vs. 30 mg within 0 and 1 mg varenicline ($p<0.001$), and between 0 vs. 10 mg within 2 mg varenicline ($p=0.006$). Importantly, a priori planned comparisons within 30 mg METH revealed a significant difference between 0 vs. 2 mg varenicline ($p=0.002$), but not between 0 vs. 1 mg ($p=0.902$) or 1 vs. 2 mg varenicline ($p=0.047$).

For ‘High’ (Fig. 2b), the effect of varenicline was not-significant ($F_{2,32}=0.82; p=0.452$), but there was a significant effect of METH ($F_{2,32}=31.65; p<0.001$) and a significant METH×varenicline interaction ($F_{4,152}=2.55; p=0.047$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 mg within 0, 1, and 2 mg varenicline ($p<0.001$), between 10 vs. 30 mg within 0 and 1 mg varenicline ($p<0.001$), and between 0 vs. 10 mg within 2 mg varenicline ($p=0.008$). A priori planned comparisons within 30 mg METH revealed a significant difference between 1 vs. 2 mg varenicline ($p=0.006$), but not between 0 vs. 2 mg ($p=0.067$).

For ‘Stimulated’ (Fig. 2c), there was a significant effect of METH ($F_{2,32}=19.58; p<0.001$), although the effect of varenicline ($F_{2,32}=2.34; p=0.107$), and the METH×varenicline interaction were not significant ($F_{4,152}=1.53; p=0.205$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 mg within 0, 1, and 2 mg varenicline ($p=0.002$) and between 0 vs. 10 mg ($p=0.004$), but not between 10 vs. 30 mg ($p=0.030$).
Any drug effect, a priori planned comparisons within 30 mg METH revealed a significant difference between 0 vs. 2 mg varenicline ($p=0.009$).

For ‘Drug liking’ (Fig. 2d), there was a significant effect of METH ($F_{2,32}=25.46; p<0.001$) but not a significant effect of varenicline ($F_{2,32}=0.11; p=0.898$) or a
significant METH × varenicline interaction ($F_{4,152} = 2.29; p = 0.068$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 mg within 0, 1, and 2 mg varenicline ($p < 0.001$) and between 10 vs. 30 mg within 0 and 1 mg varenicline ($p < 0.001$). A priori planned comparisons within 30 mg METH revealed no differences between 0 vs. 2 mg ($p = 0.064$) or between other doses of varenicline.

For ‘Good effects’ (Fig. 2c), there was a significant effect of METH ($F_{2,32} = 31.73; p < 0.001$) but not a significant effect of varenicline ($F_{2,32} = 0.43; p = 0.653$) or a significant METH × varenicline interaction ($F_{4,152} = 1.504; p = 0.212$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 mg within 0, 1, and 2 mg varenicline ($p < 0.001$), between 10 vs. 30 mg within 0 and 1 mg varenicline ($p = 0.002$), and between 0 vs. 10 mg within 0 and 2 mg varenicline ($p < 0.003$). A priori planned comparisons within 30 mg METH revealed that differences between 0 vs. 2 mg varenicline did not reach statistical significance ($p = 0.103$).

Craving measures

For ‘Desire’ there were no significant effects of METH ($F_{2,32} = 2.87; p = 0.071$) or varenicline ($F_{2,32} = 0.56; p = 0.578$), and no significant METH × varenicline interaction ($F_{4,152} = 0.61; p = 0.661$). A priori planned comparisons within 30 mg METH revealed no significant differences between varenicline doses ($p = 1.00$).

For ‘Likely to use if given access’, there were no significant effects of either METH ($F_{2,32} = 0.49; p = 0.617$) or varenicline ($F_{2,32} = 0.28; p = 0.758$), and no significant METH × varenicline interaction ($F_{4,152} = 0.15; p = 0.962$). Similar to ‘Desire’, a priori planned comparisons within 30 mg METH revealed no significant differences between varenicline doses ($p = 1.00$).

Negative measures

For ‘Bad Effects’ there was a significant effect of METH ($F_{2,32} = 9.51; p < 0.001$) but not a significant effect of varenicline ($F_{2,32} = 0.73; p = 0.703$) or a significant METH × varenicline interaction ($F_{4,152} = 0.40; p = 0.114$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 mg METH within 1 mg varenicline ($p = 0.001$). A priori planned comparisons within 30 mg METH revealed no significant differences between varenicline doses ($p > 0.60$).

For ‘Depressed’ there was a significant effect of METH ($F_{2,32} = 6.57; p = 0.004$) but not a significant effect of varenicline ($F_{2,32} = 0.56; p = 0.577$) or a significant METH × varenicline interaction ($F_{4,152} = 1.73; p = 0.154$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 mg METH ($p = 0.003$). A priori planned comparisons within 30 mg METH revealed no significant differences between varenicline doses ($p > 0.40$).

Finally, for ‘Anxious’ there were no significant effects of either METH ($F_{2,32} = 0.80; p = 0.458$) or varenicline ($F_{2,32} = 0.19; p = 0.828$), and no significant METH × varenicline interaction ($F_{4,152} = 1.94; p = 0.114$). A priori planned comparisons within 30 mg METH revealed no significant differences between varenicline doses ($p > 0.10$).
Cardiovascular effects

For heart rate (Fig. 3a), there was a significant effect of METH ($F_{2,32}=24.74; p<0.001$) but not a significant effect of varenicline ($F_{2,32}=0.96; p=0.393$) or a significant METH×varenicline interaction ($F_{4,152}=0.60; p=0.667$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 mg within 0, 1, and 2 mg varenicline ($p<0.001$) and between 10 vs. 30 mg within 0, 1 and 2 mg varenicline ($p<0.004$). A priori planned comparisons within 30 mg METH revealed no significant differences between varenicline doses ($p>0.30$).

For systolic BP (Fig. 3b), there was a significant effect of METH ($F_{2,32}=44.84; p<0.001$) but not a significant effect of varenicline ($F_{2,32}=0.37; p=0.696$) or a significant METH×varenicline interaction ($F_{4,152}=1.15; p=0.340$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 within 0, 1, and 2 mg varenicline ($p<0.001$), between 10 vs. 30 within 0 mg varenicline ($p<0.001$), and between 0 vs. 10 mg within 0, 1, and 2 mg varenicline ($p<0.016$). A priori planned comparisons within 30 mg METH revealed no significant differences between varenicline doses ($p>0.18$).

For diastolic BP (Fig. 3c), there was a significant effect of METH ($F_{2,32}=36.41; p<0.001$) but not a significant effect of varenicline ($F_{2,32}=0.01; p=0.993$) or a significant METH×varenicline interaction ($F_{4,152}=1.67; p=0.168$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 within 0, 1, and 2 mg varenicline ($p<0.004$), between 10 vs. 30 within 1 mg varenicline ($p<0.001$), and between 0 vs. 10 mg within 0 mg varenicline ($p=0.11$). A priori planned comparisons within 30 mg METH revealed no significant differences between varenicline doses ($p>0.40$).

Reinforcing effects

For day 6 ratings of ‘How much would you ‘pay’ for the dose you just received?’ (Fig. 4a), there was a significant effect of METH ($F_{2,32}=46.49; p<0.001$) but not a significant effect of varenicline ($F_{2,32}=0.21; p=0.810$) or a significant METH×varenicline interaction ($F_{4,152}=0.26; p=0.900$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 30 mg within 0, 1, and 2 mg varenicline ($p<0.001$), between 10 vs. 30 mg within 0, 1, and 2 mg varenicline ($p<0.001$), and between 0 vs. 10 mg ($p=0.008$). A priori planned comparisons within 30 mg METH revealed no significant differences between varenicline doses ($p>0.90$).

For day 7 ratings of ‘How much would you ‘pay’ for the dose you just received?’ (Fig. 4b), there was a significant effect of METH ($F_{1,16}=55.15; p<0.001$) but not a significant effect of varenicline ($F_{2,32}=0.99; p=0.379$) or a significant METH×varenicline interaction ($F_{2,101}=0.99; p=0.382$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 10 mg within 0, 1, and 2 mg varenicline ($p<0.001$). A priori planned comparisons within 30 mg METH revealed no differences between 0 vs. 2 mg ($p=0.219$), or other doses of varenicline.

For day 7 number of ‘Choices’ made to smoke METH (Fig. 4c), there was a significant effect of METH ($F_{1,16}=118.78; p<0.001$) but not a significant effect of varenicline ($F_{2,32}=0.24; p=0.789$) or a significant METH×varenicline interaction ($F_{2,101}=0.07; p=0.935$). Post-hoc comparisons of METH revealed significant differences between 0 vs. 10 mg within 0, 1, and 2 mg varenicline ($p<0.001$). A priori planned comparisons within 30 mg METH revealed no differences between doses of varenicline ($p>0.90$).

Discussion

This is the first study to examine the safety and subjective effects of short-term oral varenicline treatment in non-treatment-seeking METH-dependent volunteers. We
found that smoked METH increased positive subjective effects ratings, which agrees with previous reports for intranasal (Rush et al., 2011), intravenous (De La Garza et al., 2012), and smoked (Perez-Reyes et al., 1991) routes of administration. Relative to placebo, treatment with 2 mg varenicline reduced all of the positive subjective ratings produced by 30 mg METH, although this reduction only reached significance for two of the five. Varenicline had minimal effects on cardiovascular measures and co-administration of varenicline with METH was well tolerated, safe, and not associated with neuropsychiatric or dose-dependent AEs.

The dose-dependent effects of varenicline reported here are in agreement with the enhanced reductions in tobacco withdrawal symptoms observed with the 2 mg vs. 1 mg dose (Cahill et al., 2011). In fact, after only 2 full days of treatment with 2 mg, varenicline significantly attenuated the positive subjective effects produced by smoked METH, which is encouraging given that the standard regimen for tobacco cessation is 12 wk, and blunted responses to cigarette cues are demonstrated after 3 wk of treatment, although earlier time-points were not evaluated (Franklin et al., 2011). This suggests that the efficacy of varenicline to reduce METH-induced effects may be enhanced when a longer treatment regimen is used, particularly in treatment-seeking addicts enrolled in an outpatient protocol.

The efficacy of varenicline to attenuate the positive effects of METH exceeds that of bupropion (Newton et al., 2006), and bupropion was subsequently found to reduce METH use among relatively less frequent METH users in outpatient clinical trials (Elkashef et al., 2008; Shoptaw et al., 2008). Related to our data, the results of a preliminary clinical trial demonstrated that varenicline (2 mg/d for 8 wk) tended to decrease cocaine use in cocaine-dependent volunteers (Plebani et al., 2012). Similarly, preliminary findings from an outpatient clinical trial by Shoptaw and colleagues suggest that varenicline (2 mg/d for 8 wk) enhanced retention and abstinence rates in METH-dependent volunteers (Brensifer et al., 2013).

We also evaluated the reinforcing effects of METH using a choice paradigm. As previously reported for intravenous METH (De La Garza et al., 2008a, 2012) smoked METH was significantly more reinforcing than placebo. However, varenicline treatment did not reduce total choices for METH, which is also in agreement with other cholinergic (De La Garza et al., 2008a, 2012) as well as putative dopaminergic (De La Garza et al., 2010) treatments that, on the one hand, reduce the subjective effects of METH, but on the other hand, do not reduce total choices for METH. We have previously postulated that short-term treatment protocols typically utilized for phase I clinical trials can be effective for changing how an individual perceives the effects of a drug (i.e. subjective effects), but may not be sufficient to change drug-seeking behavior (i.e. choices to receive a drug during self-administration) (De La Garza et al., 2008a). This is not unexpected as several research groups also report divergences between subjective vs. reinforcing effects produced by METH (Hart et al., 2001) and cocaine (Haney et al., 1999; Sofuoglu et al., 2000). In fact, given that the individuals enrolled in this and other phase I clinical trials are not seeking treatment for their drug use, it is not surprising that they typically choose drug over a small amount of monetary compensation.

Although behavioral treatments, including cognitive behavioral therapy and contingency management are available (Lee and Rawson, 2008), they are only modestly effective in reducing METH use. Similarly, although direct DA agonist treatments reduce both subjective effects and use of METH to some extent (Tiihonen et al., 2007; Longo et al., 2010), their therapeutic potential is limited.
by the possibility of abuse. Medications that have no abuse liability but are efficacious in reducing METH use could be integrated with behavioral therapies, which would represent a significant advancement in novel treatments for METH dependence. The current results suggest that varenicline, or other treatments that enhance cholinergic neurotransmission, may be a promising way to support treatments for METH dependence.

ACh-induced activation of laterodorsal tegmentum muscarinic and nACh receptors increases both, neuronal firing of ventral tegmental area (VTA) DA cell bodies (Omelchenko and Sesack, 2006), and DA release (Dobbs and Mark, 2012). Moreover, nACh receptor β2 subunit knockout mice exhibit a global decrease in the excitability of midbrain DA neurons (Mameli-Engvall et al., 2006) and inactivation of the laterodorsal tegmentum decreases burst firing of DA neurons (Grace et al., 2007). In fact, accumulating evidence suggests that the abuse-related behavioral effects of METH are mediated by cholinergic activation of the laterodorsal tegmentum. For example in rodents, systemic METH administration increases both DA and ACh in the VTA (Dobbs and Mark, 2008), and interactions between DA and ACh within the VTA and nucleus accumbens mediate, at least in part, the rewarding and locomotor activating properties of METH (Taguchi et al., 1998). In humans, although a potential compensatory up-regulation of the vesicular ACh transporter appears to maintain homeostasis of neuronal cholinergic activity in METH addicts (Siegal et al., 2004), post-mortem data indicate that choline acetyltransferase, a presynaptic enzyme necessary for catalyzing the synthesis of ACh, is down-regulated in heavy METH users (Kish et al., 1999). Thus the ability of varenicline to elicit a moderate increase of mesolimbic DA, by acting as a partial agonist at α4β2 nACh receptors, may underlie its ability to attenuate the positive subjective effects of METH. Through this mechanism coupled with its moderately stimulating effects (Cahill et al., 2011), longer-term varenicline treatment may decrease craving and withdrawal symptoms by counteracting the dopaminergic hypofunction that occurs in the striatum during METH withdrawal (Volkow et al., 2001). In fact, given that decreased methylphenidate-induced DA release during withdrawal is predictive of relapse to METH use (Wang et al., 2012), it would be interesting to determine whether varenicline treatment ultimately normalizes pharmacologically-induced striatal DA release in METH addicts.

Potential limitations

Whereas this is the first study to show the efficacy of varenicline to reduce the positive subjective effects of smoked METH, the sample size was relatively small. Importantly however, the within-subject design of this study maximized statistical power and a power analysis was calculated a priori assuming a low correlation (0.3) among conditions (Cohen, 1988) and indicated a within-subjects sample of $n=16$ per condition would allow detection of medium to large effects (approximately $d=0.80$) when comparing groups, with power=0.81 and one-tailed alpha=0.05 (Cohen, 1988). Indeed, this effect size was similar to differences between placebo and experimental conditions from our recently published data concerning the effects of bupropion (Newton et al., 2005, 2006) and rivastigmine (De La Garza et al., 2008a,b) on subjective and cardiovascular responses produced by METH.

Using a within-subjects design, we recently compared the subjective and cardiovascular effects produced by smoked vs. intravenous METH ($n=16$) and found differences only on subjective ratings associated with craving, but not on the positive subjective measures (Mahoney et al., 2013). Nonetheless, the possibility remains that the outcome measures could have been influenced because METH was smoked in the current study and 7 of the participants did not typically smoke METH when they used outside of the laboratory (Table 2).

Finally, although smoking sessions were conducted carefully to maintain the single blind, the lack of an FDA-approved placebo for METH may limit validity/interpretation of the 0 mg METH condition. However, it seems unlikely that smoking any non-psychoactive substance would have significantly affected the results, especially as 0 (empty pipes), 10, and 30 mg METH dose-dependently affected the positive subjective ratings (Fig. 2). Nonetheless, the 0 mg METH data should be interpreted with appropriate caution.

Summary

In summary, our results suggest that the nAChR system holds promise as a medication target for METH use disorders. In METH-dependent participants we found that, despite short-term treatment, varenicline attenuated the positive subjective effects produced by smoked METH. Given that short-term treatment with varenicline was well tolerated among active METH users, alone and in combination with METH, clinical trials examining varenicline as a primary treatment for METH dependence and as a potential dual treatment for METH and nicotine dependence should continue to be explored.

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