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The effects of varenicline on methamphetamine self-administration and drug-primed reinstatement in female rats

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Abstract

While research has revealed heightened vulnerability to meth addiction in women, preclinical models rarely use female subjects when investigating meth seeking and relapse. The goal of the present study was to examine the effects of varenicline (Chantix[®]), a partial $\alpha 4\beta 2$ and full $\alpha 7$ nicotinic acetylcholine receptor agonist, on meth self-administration and reinstatement in female rats. Sprague-Dawley rats were surgically implanted with an indwelling jugular catheter. Half of the rats were then trained to self-administer meth (0.056 mg/kg/infusion) on a variable ratio 3 schedule of reinforcement; the other half earned intravenous saline during daily, 2 hour sessions. When responding stabilized, varenicline (0.0, 0.3, 1.0, 3.0 mg/kg) was tested to determine how it altered meth taking. Varenicline was probed on 4 test days; each test separated by 2 standard self-administration sessions to assure responding remained stable. Following this testing was 15 extinction sessions. Twenty-four hours after the last extinction session were four consecutive days of meth-primed reinstatement. The same 4 doses of varenicline were examined to determine how it altered reinstatement triggered by 0.3 mg/kg meth (IP). Rats readily self-administered meth. The higher doses of varenicline did not affect meth-taking in a specific fashion as active lever pressing was also slightly reduced in rats that has access to saline in the self-administration phase. Female rats displayed robust meth-primed reinstatement. Notably, the lower doses of varenicline increased meth-primed reinstatement. This amplified susceptibility to reinstatement (i.e., relapse) may be an impediment for the use of varenicline as a therapeutic to treat meth use disorder.

Keywords

Relapse; Chantix[®]; Stimulant Abuse; Nicotinic Acetylcholine Receptor

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Authors contribution

All authors contributed significantly to the construction of the experimental design, data acquisition, and manuscript preparation. All authors have read and approved this manuscript.

Conflicts of interest

There are no conflicts of interest to report.

1. Introduction

Long-term abuse of methamphetamine (meth) can result in severe dental problems, malnutrition, damage to the cardiovascular system, memory loss, psychotic behavior (including paranoia, hallucinations, and delusions), anxiety, confusion, insomnia, mood disturbances, and violent behavior (National Institute on Drug Abuse, 2013). These health problems last for months to years following cessation of use (Volkow *et al*, 2001a). Despite the well-documented dangers of meth use, over 12 million people in the United States (4.7% of the population) report using meth at least once (Substance Abuse and Mental Health Services Administration, 2013) and 1.2 million people report using in the past year (Substance Abuse and Mental Health Services, 2013). Hospital emergency departments reported over 102,000 cases in which patients were admitted for meth-related issues, representing 8.2% of all emergency room visits for illicit drugs (Center for Behavioral Health Statistics and Quality, 2013). In addition to the health impact of meth use, the economic burden to society is quite high. The RAND corporation estimates the cost to the United States to be as high as \$48.3 billion (Nicosia *et al*, 2009). The well-documented negative health consequences of chronic meth use, in conjunction with the high economic strain to society, make the search for effective meth treatments a priority (Brackins *et al*, 2011).

Treatments for meth dependence remain inadequate, with the majority of addicts returning to use within 6 months of treatment (Brackins *et al*, 2011; Brecht *et al*, 2004). Identification of medications and/or targets efficacious in reducing meth-taking or prolonging abstinence are critical to establishing more effective treatments. Dopaminergic hypofunction during drug abstinence likely contributes to meth dependence (Volkow *et al*, 2001b). Some medications (e.g., bupropion, modafinil, dextroamphetamine, rivastigmine) that assist in recovery of dopaminergic function following meth abuse are potential therapeutics for meth cessation (De La Garza *et al*, 2012; De La Garza *et al*, 2010; Elkashef *et al*, 2008; Heinzerling *et al*, 2014; Longo *et al*, 2010; McGregor *et al*, 2008; Newton *et al*, 2005, 2006; Rau *et al*, 2005; Reichel *et al*, 2008; Reichel *et al*, 2009; Verrico *et al*, 2013; Volkow *et al*, 2009). Activation of nicotinic acetylcholine receptors (nAChRs) increases dopamine release (Dobbs and Mark, 2012). Medications known to increase acetylcholine via acetylcholinesterase inhibition reduced the positive subjective effects of meth in humans (De La Garza *et al*, 2008a; De La Garza *et al*, 2012; De La Garza *et al*, 2008b) and decreased meth-primed reinstatement (i.e., pre-clinical model of relapse) in rats (Hiranita *et al*, 2006; Hiranita *et al*, 2008).

With these mechanisms in mind, varenicline is of potential interest. Varenicline is a partial $\alpha 4\beta 2$ and full $\alpha 7$ nAChR agonist (Coe *et al*, 2005a; Coe *et al*, 2005b; Gonzales *et al*, 2006; Mihalak *et al*, 2006; Smith *et al*, 2007) currently approved by the United States Food and Drug Administration for treatment of nicotine dependence under the trade name Chantix®. As detailed in Table 1, pretreatment with varenicline reduces nicotine self-administration in pre-clinical models, (see Table 1; Chang *et al*, 2015; Costello *et al*, 2014; Funk *et al*, 2015; George *et al*, 2011; Goeders *et al*, 2012; Hall *et al*, 2015; Le Foll *et al*, 2012; Mello *et al*, 2014; O'Connor *et al*, 2010; Panlilio *et al*, 2015; Rollema *et al*, 2007; Scuppa *et al*, 2015; Wouda *et al*, 2011). Similarly, some studies have reported reduced intake of ethanol (see

Table 2; Feduccia *et al*, 2014; Ginsburg and Lamb, 2013; Hendrickson *et al*, 2010; Kamens *et al*, 2010; Kaminski and Weerts, 2014; Randall *et al*, 2015; Sotomayor-Zárate *et al*, 2013; Steensland *et al*, 2007; Wouda *et al*, 2011). Interestingly, other published reports have either shown no effect on ethanol intake (Scuppa *et al*, 2015), or an increase in ethanol intake at certain doses (Ginsburg and Lamb, 2013). Pre-clinical research is also mixed regarding the effects of varenicline on cocaine self-administration (see Table 3), with investigators reporting a decrease in intake (Guillem and Peoples, 2010), no effect on intake (Mello *et al*, 2014), or an increase in cocaine intake (Gould *et al*, 2011). As for meth, varenicline reduced the positive subjective effects of meth in humans; an effect possibly mediated by increased mesolimbic dopamine via nAChR agonism (Verrico *et al*, 2014; Zorick *et al*, 2009). This latter finding, combined with the successful preclinical work with other abused drugs just described, has led to the suggestion that varenicline may be a potential pharmacotherapy for meth abuse (Verrico *et al*, 2014; Zorick *et al*, 2009). Albeit feasible, there remains a clear need for basic research determining the efficacy of this suggested treatment.

While converging evidence indicates that women are particularly susceptible to meth dependence (Brecht *et al*, 2004; Dluzen and Liu, 2008; Hser *et al*, 2005; Lin *et al*, 2004; Rawson *et al*, 2005; Westermeyer and Boedicker, 2000; Wu *et al*, 2007), preclinical animal research on meth rarely uses female subjects (Cox *et al*, 2013; Holtz *et al*, 2012; Kucerova *et al*, 2009; Reichel *et al*, 2012; Roth and Carroll, 2004). This situation leaves a critical need for basic science research on meth-taking/seeking in females. The goal of the present research was to help address this dearth by examining the effects of a range of varenicline doses on meth self-administration (i.e., intake) and meth-primed reinstatement (i.e., relapse) in female rats.

2. Materials and Methods

2.1.1 Subjects

Female Sprague-Dawley rats (n=20), approximately 9 weeks of age, were purchased from Harlan Laboratories Inc. (Indianapolis, IN, USA). Rats were housed individually in clear polycarbonate cages (35.5 × 32 × 18 cm; length × width × depth). TEK-Fresh® cellulose bedding lined the cages. Rats had *ad libitum* access to water in the home cages. Following acclimation to the colony, rats were food restricted to maintain them at 90% of their free feeding weight. The colony room was maintained on a daily 6:00 AM lights on to 6:00 PM lights off cycle. This study was conducted during the light portion of this cycle. The protocols were approved by the University of Nebraska-Lincoln Institutional Animal Care and Use Committee.

2.1.2 Apparatus

For the present study, we used 10 conditioning chambers (ENV-008CT; Med Associates, Georgia, VT, USA) enclosed in sound-attenuating cubicles. Chambers measured 30.5×24.1×21.0 cm. A variable-speed syringe pump (PMH-100VS; Med-Associates) was located outside each cubicle. Tygon® tubing was threaded from the pump syringe, through a leash, into the chamber where it was to be attached to the catheter port on the back of the rat. A recessed receptacle (5.2×5.2×3.8 cm) was centered on one sidewall of each chamber. A

dipper arm, when raised, provided access to 0.1 ml of 26% (w/v) sucrose in this recessed receptacle. Two retractable levers were located on each side of the receptacle. A white cue light (2.54-cm diameter; 28V, 100-mA) was mounted 7 cm above each lever. A house light (two white 28V, 100-mA lamps) was located in the cubicle, 10 cm above the Perspex chamber ceiling. An infrared emitter/detector unit was located 4 cm above the rod floor and 14.5 cm from the side wall containing the receptacle. The number of times this beam was broken provided a measure of chamber activity.

2.1.3 Drugs

(+)-Methamphetamine hydrochloride obtained from Sigma-Aldrich (St. Louis, MO, USA) was dissolved in 0.9% sterile saline. Meth was infused intravenously at 35.74 μ l over 1 sec at 0.056 mg/kg/infusion. Meth for drug-primed reinstatement was administered by intraperitoneal (IP) injections at 0.3 mg/kg. Dose for self-administration and drug-primed reinstatement were based on previous research (Duryee *et al*, 2009; Reichel *et al*, 2012). Varenicline tartrate was generously provided by NIDA (RTI, Research Triangle Park, NC, USA). Varenicline was dissolved in 0.9% saline and injected IP. All doses are reported as salt weight.

2.2.1 Preliminary Lever Training

Rats were trained to lever press following colony acclimation and food restriction. Sessions began with illumination of the house light and insertion of one of the two levers (randomly selected). Following a lever press, or a lapse of 15 sec, sucrose was available for 4 sec, the lever was retracted, and a timeout commenced (average duration=60 sec; range 30-89 sec). Following the timeout, these procedures were repeated with the caveat that the same lever was not presented more than twice consecutively. Sessions were completed when the rat received 60 sucrose deliveries; 65 to 80 min depending on individual performance. Rats were trained until a lever press was made on at least 80% of lever insertions. All rats met criterion between sessions 3 to 5.

2.2.2 Catheter Surgery and Recovery

Indwelling jugular catheters were implanted using our standard protocol [previously described in (Charntikov *et al*, 2013)]. Briefly, rats were anesthetized with a 1 ml/kg intramuscular (IM) injection of a 2:1 ratio cocktail of ketamine HCl (100 mg/ml) and xylazine HCl (20 mg/ml) and then prepared for surgery and catheter implantation. Following surgery, rats were administered buprenorphine (0.1 mg/kg, SC) for pain management and atipamezole (0.5 mg/kg, IM) to terminate anesthesia. Buprenorphine was again administered 24 h post-surgery. Rats were allowed to recover for 7 days. During recovery, they remained in their home cages and catheters were flushed daily with a cocktail of 0.2-ml baytril (5.0 mg/ml) and heparin (30 Units/ml). Catheter patency was checked on the last day of recovery by IV infusion of 0.05-ml xylazine (20 mg/ml). Rats that displayed motor ataxia within 20 sec were considered patent(Charntikov *et al*, 2013; Reichel *et al*, 2008). Patency was again checked after completion of the self-administration phase; 3rats(saline group) were excluded from the study and analyses for not having patent catheters.

2.2.3 Post-Surgery Training

Following recovery, rats were placed on a variable ratio 3 (VR3) schedule of sucrose reinforcement. Under the VR3 schedule, on average every 3rd lever press (range 1 to 5) was followed by 4-sec access to sucrose. Levers were again inserted individually with the condition that the same lever was not inserted more than 2 times in a row. These procedures produced robust responding with both levers having a similar reinforcement history. This training lasted for 3 daily 1-h sessions conducted on consecutive days. On session 3, all rats earned more than 80% of the 60 possible sucrose deliveries.

2.2.4 Self-administration

Prior to this phase, rats were randomly assigned to 1 of 2 IV solutions: meth or saline. This produced 2 separate groups: meth (n=10) and saline (n=7 after loss from patency tests). Rats were randomly assigned which of the two levers served as the active (meth or saline infusion) vs. inactive lever. Sessions were 120 min and conducted daily, 7 days per week. Before a rat was attached to the leash/tubing at the start of each session, the catheter was flushed with 0.2-ml heparin (30 Units/ml) in sterile saline. The session commenced with insertion of both levers and priming of the catheter with meth or saline [ca. 31 µl (90% of internal catheter volume)]. Requisite VR3 responding on the active lever initiated an infusion of meth (0.056 mg/kg/infusion) or saline, retraction of both levers, and illumination of the house light for a 20-sec timeout. Following the timeout, both levers were extended and the house light was terminated. Responding on the inactive lever was recorded but had no programmed outcome. After each session, the catheter was flushed with a 0.2-ml cocktail of baytril (5.0 mg/ml) and heparin (30 Units/ml) in sterile saline. Rats received 19 self-administration sessions before testing varenicline.

2.2.5 Effects of Varenicline on Self-administration

In this phase, we examined the effects of varenicline [0.0 (saline), 0.3, 1, and 3 mg/kg] on meth and saline self-administration. The order in which doses were tested for each rat was pseudo-randomly assigned via a Latin-square design. Each test of varenicline was separated by at least 2 standard self-administration sessions. Meth rats were only tested if they reached criteria of no more than 20% variance in active lever presses between the two intervening self-administration sessions and at least 80% of baseline active lever responding. Baseline in this phase was the average of the last 2 self-administration sessions before starting varenicline testing. Saline rats were not required to meet these criteria because their low response rate meant that a change in 1 or 2 presses often reflected a substantial change in percentage of responding. Only 1 rat did not meet criteria. Just 1 additional training day was needed for this rat to meet criteria and, hence, be tested. Varenicline test sessions were similar to self-administration sessions except the assigned dose of varenicline was administered IP 20 min before the session. After rats were tested on all varenicline doses, 2 additional self-administration sessions were given to verify stable responding before starting the extinction phase 24 h later.

2.2.6 Extinction

Extinction sessions were similar to self-administration sessions except meth and saline were no longer infused. Requisite VR3 responding on the active lever still produced the same cues and the timeout. Extinction was conducted daily for 15 consecutive sessions.

2.2.7 Effects of Varenicline on Meth-Primed Reinstatement

Following 24 h after the last extinction session, rats began varenicline testing against meth-primed reinstatement. The same 4 doses of varenicline (0.0, 0.3, 1, and 3 mg/kg) were examined. The order of testing was again pseudo-randomly assigned via a Latin-square design. Reinstatement was tested across 4 consecutive days. Reinstatement sessions were identical to extinction session except they were truncated to 70 min. This decision was based on unpublished data from our lab using similar training protocols revealing that nearly all responding evoked by a meth-prime occurred in the first 70 min of the reinstatement session. Rats received their assigned dose of varenicline 20 min before the start of the session and then received a 0.3 mg/kg dose of meth 15 min before the session began.

2.3 Data Analyses

Analyses of active lever-pressing and locomotor activity during the self-administration and the extinction phase were performed using two-factor ANOVAs with Group (meth vs. saline) as a between-subjects factor and Sessions as a within-subjects factor. Data from both varenicline testing phases were analyzed using two-factor ANOVAs with Group and a between-subjects factor and Dose as a within-subjects factor. For all analyses, significant main effects or interactions were followed by post-hoc pairwise comparisons. All pairwise comparisons employed the Holm-Bonferroni method for controlling the family-wise error rate with significance set at $p < 0.05$ (Holm, 1979).

On a few occasions there were inconsistent and high counts from a few of the infrared beams in different phases of the experiment. Exclusions of locomotor data were determined by outlier analyses using Tukey's hinges. One rat (saline) was excluded in the self-administration phase, one rat was excluded from analyses in the extinction phase (saline), and one was excluded from reinstatement (saline) phase.

3. Results

3.1 Self-administration

Analysis of active lever-pressing (Figure 1A) revealed significant main effects of Group [$F(1,15)=27.2$; $p < 0.001$] and of Session [$F(18,270)=10.5$; $p < 0.001$], as well as a Group $\times$ Session interaction [$F(18,270)=6.32$; $p < 0.001$]. Post-hoc analyses on the interaction revealed significantly higher active lever-pressing in saline rats than meth rats on session 1 ($p=0.023$); this pattern substantively reversed with higher active lever-pressing in meth rats than saline rats on sessions 3 through 19 ($p=0.048$). Inactive lever responding for both groups was near zero throughout the experiment (data not shown). The mean number of inactive responses ($\pm$ SEM) on the last 3 days of self-administration for the saline group was 2.19 presses (± 0.68) and for the meth group was 8.33 responses (± 2.15).

In the initial self-administration phase, analysis of locomotor activity (Figure 1B) revealed a main effect of Group [$F(1,14)=8.76$; $p=0.010$], a main effect of Session [$F(18,252)=2.85$; $p<0.001$], and a Group $\times$ Session interaction [$F(18,252)=1.73$; $p=0.035$]. Post-hoc analyses on the interaction suggests that the locomotor effects of meth intake decreased across sessions. Specifically, activity in the meth rats was higher than saline rats across sessions 1 through 10, and on session 14 ($p=0.045$).

3.2 Effects of Varenicline on Self-administration

Analysis of active lever-pressing (Figure 2A) revealed a significant effect of Group [$F(1,15)=91.1$; $p<0.001$] and of Dose [$F(3,45)=5.85$; $p=0.002$], but no interaction [$F<1$]. The main effect of Group indicated that active lever-pressing remained higher in meth than saline rats. Post-hoc tests on the main effect of Dose revealed a significant decrease in active lever-pressing by 1.0 and 3.0 mg/kg varenicline relative to saline ($p=0.017$), and significantly lower active lever-pressing with the 3.0 mg/kg dose relative to the 0.3 mg/kg dose ($p=0.047$).

For locomotor activity (Figure 2B), neither main effect [$F(1,14)=2.16$; $p=0.106$] nor the interaction [$F<1$] was significant. Continuing the trend seen earlier of meth no longer increasing chamber activity. Further, pretreatment with varenicline had no detectable effect on activity.

3.3 Extinction

Analysis of active-lever pressing (Figure 3A) revealed main effects of Group [$F(1,15)=7.18$; $p=0.017$] and of Session [$F(14,210)=8.33$; $p<0.001$], as well as a significant Group $\times$ Session interaction [$F(14,210)=8.30$; $p<0.001$]. Active lever-pressing was higher in the meth than saline rats across sessions 1 to 3 and 5 to 8.

Analysis of locomotor activity (Figure 3B) found a main effect of Session [$F(14,196)=4.83$; $p<0.001$]. The main effect of Group [$F<1$] and the Group $\times$ Sessions interaction [$F(14,196)=1.55$; $p=0.098$] were not significant. For the main effect of Group, activity was higher on session 1 compared to sessions 6 and 9, and higher activity on sessions 12 and 13 relative to sessions 4 and 6-9 ($p=0.039$).

3.4 Effects of Varenicline on Meth-Primed Reinstatement

Analysis of active lever-pressing (Figure 4A) revealed a main effect of Group [$F(1,15)=11.2$; $p=0.004$] and a main effect of Dose [$F(3,45)=12.5$; $p<0.001$]; the interaction was not significant [$F<1$]. The main effect of Group reflects the increased lever pressing triggered by meth (i.e., reinstatement). For the main effect of Dose, the 0.3 and 1.0 mg/kg doses of varenicline enhanced active lever pressing relative to saline or 3.0 mg/kg varenicline ($p=0.008$).

Analysis of locomotor activity (Figure 4B) revealed a main effect of Dose [$F(3,42)=3.91$; $p=0.015$]. The main effect of Group [$F(1,14)=3.27$; $p=0.092$] and the interaction [$F<1$] were not significant. Post-hoc analyses found higher locomotor activity at the 0.3 and 1.0 mg/kg varenicline doses compared to 3.0 mg/kg ($p=0.047$). Notably, no differences were detected between any varenicline dose and saline ($p=0.285$).

4. Discussion

In the present study, we found that female rats readily self-administered meth (0.056 mg/kg/inf) on a VR3 schedule, displaying robust active-lever responding for meth compared to responding for saline with the same timeout stimuli. Further, varenicline (1 and 3 mg/kg) slightly but significantly reduced active lever responding regardless of whether IV meth and saline was available in the self-administration phase. Additionally, when varenicline (0.3 and 1 mg/kg) was tested during meth-primed reinstatement, active lever responding was non-specifically increased suggesting that varenicline may, in fact, increase relapse-related behaviors. As discussed later, this finding casts concern on the use of varenicline to treat meth addiction in females.

As discussed in the Introduction and outlined in Tables 1 to 3, self-administration of nicotine, ethanol, and cocaine can be reduced by varenicline pretreatment. However, along with some studies reporting no effect or enhanced drug self-administration, there are reports that also find a non-specific effect of varenicline. Such non-specific effects include a reduction in inactive lever responding (Chang *et al*, 2015; George *et al*, 2011), a decrease in locomotor activity (Randall *et al*, 2015), or an attenuation of responding maintained by a non-drug reinforcer (Ginsburg and Lamb, 2013; Gould *et al*, 2011; O'Connor *et al*, 2010). Consistent with these latter reports, we found a non-specific effect of varenicline pretreatment in the self-administration phase of the present study; active lever pressing was reduced in the saline condition in a manner similar to the meth condition.

Presumably, active lever responding in the saline condition was maintained by the weak reinforcing effects of timeout stimuli (cf. Caggiula *et al*, 2009; Chaudhri *et al*, 2006b; Palmatier *et al*, 2006). Perhaps varenicline blocked the weak reinforcing effects of the sensory stimuli used in the time out. Alternatively, the weak and transient reduction in active lever pressing during self-administration may reflect nausea induced by varenicline. Nicotinic acetylcholine receptor agonists like nicotine commonly have initial nauseating effects that can condition taste aversions and induce hypolocomotion in rats (Iwamoto and Williamson, 1984; Kumar *et al*, 1983; Malcolm *et al*, 2015; Reavillet *et al*, 1990; Rinker *et al*, 2008; Shoaib *et al*, 2003; Slemmer *et al*, 2000; Stoleran *et al*, 1997). Although we did not see hypolocomotion with varenicline pretreatment, such an observation may have been obscured by the already quite low activity in the saline pretreatment condition (Figure 2B). As for the potential aversive effects of varenicline, we are not aware of any research characterizing its aversive effects and associated tolerance to such effects in rats. Notably, one of the consistent side-effects of varenicline in humans is nausea (Oncken *et al*, 2006). From our perspective, this discussion highlights the need for future research on potential conditioned aversive effects of varenicline and, if such effects are found, will tolerance develop and under what conditions. Further, would the effects of varenicline on meth self-administration differ if the rats were not naïve to its effects?

One methodological strength of the current study was the inclusion of a saline condition. Recall that the only difference between the meth condition and the saline condition is the type of infusion (meth or saline); pre-training, infusion/timeout cues, progression through the study, etc. were identical. This saline benchmark allowed for careful analysis of the

behavior controlled by meth compared to that controlled by the weak reinforcing effects of infusion cues (Caggiula *et al*, 2009; Chaudhri *et al*, 2006b; Palmatier *et al*, 2006). In fact, without this group, we would not have concluded that the decrease in active lever pressing in the meth condition reflected a non-specific effect of varenicline. Previous research has utilized a non-drug reinforcer (i.e., food pellets) to investigate non-specific varenicline effects (see Tables 1 to 3). Albeit an interesting and informative comparison condition, the use of a non-drug reinforcer does not provide a baseline measure of responding maintained by the self-administration cues alone. As noted already, this cue-maintained responding can be a quite useful benchmark for interpreting certain data patterns. As another example of its utility in the present study, a comparison between the two groups during extinction allowed us to assess whether and when responding previously reinforced by meth reached a level similar to that maintained by cues alone (saline group). Of course, practical disadvantages of including this saline plus cue-maintained self-administration group is the increased costs, as well as the additional labor and chamber time. Regardless, under certain circumstances, investigators might want to consider doing so when interpretation of data patterns from behavioral manipulations (e.g., extinction) and pharmacological manipulations (e.g., see later discussion of reinstatement) may be enriched.

Relative to the saline comparison, meth rats displayed robust reinstatement when pretreated with a 0.3 mg/kg meth-trigger (Figure 4A). This finding is consistent with previous studies (Cox *et al*, 2013; Holtz *et al*, 2012; Reichel *et al*, 2012). Interestingly, when a low dose of varenicline (0.3 and 1 mg/kg) was administered in conjunction with the meth-prime, responding was increased above reinstatement levels triggered by the meth-prime alone. This effect was not specific to the meth group. Both groups (saline and meth) increased responding following the meth-trigger + 0.3 or 1.0 mg/kg varenicline (Nb. This is another example of the advantage of including the saline condition). The increased reinstatement cannot be fully explained by an increase in general locomotor activity; recall that varenicline did not significantly alter locomotor activity relative to saline (Figure 4B).

A review of the effects of varenicline on drug-seeking behavior revealed that this increase was not an anomaly. Other studies have reported an increase in reinstatement when nicotine was previously self-administered (La Foll *et al*, 2012; Wouda *et al*, 2011), as well as when cocaine was previously self-administered (Guillem and Peoples, 2010). This effect of varenicline on relapse-like behavior is not universal (see Tables 1 to 3). Although it is unclear what experimental factors permit observing or not observing such an effect, there is one possible account of varenicline-induced reinstatement that has some empirical support. That account posits that the lower doses of varenicline enhance the weak reinforcing effects of the timeout/infusion cues. Numerous studies have shown that the nAChR agonist nicotine enhances responding for weakly reinforcing sensory stimuli (e.g., a visual stimulus; Barret and Bevins, 2013; Barrett and Bevins, 2012; Bevins and Palmatier, 2004; Caggiula *et al*, 2009; Cassidy and Dallery, 2014; Chaudhri *et al*, 2006a; Chaudhri *et al*, 2006b; Donny *et al*, 2003; Paterson, 2009; Spiller *et al*, 2009). In fact, low doses of varenicline also enhanced responding maintained by a visual stimulus (Barrett, 2014; Schassburger *et al*, 2015), as well as responding maintained by brain stimulation (Spiller *et al*, 2009). This enhancement

effect appears to be mediated, at least in part, by $\alpha 4\beta 2$ -containing nAChRs (Barrett, 2014; Schassburger *et al*, 2015; Spiller *et al*, 2009).

The contrasting results between the early effects of varenicline slightly decreasing responding during the self-administration phase and, then, in the later meth-primed reinstatement phase increasing responding requires some discussion. One possibility briefly noted earlier suggested that varenicline may have some early aversive effects in females that show quick tolerance. Consistent with the suggestion is the observation that tolerance to the early aversive effects of nAChR agonists, at least in male rats, is quite common following repeated administration (Iwamoto *et al*, 1984; Reavill *et al*, 1990; Stoleran *et al*, 1997). For example, Iwamoto and Williamson (1984) found that as little as 2 days of nicotine pretreatment (SC 0.5 mg/kg per day) prevented later acquisition of a nicotine-conditioned taste aversion. In our study, each rat was administered 3 different doses of the partial nAChR agonist, varenicline, during the self-administration phase. This treatment regimen may produce tolerance, allowing varenicline enhancement of sensory reinforcement to be detected in the subsequent reinstatement phase.

Varenicline has been shown to be an effective pharmacotherapy in reducing the positive subjective effects produced by meth in human meth users (Varrico *et al*, 2014). While the present study demonstrated a varenicline reduction in meth self-administration, this reduction was quite small and was not specific to a meth. Additionally, pretreatment with varenicline in the meth-primed reinstatement phase revealed increased drug-seeking behavior. If these findings generalize to a treatment population, then the clinical implications are clear. Varenicline may increase vulnerability to relapse in females via enhancement of drug-associated cues. Amplified susceptibility to relapse would serve as a major impediment to the effective utilization of varenicline in the treatment of meth dependence.

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Highlights

- Female Sprague-Dawley rats readily self-administered methamphetamine.
- Varenicline attenuated responding during self-administration.
- Female rats displayed robust reinstatement of active lever pressing.
- Reinstatement responding was increased following varenicline administration.

Figure 1.

Panel **A** displays active lever presses in acquisition sessions for rats responding on a VR3 for meth (filled circles) and saline (open circles). Panel **B** displays the general locomotor activity by session, measured in beam breaks, for the meth and saline groups.

Figure 2.

Panel **A** shows the active lever presses of females responding on a VR3 for meth (filled circles) and saline (open circles) following varenicline treatment. Panel **B** shows the locomotor activity (measured in beam breaks) in the meth and saline groups following varenicline treatment.

Figure 3.

Panel **A** displays active lever presses over extinction sessions for rats in the meth (filled circles) and saline (open circles) groups. Panel **B** shows the locomotor data (measured by beam breaks) during the extinction sessions for rats in the meth and saline groups.

Figure 4.

Panel **A** displays the active lever presses of rats following treatment of varenicline during meth-primed reinstatement. The meth group is shown by the filled circles and the saline group by the open circles. Panel **B** displays the general locomotor data during varenicline treatment of meth-primed reinstatement.

Table 1

Effects of varenicline on nicotine intake and seeking.

Reference	Species	Nicotine Dose	Dose of Varenicline & Effect on SA	Varenicline Effect on Reinstatement	Varenicline Effect on Inactive-lever Responding	Varenicline Effect on Alternate Reinforcer Responding
Chang et al. 2015	Rat: male	0.03 mg/inf; IV	1.7 ↓		1.7 ↓	<u>Food Pellet</u> 1.7 –
Costello et al. 2014	Rat: Male	Nic; 0.015 mg/kg/inf; IV Cigarette Smoke Extract (CSE); 0.015 mg/kg/inf; IV	<u>Nic</u> 0.3 – 1.0 ↓ 3.0 ↓ <u>CSE</u> 0.3 – 1.0 ↓ 3.0 ↓		<u>Nic</u> 0.3 – 1.0 – 3.0 – <u>CSE</u> 0.3 – 1.0 – 3.0 –	
Funk et al. 2015	Rat: Male	0.03 mg/kg/inf; IV	1.0 – 2.0 ↓			
George et al. 2011	Rat: Male	0.03 mg/kg/inf; IV	0.3; – 1.0: – 3.0: ↓		0.3 – 1.0 ↓ 3.0 ↓	
Goeders et al. 2012	Rat: Male	0.03 mg/kg/inf; IV	1.0 ↓			
Hall et al. 2015	Rat: Female	0.03 mg/kg/inf; IV	0.3; – 1.0: ↓ 3.0: ↓		0.3 – 1.0 – 3.0 –	
Le Foll et al. 2012	Rat: Male	0.03 mg/kg/inf; IV	0.3 ↓ 1.0 ↓ 3.0 ↓	<u>Cue-Induced</u> 0.3 ↑ 1.0 ↓ 3.0 ↓	0.3 – 1.0 – 3.0 –	<u>Food Pellets</u> 0.3 – 1.0 – 3.0 –
Mello et al. 2014	Rhesus Monkey: 4 Male, 2 female	0.001 & 0.0032 mg/kg/inf; IV	<i>Chronic Varenicline Treatment</i> <u>0.001</u> 0.004/hr – 0.04/hr – <u>0.0032</u> 0.004/hr – 0.04/hr ↓			<u>Food Pellets</u> 0.004/hr – 0.04/hr –
O'Connor et al. 2010	Rat: Male	0.015 mg/kg/inf; IV	0.3 ↓ 1.0 ↓ 3.0 ↓	<u>Cue-Induced</u> 0.3 – 1.0 – 3.0 – <u>Prime-Induced</u> 0.3 ↓ 1.0 ↓ 3.0 ↓ <u>Cue + Prime</u> 0.3 ↓ 1.0 ↓ 3.0 ↓	<i>Self-Administration Not Discussed</i> <u>Cue-Induced</u> 0.3 – 1.0 – 3.0 – <u>Prime-Induced</u> 0.3 – 1.0 – 3.0 – <u>Cue + Prime</u> 0.3 – 1.0 ↓ 3.0 ↓	<u>Food Pellets</u> 0.3 – 1.0 – 3.0 ↓

Reference	Species	Nicotine Dose	Dose of Varenicline & Effect on SA	Varenicline Effect on Reinstatement	Varenicline Effect on Inactive-lever Responding	Varenicline Effect on Alternate Reinforcer Responding
Panlilio et al. 2015	Rat: Male	0.03 mg/kg/inf; IV	0.1: – 0.3: – 1.0: – 1.5: ↓			<u>Sucrose</u> 0.1: – 0.3: – 1.0: – 1.5: –
Rollema et al. 2007	Rat: Male	0.03 mg/kg/inf; IV	1.0 ↓ 1.78 ↓ 3.0 ↓			<u>Food Pellets</u> 1.0 ↑ 1.78 ↑ 3.0 –
Scuppa et al. 2015	Rat: Male	0.03 mg/kg/inf IV	0.3 – 1.0 ↓ 3.0 ↓			
Wouda et al. 2011	Rat: Male	0.04 mg/kg/inf; IV	0.5 – 1.5 ↓ 2.5 ↓	<u>Cue-Induced</u> 0.5 ↑ 1.5 – 2.5 –	0.5 – 1.5 – 2.5 –	<u>Sucrose</u> 0.5 ↑ 1.5 ↑ 2.5 ↑

Table 2

Effects of varenicline on alcohol intake and seeking.

Reference	Species	Nicotine Dose	Dose of Varenicline & Effect on SA	Varenicline Effect on Reinstatement	Varenicline Effect on Inactive-lever Responding	Varenicline Effect on Alternate Reinforcer Responding
Chang et al. 2015	Rat: male	0.03 mg/inf; IV	1.7 ↓		1.7 ↓	<u>Food Pellet</u> 1.7 –
Costello et al. 2014	Rat: Male	Nic; 0.015 mg/kg/inf; IV Cigarette Smoke Extract (CSE); 0.015 mg/kg/inf; IV	<u>Nic</u> 0.3 – 1.0 ↓ 3.0 ↓ <u>CSE</u> 0.3 – 1.0 ↓ 3.0 ↓		<u>Nic</u> 0.3 – 1.0 – 3.0 – <u>CSE</u> 0.3 – 1.0 – 3.0 –	
Funk et al. 2015	Rat: Male	0.03 mg/kg/inf; IV	1.0 – 2.0 ↓			
George et al. 2011	Rat: Male	0.03 mg/kg/inf; IV	0.3; – 1.0: – 3.0: ↓		0.3 – 1.0 ↓ 3.0 ↓	
Goeders et al. 2012	Rat: Male	0.03 mg/kg/inf; IV	1.0 ↓			
Hall et al. 2015	Rat: Female	0.03 mg/kg/inf; IV	0.3; – 1.0: ↓ 3.0: ↓		0.3 – 1.0 – 3.0 –	
Le Foll et al. 2012	Rat: Male	0.03 mg/kg/inf; IV	0.3 ↓ 1.0 ↓ 3.0 ↓	<u>Cue-Induced</u> 0.3 ↑ 1.0 ↓ 3.0 ↓	0.3 – 1.0 – 3.0 –	<u>Food Pellets</u> 0.3 – 1.0 – 3.0 –
Mello et al. 2014	Rhesus Monkey: 4 Male, 2 female	0.001 & 0.0032 mg/kg/inf; IV	<i>Chronic Varenicline Treatment</i> <u>0.001</u> 0.004/hr – 0.004/hr – <u>0.0032</u> 0.004/hr – 0.04/hr ↓			<u>Food Pellets</u> 0.04/hr – 0.04/hr –
O'Connor et al. 2010	Rat: Male	0.015 mg/kg/inf; IV	0.3 ↓ 1.0 ↓ 3.0 ↓	<u>Cue-Induced</u> 0.3 – 1.0 – 3.0 – <u>Prime-Induced</u> 0.3 ↓ 1.0 ↓ 3.0 ↓ <u>Cue + Prime</u> 0.3 ↓ 1.0 ↓ 3.0 ↓	<i>Self-Administration Not Discussed</i> <u>Cue-Induced</u> 0.3 – 1.0 – 3.0 – <u>Prime-Induced</u> 0.3 – 1.0 – 3.0 – <u>Cue + Prime</u> 0.3 – 1.0 ↓ 3.0 ↓	<u>Food Pellets</u> 0.3 – 1.0 – 3.0 ↓

Reference	Species	Nicotine Dose	Dose of Varenicline & Effect on SA	Varenicline Effect on Reinstatement	Varenicline Effect on Inactive-lever Responding	Varenicline Effect on Alternate Reinforcer Responding
Panlilio et al. 2015	Rat: Male	0.03 mg/kg/inf; IV	0.1: – 0.3: – 1.0: – 1.5: ↓			<u>Sucrose</u> 0.1: – 0.3: – 1.0: – 1.5: –
Rollema et al. 2007	Rat: Male	0.03 mg/kg/inf; IV	1.0 ↓ 1.78 ↓ 3.0 ↓			<u>Food Pellets</u> 1.0 ↑ 1.78 ↑ 3.0 –
Scuppa et al. 2015	Rat: Male	0.03 mg/kg/inf IV	0.3 – 1.0 ↓ 3.0 ↓			
Wouda et al. 2011	Rat: Male	0.04 mg/kg/inf; IV	0.5 – 1.5 ↓ 2.5 ↓	<u>Cue-Induced</u> 0.5 ↑ 1.5 – 2.5 –	0.5 – 1.5 – 2.5 –	<u>Sucrose</u> 0.5 ↑ 1.5 ↑ 2.5 ↑

Table 3

Effects of varenicline on cocaine intake and seeking.

Reference	Species	Cocaine Dose	Dose of Varenicline & Effect on SA	Varenicline Effect on Reinstatement	Varenicline Effect on Inactive-lever Responding	Varenicline Effect on Alternate Reinforcer Responding
Mello et al. 2014	Rhesus Monkey; 4 Male, 2 female	0.0032 & 0.01 mg/kg/inf; IV	<i>Chronic Varenicline Treatment</i> 0.01 0.004 mg/kg/hr – 0.04 mg/kg/hr – 0.0032 0.004 mg/kg/hr – 0.04 mg/kg/hr –			<u>Food Pellets</u> 0.004 mg/kg/hr – 0.04 mg/kg/hr –
Gould et al 2011	Rhesus Monkey; Male	0.01-0.56 mg/kg/inf; IV	0.3 BID ↑ 0.56 BID ↑			<u>Food Pellets</u> 0.3 BID – 0.56 BID ↓
Guillem & Peoples 2010	Rat; Male	0.75 mg/kg/inf; IV	0.3 – 1.0 ↓ 2.0 ↓	<u>Cue-Induced</u> 0.1 ↓ 0.3 ↓ 2.0 ↑ <u>Drug-Prime</u> 0.1 ↓ 0.3 ↓		<i>Cue-Induced Reinstatement of Sucrose</i> 0.1 – 0.3 –