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Research report

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

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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.

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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 α4β2 and full α7 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 h 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.



## 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 [59]. These health problems last for months to years following cessation of use [91]. 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 and 1.2 million people report using in the past year [88]. 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 [9]. 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 [62]. 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 [4].

Treatments for meth dependence remain inadequate, with the majority of addicts returning to use within 6 months of

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treatment [4,5]. 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 [92]. Some medications (e.g., bupropion, modafinil, dextroamphetamine, rivastigmine) that assist in recovery of dopaminergic function following meth abuse are potential therapeutics for meth cessation [19,21,26,37,52,55,60,61,69,74,75,89,93]. Activation of nicotinic acetylcholine receptors (nAChRs) increases dopamine release [23]. Medications known to increase acetylcholine via acetylcholinesterase inhibition reduced the positive subjective effects of meth in humans [18,19,20] and decreased meth-primed reinstatement (i.e., pre-clinical model of relapse) in rats [39,40].

With these mechanisms in mind, varenicline is of potential interest. Varenicline is a partial α4β2 and full α7 nAChR agonist [14,15,32,58,83] 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

**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 |
|---|---|---|---|---|---|---|
| [10] | Rat: male | 0.03 mg/inf; IV | 1.7 ↓ | | 1.7 ↓ | Food pellet<br>1.7 – |
| [16] | Rat: male | Nic;<br>0.015 mg/kg/inf; IV<br>cigarette smoke extract (CSE);<br>0.015 mg/kg/inf; IV | Nic<br>0.3 –<br>1.0 ↓<br>3.0 ↓<br>CSE<br>0.3 –<br>1.0 ↓<br>3.0 ↓ | | Nic<br>0.3 –<br>1.0 –<br>3.0 –<br>CSE<br>0.3 –<br>1.0 –<br>3.0 – | |
| [28] | Rat: male | 0.03 mg/kg/inf; IV | 1.0 –<br>2.0 ↓ | | | |
| [29] | Rat: male | 0.03 mg/kg/inf; IV | 0.3: –<br>1.0: –<br>3.0: ↓ | | 0.3 –<br>1.0 ↓<br>3.0 ↓ | |
| [31] | Rat: male | 0.03 mg/kg/inf; IV | 1.0 ↓ | | | |
| [36] | Rat: female | 0.03 mg/kg/inf; IV | 0.3: –<br>1.0: ↓<br>3.0: ↓ | | 0.3 –<br>1.0 –<br>3.0 – | |
| [50] | Rat: male | 0.03 mg/kg/inf; IV | 0.3 ↓<br>1.0 ↓<br>3.0 ↓ | Cue-induced<br>0.3 ↑<br>1.0 ↓<br>3.0 ↓ | 0.3 –<br>1.0 –<br>3.0 – | Food pellets<br>0.3 –<br>1.0 –<br>3.0 – |
| [57] | Rhesus monkey: 4 male, 2 female | 0.001 & 0.0032 mg/kg/inf; IV | Chronic varenicline treatment<br>0.001<br>0.004/h –<br>0.04/h –<br>0.0032<br>0.004/h –<br>0.04/h ↓ | | | Food pellets<br>0.004/hrp –<br>0.04/hrp – |
| [63] | Rat: male | 0.015 mg/kg/inf; IV | 0.3 ↓<br>1.0 ↓<br>3.0 ↓ | Cue-induced<br>0.3 –<br>1.0 –<br>3.0 –<br>Prime-induced<br>0.3 ↓<br>1.0 ↓<br>3.0 ↓<br>Cue + prime<br>0.3 ↓<br>1.0 ↓<br>3.0 ↓ | Self-administration<br>Not discussed<br>Cue-induced<br>0.3 –<br>1.0 –<br>3.0–<br>Prime-induced<br>0.3 –<br>1.0 –<br>3.0 –<br>Cue + prime<br>0.3 –<br>1.0 ↓<br>3.0 ↓ | Food pellets<br>0.3 –<br>1.0 –<br>3.0 ↓ |
| [66] | Rat: male | 0.03 mg/kg/inf; IV | 0.1: –<br>0.3: –<br>1.0: –<br>1.5: ↓ | | | Sucrose<br>0.1: –<br>0.3: –<br>1.0: –<br>1.5: – |
| [77] | Rat: male | 0.03 mg/kg/inf; IV | 1.0 ↓<br>1.78 ↓<br>3.0 ↓ | | | Food pellets<br>1.0 ↑<br>1.78 ↑<br>3.0 – |
| [80] | Rat: male | 0.03 mg/kg/inf IV | 0.3 –<br>1.0 ↓<br>3.0 ↓ | | | |
| [95] | Rat: male | 0.04 mg/kg/inf; IV | 0.5 –<br>1.5 ↓<br>2.5 ↓ | Cue-induced<br>0.5 ↑<br>1.5 –<br>2.5 – | 0.5 –<br>1.5 –<br>2.5 – | Sucrose<br>0.5 ↑<br>1.5 ↑<br>2.5 ↑ |