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Research report

# Effects of varenicline on operant self-administration of alcohol and/or nicotine in a rat model of co-abuse

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## HIGHLIGHTS

- Alcohol self-administration in rats was not affected by varenicline.
- Nicotine self-administration in rats was modestly reduced by varenicline.
- Nicotine did not modify the effects of varenicline on alcohol self-administration.
- Alcohol did not modify the effects of varenicline on nicotine self-administration.
- Reinstatement of alcohol seeking induced by alcohol cues + prime was blocked by varenicline.

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## ABSTRACT

Alcohol and nicotine (in the form of tobacco) are often taken together, with increased negative health consequences. Co-use may modify intake of one or both of the drugs, or the effects of drugs used to treat nicotine or alcohol addiction. Varenicline is commonly prescribed as an aid to enhance quitting smoking. More recently it has been shown to reduce alcohol intake in humans and laboratory animals. There is little work investigating the role of co-exposure to alcohol and nicotine in the effects of varenicline. In pilot clinical studies, it has been reported that smoking enhances varenicline's effectiveness as a treatment for alcohol misuse, but this relationship has not been systematically investigated. To help resolve this, we examined if the effects of varenicline on alcohol and nicotine self-administration (SA) in rats are modified when the two drugs are taken together. Rats were trained on alcohol SA, and some were implanted with i.v. catheters for nicotine SA. Groups of animals then lever pressed for alcohol or nicotine alone, and another group lever pressed for alcohol and nicotine, using a two lever choice procedure. Varenicline did not affect alcohol SA. Varenicline reduced nicotine SA modestly. Access to both alcohol and nicotine reduced self-administration of either drug, but did not change the effects of varenicline. We found that in rats with a history of alcohol SA, varenicline reduced reinstatement of extinguished alcohol seeking induced by exposure to an alcohol prime combined with cues previously associated with alcohol.


## 1. Introduction

Addictions to alcohol and nicotine (most often in the form of smoked tobacco) have major impacts on health and society. Roughly 4% of American adults are alcohol-dependent and 8% can be classified as having an alcohol use disorder [1], while 18% are classified as smokers [2]. Alcohol and nicotine are often taken together [3,4], intake of one can increase intake of the other [5,6] and their negative health effects are greatly increased with co-abuse [7,8]. Co-use also has important treatment implications as it may change the effects of drugs used to treat alcohol and nicotine addiction [9–11]. With the exception of our recent report [12], there is no preclinical work systematically exploring this interaction.

Varenicline is prescribed to aid quitting smoking [12]. It is a full agonist at the α7, and a partial agonist at the α4β2 nicotinic cholinergic receptor (nAChR) and can reduce nicotine self-administration (SA) in laboratory animals responding on fixed [13–15] and progressive ratio schedules [16], although there are inconsistencies in

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the effective dose. Varenicline can affect reinstatement of nicotine seeking in animal models of relapse, but its effects may depend on the dose of varenicline, the nature of the reinstating stimulus or other factors [14–16].

Varenicline may also be useful in treating alcohol dependence or misuse. In a human experimental study, it reduced the number of drinks consumed during an alcohol SA period and reduced craving for alcohol and its positive effects after a priming drink [17]. Data from more extensive clinical trials support these observations [18,19]. Work using animal models of alcohol SA and relapse are consistent with this human data. Varenicline can reduce drinking and operant SA of alcohol, but as is the case for nicotine SA, there is variability in the effective doses reported [15,20–22].

Co-use of alcohol and nicotine can modify the effects of drugs used to treat addiction to either drug [9–11]. For example, in heavy drinkers that smoke, naltrexone is more effective in reducing alcohol intake [9,11] and is also more effective in enhancing smoking quit rates in smokers treated with nicotine replacement that also drink heavily [9]. In support of this, we found that co-exposure to alcohol and nicotine potentiated the inhibitory effect of naltrexone on alcohol SA in rats [12].

There is little systematic work on the role of alcohol and nicotine co-exposure in the effects of varenicline. Varenicline was reported in one clinical study to be more effective in reducing drinking in smokers than in nonsmokers [19], but was unrelated to smoking status in another [18]. Varenicline reduced the increases in alcohol SA and drinking produced by acute injections of nicotine in rats [23]. Varenicline reduced both alcohol and nicotine intake in rats when presented under two lever choice conditions [24], but there were no single drug alone control groups in that study to evaluate the effects of co-exposure.

To help resolve these issues, we will examine the effects of varenicline on alcohol and nicotine SA when the drugs are administered separately or when co-administered using a two lever choice procedure. We then examined the effects of varenicline on reinstatement of alcohol seeking induced by exposure to alcohol-associated cues combined with an alcohol prime.

## 2. Materials and methods

### 2.1. Animals

Male Wistar rats, 200–225 g were obtained from Charles River (Montreal, Quebec). Rats were individually housed and fed 25 g of lab chow in the home cage after the daily operant sessions. This mild food restriction was used to prevent excessive weight gain in the animals, but allows normal growth. Tap water was available ad libitum in the home cage. The vivarium temperature was 21 °C and lights were on from 7 p.m. to 7 a.m. Procedures followed the National Institutes of Health "Principles of laboratory animal care" (Eighth edition, 2011) and were approved by the animal care committee of the Centre for Addiction and Mental Health.

### 2.2. Apparatus

Self-administration (SA) of alcohol and/or nicotine was done in 16 chambers operated by a Med Associates (Georgia, VT) interface. Each chamber (30 × 21 × 21 cm) was equipped with two retractable levers and two infusion pumps, one for delivering alcohol into a drinking receptacle, and one for delivering nicotine solution through an i.v. catheter line. For alcohol SA, lever responding activated the infusion pump (Razel Sci., Stamford, CT) for 5 s, delivering 0.19 ml of alcohol solution (12% w/v) into the receptacle, with each delivery accompanied by a flashing white cue light above the lever (0.5 s on, 0.5 s off) for 5 s. For nicotine SA, lever responding activated the infusion pump for 0.5 s delivering the nicotine solution (30 μg/kg/delivery) via the i.v. catheter that was accompanied by a continuously illuminated white cue light above the lever for 5 s. In sessions when only alcohol or nicotine was available, an inactive lever was also present; responses on this lever had no programmed consequences, but were recorded. In sessions when both alcohol and nicotine were available, there was no inactive lever. Positions of the alcohol and nicotine-associated levers or inactive levers were counterbalanced across animals. The chambers also had a red house light illuminated during the SA session. At the end of SA sessions involving alcohol, receptacles were checked for unconsumed alcohol; if present, it was measured and used to calculate the deliveries consumed [12]. In the present experiments, unconsumed alcohol was rarely found.

### 2.3. Catheter or sham catheter surgery

Rats were anaesthetized using isoflurane/oxygen. Incision sites were treated with a local anesthetic (0.1 ml bupivacaine, 0.125%, s.c.). Penicillin (30 000 U, i.m.) was administered prior to surgery and buprenorphine (0.01 mg/kg, s.c.) as an analgesic afterwards. Catheters were constructed in-house and implanted into the right jugular vein as previously described [25] and exited between the scapulae and were attached to a 22-gauge cannula connected to the fluid swivel system. They were capped with a short length of heat-sealed plastic tubing. Catheters were flushed daily with 0.1 ml of a sterile heparin-saline solution (50 U/ml); their patency was tested weekly by i.v. injections of sodium methohexital (0.05 mg/kg). Data from animals that did not show rapid anesthesia following i.v. methohexital injection were excluded. Rats receiving sham catheter surgery (the alcohol alone group in Exp. 1) were treated in the same way except they received a 1 cm long incision between the scapulae that was then sutured. Animals recovered for 1 week before initiation of experiments.

### 2.4. Procedures

#### 2.4.1. Experiment 1: effects of varenicline on SA of alcohol, nicotine or alcohol + nicotine

All rats were trained to self-administer alcohol. They received daily limited access sessions (30 min) with the choice between water and alcohol in Richter tubes, with 5 d each at 3, 6 and 12% (w/v) and were then trained on operant alcohol SA (12%) in daily 1 h sessions. Animals received 5 daily sessions each at FR-1, FR-2 and FR-3 with a 5 s timeout, with only the alcohol lever present. They then received 5 daily sessions at FR-3, but after each alcohol delivery, the lever retracted for a 30 s timeout period.

Animals were assigned to 3 groups, matched according to the mean numbers of alcohol deliveries received over the last 2 days of alcohol SA. Animals in groups that would self-administer nicotine alone ($n = 12$) or both drugs ($n = 12$) received catheter surgery, while those that would self-administer alcohol alone ($n = 12$) received sham catheter surgery. After recovery, further operant training occurred as follows: *Alcohol alone*: rats continued to receive daily 2 h alcohol SA sessions at FR-3 with levers retracting during the 30 s timeout. *Nicotine alone*: rats were trained to self-administer nicotine in 2 h daily sessions at FR3 with lever retraction after each nicotine delivery for the 30 s timeout. *Alcohol + nicotine*: rats were trained to self-administer nicotine for 15 days at FR-3 with lever retraction after delivery for the 30 s timeout, and then received daily 2 h sessions with opportunity to self-administer alcohol and nicotine concurrently, both at FR-3. After delivery of either drug, both levers retracted for the 30 s timeout, and the ratio was reset to FR-3 for both drugs. Testing for the effects of varenicline commenced after alcohol, nicotine or alcohol + nicotine SA became stable (about 10 days). Two rats that consumed less than 0.4 g/kg