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Varenicline Potentiates Alcohol-Induced Negative Subjective Responses and Offsets Impaired Eye Movements

Emma Childs, Daniel J. O. Roche, Andrea C. King, and Harriet de Wit

Background: Varenicline (VAR) is a partial nicotinic receptor agonist that is an effective smoking cessation medication. Preliminary evidence indicates that it may also reduce alcohol consumption, but the underlying mechanism is not clear. For example, VAR may reduce alcohol consumption by attenuating its subjectively rewarding properties or by enhancing its aversive effects. In this study, we examined the effects of an acute dose of VAR upon subjective, physiological, and objective responses to low and moderate doses of alcohol in healthy social drinkers.

Methods: Healthy men and women ($N = 15$) participated in 6 randomized sessions; 3 sessions each with 2 mg VAR and placebo (PL) followed 3 hours later by a beverage containing PL, low-dose alcohol (0.4 g/kg), or high-dose alcohol (0.8 g/kg). Subjective mood and drug effects (i.e., stimulation, drug liking), physiological measures (heart rate, blood pressure), and eye tracking tasks were administered at various intervals before and after drug and alcohol administration.

Results: VAR acutely increased blood pressure, heart rate, ratings of dysphoria and nausea, and also improved eye tracking performance. After alcohol drinking (vs. PL), VAR increased dysphoria and tended to reduce alcohol liking ratings. It also attenuated alcohol-induced eye-tracking impairments. These effects were independent of the drug's effects on nausea before drinking.

Conclusions: Our data support the theory that VAR may reduce drinking by potentiating aversive effects of alcohol. VAR also offsets alcohol-induced eye movement impairment. The evidence suggests that VAR may decrease alcohol consumption by producing effects, which oppose the rewarding efficacy of alcohol.

Key Words: Varenicline, Alcohol, Subjective Effects, Eye-Tracking.

VARENICLINE (VAR) (CHANTIX[®]) is a partial nicotinic receptor agonist that is an effective smoking cessation aid. Anecdotally, some smokers treated with VAR report that they consume less alcohol, which suggests that the drug may also be an efficacious treatment for alcoholism. Indeed, there is evidence from controlled studies in rodents and humans that VAR reduces alcohol consumption (Bito-Onon et al., 2011; Kamens et al., 2010a; McKee et al., 2009; Steensland et al., 2007; Wouda et al., 2011). However, the mechanisms by which VAR reduces alcohol drinking remain unclear.

Among its many other actions, alcohol is known to act on the nicotinic acetylcholine receptor (nAChR) where it potentiates the effects of acetylcholine and nicotine (Davis and De Fiebre, 2006; Ei-Fakahany et al., 1983). In rodents, nAChRs

reportedly mediate the effects of alcohol upon locomotor activity, cognition, and alcohol self-administration. Nicotine enhances the locomotor activating (Blomqvist et al., 1992; Johnson et al., 1995) and interoceptive effects of alcohol (Signs and Schechter, 1986), and it increases alcohol drinking (Bito-Onon et al., 2011; Clark et al., 2001; Lopez-Moreno et al., 2004; Potthoff et al., 1983; Smith et al., 1999), and reinstates alcohol seeking (Le et al., 2003). Nicotinic antagonists attenuate these effects (Blomqvist et al., 1992, 1997, 2002).

Some of the interactions between alcohol and nicotine may be mediated by nAChRs within the mesolimbic dopamine system. Animal studies show that, when administered together, nicotine and alcohol produce synergistic effects on mesolimbic dopamine system activity as well as additive effects on dopamine turnover in the brain and release in the nucleus accumbens (Clark and Little, 2004; Johnson et al., 1995; Tizabi et al., 2007). In addition, nicotinic antagonists attenuate alcohol-induced effects in the mesolimbic dopamine system (Blomqvist et al., 1992, 1997; Soderpalm et al., 2000). Moreover, in humans, nicotine potentiates the subjective rewarding effects, craving, and consumption of alcohol, while nicotinic antagonists attenuate these effects (Acheson et al., 2006; Blomqvist et al., 2002; Chi and de Wit, 2003; Kouri et al., 2004; Penetar et al., 2009; Young et al., 2005). A partial nAChR agonist like VAR might either potentiate the effects

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of alcohol (through its agonist effects) or block the effects of alcohol, by occupying the receptors. Recently, it was reported that VAR reduced alcohol-induced dopamine release in the nucleus accumbens (Ericson et al., 2009), suggesting that it may decrease alcohol-associated reward and motivational effects in humans through its effects on mesolimbic dopaminergic transmission.

VAR interacts with several nicotinic receptor subtypes. It is a partial agonist at $\alpha 4\beta 2$, $\alpha 3\beta 2$, and $\alpha 6$ receptors and a full agonist at $\alpha 7$ and $\alpha 3\beta 4$ (Coe et al., 2005; Rollema et al., 2007). Overall, VAR antagonizes effects mediated by $\alpha 4\beta 2$, $\alpha 3\beta 2$, and $\alpha 6$ receptors, making these receptors good candidates for actions on alcohol effects. There is evidence that VAR reduces self-reported alcohol craving and consumption in heavy drinking smokers (McKee et al., 2009), and increases aversive effects of alcohol, such as its sedative and ataxic effects (Kamens et al., 2010b; Fucito et al., 2011). Collectively, these findings suggest that VAR may reduce alcohol drinking behavior by either reducing its subjectively rewarding or motivating properties or alternatively by increasing its sedative-like properties. To our knowledge, there have been no human laboratory studies to date examining the acute effects of VAR (vs. placebo [PL]) on multiple domains of alcohol responses, and at different alcohol dose levels.

In the present study, we measured the effects of acute VAR administration (0, 2 mg) on the subjective and objective (eye tracking) responses to alcohol (0, 0.4, 0.8 g/kg). We hypothesized, on the basis of previous studies (Fucito et al., 2011; Kamens et al., 2010b; McKee et al., 2009), that VAR would reduce the subjectively rewarding effects of a high alcohol dose, while increasing negative mood states, including sedation and dysphoria. We also hypothesized that VAR would counteract alcohol-induced impairments in eye tracking performance (Roche and King, 2010), specifically in the anti-saccade task where nicotine appears to have its largest effect (Larrison et al., 2004; Rycroft et al., 2006).

MATERIALS AND METHODS

Subjects

Healthy moderate-to-heavy social drinkers ($N = 15$; 7 women) who were nondependent alcohol drinking and nondependent smokers, and not currently seeking treatment for either substance, were enrolled. Exclusion criteria included a current or prior diagnosis of a Major Axis I DSM-IV disorder (American Psychiatric Association, 1994) including substance dependence within the past 2 years or a lifetime history of alcohol dependence (ascertained using a modified version of the research SCID), a serious medical condition, high blood pressure, abnormal electrocardiogram, daily use of medications, a body mass index outside of 19 to 26 kg/m², age outside of 21 to 45 years, less than high school education or lack of fluency in English, night shift work, and, in women, pregnancy, lactation, or lack of a reliable method of birth control. To be eligible, subjects had to meet criteria for heavy social drinking, which was operationally defined as consuming at least 10 alcoholic drinks per week (SAMHSA, 2007), with at least 1 weekly binge episode (5 or more drinks for men, and 4 or more drinks for women, on a single occasion) and smoke no more than 5 cigarettes per day. These criteria were chosen to be generally consistent with prior studies (Esterlis et al., 2010; King et al., 2011;

McKee et al., 2010). We chose to examine a subgroup of regular heavy drinkers because they exhibit biphasic alcohol responses (King et al., 2011) with nondependent lighter smoking patterns to avoid confounds of tobacco withdrawal or difficulty complying with 10 hours of smoking abstinence as required prior to and during the sessions. Qualifying participants signed a consent form, which stated that the study was designed to investigate the effects of a drug on the subjective and behavioral effects of alcohol. For blinding purposes, they were told that the capsule they might receive could contain a stimulant (appetite suppressant), a smoking cessation aid, alcohol, or PL (sugar). They were told that the beverages they received may or may not contain alcohol. They agreed not to consume any drugs other than their normal amounts of caffeine for 24 hours before and 12 hours after each session and not to consume any food during the sessions, other than that provided by the experimenters. They were allowed to eat as normal before sessions, but could not smoke the morning of the experimental sessions, which was verified by a breath CO level of < 7 ppm upon arrival.

Study Design

Subjects were tested individually in six 6-h experimental sessions that began at noon and were conducted at least 3 days apart. During the sessions, participants received a capsule containing 2 mg VAR or PL, followed 3 hours later by a beverage containing 0, 0.4, or 0.8 g/kg alcohol (0, 0.4, 0.8). Thus, there were 6 conditions; VAR-0, VAR-0.4, VAR-0.8, PL-0, PL-0.4, PL-0.8. The order of drug and beverage doses was determined randomly and drug and alcohol administration was double blind. Breath alcohol concentration (BrAC) levels, subjective effects, heart rate, blood pressure, and eye tracking were measured at repeated intervals before and after the capsule and the beverage was consumed in each session. We chose eye tracking tasks as an objective measure of alcohol response as performance in such tasks is impaired after alcohol ingestion, particularly at intoxicating doses (Roche and King, 2010), but enhanced after nicotine administration (Larrison et al., 2004; Rycroft et al., 2006). We chose acute VAR dosing as single doses of VAR up to 3 mg have been reported to be well-tolerated even among nonsmokers (Faessel et al., 2006) and our focus for clinical relevance was the immediate response to single doses, which have been shown to interact with nicotinic receptors (Rollema et al., 2007). Our rationale for alcohol dose selections was that 0.8 g/kg increases ratings of stimulation, liking, and wanting in heavy social drinkers (King et al., 2011) and to compare this with 0.4 g/kg, a lighter subthreshold dose, which produces more mild subjective changes. The PL beverage was included as a control for alcohol expectancy effects.

EXPERIMENTAL PROCEDURE

The University of Chicago Hospital's Institutional Review Committee for the use of human subjects approved the experimental protocol. Experimental sessions were conducted in comfortably furnished rooms with a television/VCR, magazines, and a computer for administering questionnaires.

Figure 1 shows the timing of procedures during sessions. Upon arrival (12:00 PM) at the laboratory for each session, the subject provided breath and urine samples to confirm compliance with abstinence instructions and to confirm nonpregnancy in women. The subject relaxed in the testing room before baseline (BL) subjective, vital signs, and eye tracking measures were obtained. The subject then consumed a capsule (at 12:30 PM) that contained either 2 mg VAR or PL. During the following several hours, the participant relaxed in the testing room and subjective and cardiovascular measures were obtained at regular intervals, a light lunch was given, and the eye tracking tasks were reexamined. The drinking interval began 3 hours after administration of the capsules (at 3:30 PM). This was chosen to coincide with peak plasma levels of VAR (Kikkawa et al.,

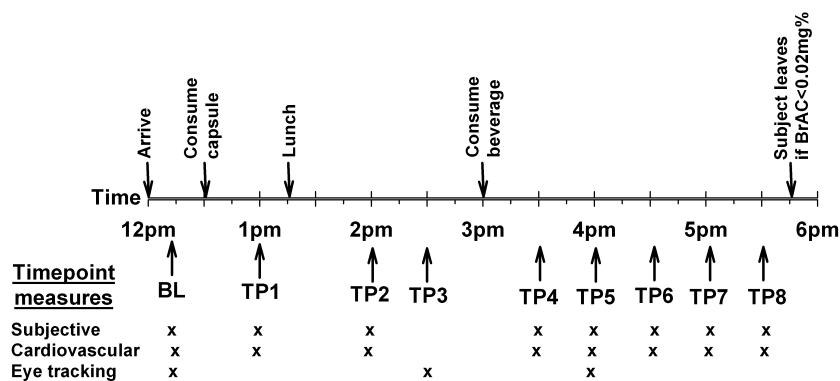


Fig. 1. Schematic showing the timing of drug and drink administration, and collection of subjective, cardiovascular, and behavioral measures during the experimental sessions. BL, baseline; TP, timepoint.

2011). As in our prior studies (e.g., King et al., 2011), participants consumed a beverage containing 0, 0.4, or 0.8 g/kg alcohol over 15 minutes (two 5-minute periods of consuming a half portion with a 5-minute rest in between). Subjective and cardiovascular measures were obtained regularly after beverage consumption (timepoints 4 to 8), and the eye tracking task was readministered during approximate peak BrAC, that is, 45 to 60 minutes after consuming the beverage. The final timepoint was at 5:30 PM (150 minutes after consumption of the beverage). In-between the measurements, participants were allowed to watch television, movies, or read. At the end of the session, participants completed a questionnaire to rate their overall experience and were then allowed to leave the laboratory. At the end of the study, participants were debriefed about the study aims and received payment.

Dependent Measures

Subjective effects of drugs were assessed using the Addiction Research Centre Inventory (ARCI; Martin et al., 1971), the Drug Effects Questionnaire (DEQ; Folstein and Luria, 1973), and the Biphasic Alcohol Effects Questionnaire (BAES; Martin et al., 1993). “Nauseated” was also assessed using an 11-point scale similar to that used in the BAES (0 “not at all” to 10 “extremely”). The Brief Questionnaire of Smoking Urges (BQSU; Tiffany and Drobes, 1991) was included to assess ratings of urge to smoke during the sessions.

Heart rate and blood pressure were measured at repeated intervals (see Fig. 1) using a digital monitor (Dinamap 1846SX; Critikon, Tampa, FL). At each interval, 3 readings were obtained and the average was used in analyses.

Eye movements were measured at 3 times (i.e., precapsule, 150 minutes postcapsule, and 45 minutes postdrink) and analyzed using the VisualEyes™ VNG system (Micromedical Technologies, Chatham, IL), a noninvasive oculographic device (for details, see Roche and King, 2010). In brief, subjects wore goggles containing a monocular camera designed to center and track the pupil of the right eye as a 2.5 × 5 mm red LED moved along a digital light bar placed 1 m in front of the subject. At each timepoint (BL, postcapsule, postbeverage), the subject tracked random horizontal and vertical targets to calibrate eye position and then completed 3 tasks: (i) Smooth Pursuit—the subject was instructed to follow a target travelling horizontally across the display in a predictable, oscillating sinusoidal waveform for 75 seconds; (ii) Pro-saccade—the subject was instructed to locate and fixate on successive targets that were presented at random locations for 1 to 3 seconds; and (iii) Anti-saccade—the subject was instructed to direct visual gaze to the mirror position on the opposite side of the midline of randomly presented targets. The outcome measure for smooth pursuit was *gain*, the ratio of the velocity of the subject’s eye to the velocity of the stimulus. For

both saccade tasks, the software calculated *latency* (the interval in milliseconds between target presentation and initiation of the saccadic eye movement), *velocity* (the peak rate in degrees/s of the saccadic eye movement), and *accuracy* (the ratio of the amplitude of the initial saccade to the amplitude of target) for all directionally correct saccades. As in Roche and King (2010), directionally incorrect saccades and those 50% below and 133% above each subject’s mean were discarded as these were likely artifacts due to movements or blinks. *Percent Accepted* refers to the number of directionally correct saccades accepted by the software, divided by the number of target presentations in each saccade task ($n = 30$). Two subjects’ eye tracking data were not analyzed due to technical difficulties.

Drugs

VAR (2 mg, CHANTIX®, Pfizer, New York, NY) was administered in opaque gelatin capsules (size 00) with dextrose filler. PL capsules contained only dextrose. Beverages consisted of flavored drink mix, water, and a sucralose-based sugar substitute and the appropriate dose of 190-proof ethanol, with 16 and 8% alcohol by volume for the high and low doses, respectively, and 1% alcohol by volume for PL as a taste mask. Women received an approximately 85% of the dose of alcohol administered to men (i.e., 0.34 or 0.68 g/kg) to adjust for gender differences in body composition (Sutker et al., 1983).

Data Analysis

Changes in the subjective and cardiovascular measures during each experimental session were calculated as the area under the curve (AUC; using the trapezoid method) relative to BL. The effects of VAR upon the measures *before drinking* were assessed by comparing the average AUC before drinking during the 3 VAR sessions to that during the PL sessions using a paired samples *t*-test. The effect of repeated exposure to VAR was assessed by comparing drug responses (before drinking) on the first, second, and third administrations using a 1 factor (Session) analysis of variance (ANOVA) with repeated measures. The effects of alcohol alone upon dependent measures, that is, during the PL pill sessions, were assessed by comparing the AUCs postdrink using a 1 factor (Drink) multivariate ANOVA. Significant effects were further examined using pair wise comparisons with correction for multiple testing. Then, effects of VAR, alcohol, and their interactive effects upon the measures were assessed using 2 within-subjects factor (Drug × Drink) multivariate analyses upon AUC values. For interactions between VAR and alcohol, the 4 primary subjective measures (BAES, Stimulation and Sedation, DEQ liking, and ARCI LSD) differences were considered significant at $p < 0.013$ (Bonferroni correction for multiple testing). For secondary measures, differences were considered significant at $p < 0.007$.

Effect sizes are reported using partial eta squared (η_p^2) for analyses of variance; 0.1, 0.3, and 0.5 are considered small, medium, and large effect sizes, respectively.

As eye tracking measures were collected at less frequent intervals than the other measures (i.e., at 3 timepoints) due to the length of time to administer this task, data were analyzed using raw data 3 factor (Pill \times Drink \times Time) repeated measures ANOVAs for smooth pursuit, saccade, and anti-saccade tasks. The effects of alcohol alone were assessed using a 2 factor (Drink \times Time) repeated measures ANOVA only within the PL pill sessions. Interactions at $p < 0.05$ were further explored with Tukey's post hoc tests. Since nausea is the most common side effect of VAR particularly during early dosing that also occurred in this study, ratings for the item "nauseated" were included as a covariate in all the above-mentioned analyses.

RESULTS

Demographic Characteristics

The demographic characteristics of participants including levels of current drinking and smoking, are shown in Table 1. The majority of subjects were of European American descent and aged in their mid-20s. Participants reported consuming on average 4.5 ± 0.2 alcohol drinks per occasion with 3.6 ± 0.4 occasions per week. Similar to prior studies, they engaged in frequent binge drinking with an average of 7.8 ± 1.1 episodes per month. They smoked on average 3.9 ± 0.7 cigarettes per smoking day, and reported an average of 3.6 ± 0.6 smoking days per week. On drinking days, they smoked an average of 4.7 ± 1.0 cigarettes. The mean Fagerström Test for Nicotine Dependence [FTND] score (Heatherston et al., 1991) for participants was 0.5 ± 0.2 (range 0 to 3), supporting the lack of physical nicotine dependence in the sample.

Effects of Varenicline Before Drinking

The effects of VAR alone (i.e., before the beverage consumption interval) are shown in Fig. 2. Relative to PL, VAR significantly increased ratings of "feel drug" [$t(14) = -4.3$, $p = 0.001$], "feel high" [$t(14) = -2.7$, $p < 0.05$], and dysphoria [ARCI LSD, $t(14) = -4.7$, $p < 0.001$], and decreased ratings of "drug liking" [$t(14) = 4$, $p = 0.001$] and "want more drug" [$t(14) = 2.9$, $p = 0.01$]. VAR increased ratings of "nauseated": mean peak scores were 0.02 ± 0.02 for PL, and 2.12 ± 0.50 for VAR: range 0 to 6 [$t(14) = -4.3$, $p = 0.001$]. However, these ratings were in the mild range (average score of 2.12 on a scale with ratings up to 10), and no subject vomited. VAR also significantly increased systolic [$t(14) = -2.3$, $p < 0.05$] and diastolic blood pressure [$t(14) = -3.4$, $p < 0.01$] and heart rate [$t(14) = -2.8$, $p < 0.05$]. Finally, there were few effects of VAR alone on eye movement responses, with the exception that VAR produced shorter latencies to initiate anti-saccades [Drug \times Time: $F(2, 24) = 4.4$, $p < 0.05$; VAR vs. PL postcapsule, $p < 0.01$], and increased the percent of accepted pro-saccades [Drug \times Time: $F(2, 24) = 3.9$, $p < 0.05$; VAR vs. PL postcapsule, $p < 0.05$]. Given that participants were light smokers, urge to smoke ratings were low, and were not significantly

Table 1. Demographic and Drug Use Characteristics of Participants

Characteristic	Mean \pm SEM (range)
N male/N female	8/7
Age (years)	26.9 ± 1.1 (21–35)
BMI (kg/m^2)	23.7 ± 0.8 (18.9–29.0)
Race	
# European American	13
# African American	1
# >1	1
Smoking characteristics	
FTND total	0.5 ± 0.2 (0–3)
# Smoking days/mo	15.5 ± 2.7 (1–26)
# Cigs/nondrinking day	1.9 ± 0.5 (1–5)
# Cigs/drinking day	4.7 ± 1.0 (1–11.2)
Alcohol drinking	
# Drinking days/mo	15.5 ± 1.6 (5–25)
# Drinks/drinking day	4.5 ± 0.2 (3–7)
# Binges in last month	7.8 ± 1.1 (2–19)
Other drug use	
Caffeine cups/wk	20.0 ± 4.8 (1–70)
Marijuana times/mo	4.2 ± 1.6 (0–15)
Lifetime drug use (% ever used)	
Marijuana	93
Opiates	93
Hallucinogens	67
Stimulants	60
Inhalants	33
Sedatives	27

BMI, body mass index; FTND, Fagerström Test for Nicotine Dependence score.

affected by VAR. The effects of VAR did not differ with repeated exposure (all $p > 0.2$).

Effects of Alcohol

Alcohol alone produced its expected effects. The 0.4 g/kg dose produced minimal eye movement or subjective effects, except for increased self-reported stimulation [Drink: $F(2, 13) = 6.1$, $p = 0.013$, $\eta_p^2 = 0.5$; 0 vs. 0.4 g/kg, $t(14) = -3.2$, $p < 0.01$]. The 0.8 g/kg dose increased ratings of "feel drug" [Drink: $F(2, 13) = 5.5$, $p = 0.018$, $\eta_p^2 = 0.5$; 0 vs. 0.8 g/kg, $t(14) = -3.4$, $p < 0.01$], "drug liking" [Drink: $F(2, 13) = 4.6$, $p = 0.03$, $\eta_p^2 = 0.4$; 0 vs. 0.8 g/kg, $t(14) = -2.5$, $p = 0.027$], "feel high" [Drink: $F(2, 13) = 7.5$, $p = 0.007$, $\eta_p^2 = 0.5$; 0 vs. 0.8 g/kg, $t(14) = -3.6$, $p < 0.01$], and urge to smoke [Drink: $F(2, 13) = 7.5$, $p = 0.03$, $\eta_p^2 = 0.4$; 0 vs. 0.8 g/kg, $t(14) = -2.6$, $p = 0.02$]. Alcohol at 0.8 g/kg also impaired smooth pursuit gain [Drink \times Time: $F(4, 48) = 4.6$, $p < 0.01$; 0 vs. 0.8 g/kg, $p < 0.001$], pro-saccade latency [Drink \times Time: $F(4, 48) = 5.1$, $p < 0.01$; 0 vs. 0.08 g/kg, $p < 0.01$], and anti-saccade latency [Drink \times Time: $F(4, 48) = 5.6$, $p < 0.001$; 0 vs. 0.8 g/kg, $p < 0.01$]. Alcohol did not significantly influence cardiovascular measures.

Varenicline Effects on Alcohol Responses

VAR significantly increased ratings of dysphoria (ARCI LSD) after consumption of both the PL beverage and 0.4 mg/kg alcohol, but not after 0.8 g/kg alcohol [see Fig. 3;

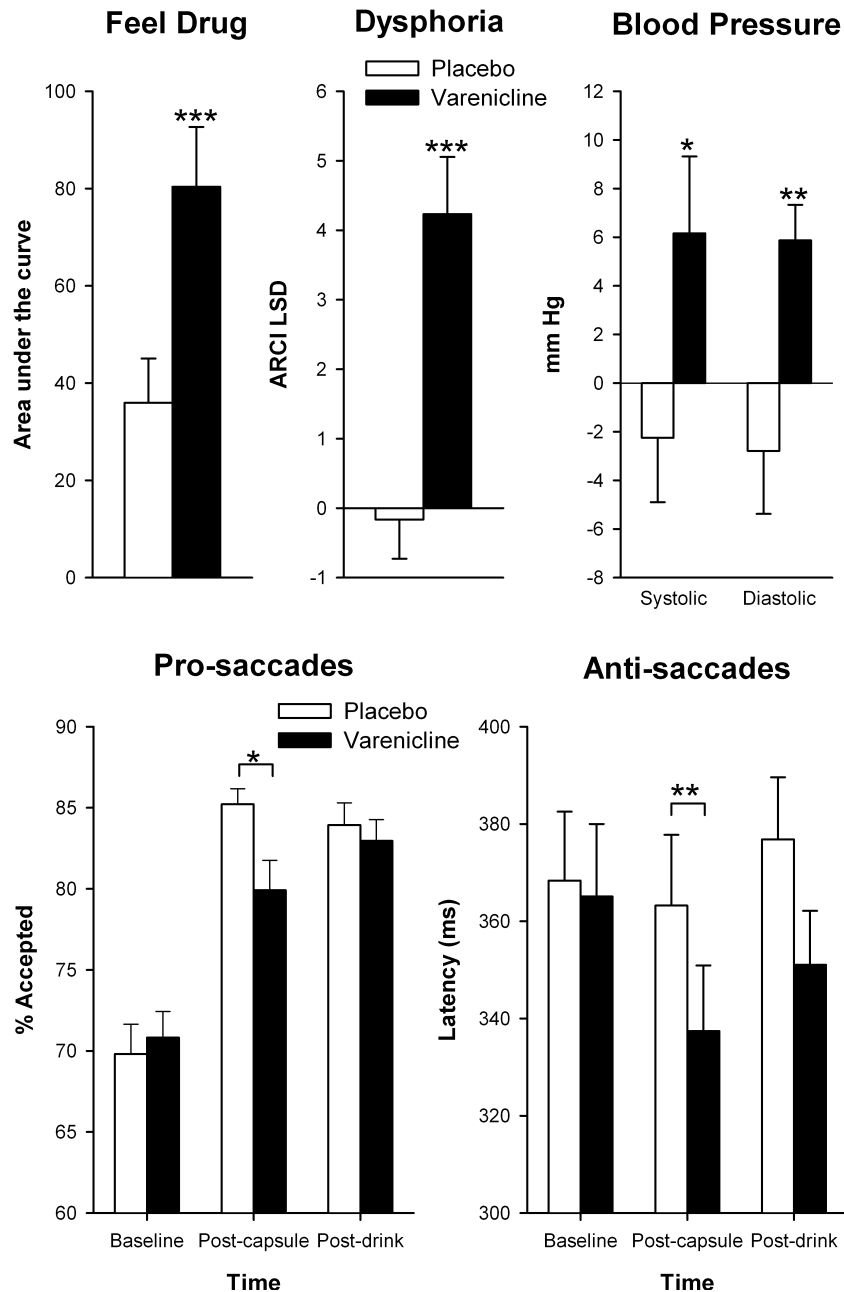


Fig. 2. Effects of varenicline (2 mg) upon subjective, cardiovascular, and eye tracking measures before drinking. Asterisks indicate a significant difference between placebo and varenicline: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Drug \times Drink: $F(2, 13) = 4.5$, $p < 0.05$, $\eta_p^2 = 0.4$] perhaps because 0.8 g/kg alcohol increased ARCI LSD by itself. VAR also tended to attenuate ratings of drug liking after 0.4 g/kg alcohol [Drug \times Drink: $F(2, 13) = 4.5$, $p < 0.08$, $\eta_p^2 = 0.3$]. VAR did not alter alcohol-induced increases in urge to smoke [Drug \times Drink: $F(2, 13) = 0.73$, $p = 0.5$, $\eta_p^2 = 0.1$].

VAR attenuated some of the effects of alcohol (0.8 g/kg) on eye movements. It reduced the alcohol-related increase in latency to initiate anti-saccades [see Fig. 4; Drug \times Drink \times Time: $F(4, 48) = 3.0$, $p < 0.05$; PL-0.8 vs. VAR-0.8, $p < 0.01$] and it increased the percentage of accepted pro-saccades [Drug \times Drink: $F(2, 24) = 3.7$, $p < 0.05$; PL-0.8

vs. VAR-0.8, $p < 0.05$]. Finally, there was a significant interaction of VAR and alcohol upon the percentage of accepted anti-saccades [Drug \times Drink \times Time: $F(4, 48) = 3.0$, $p < 0.05$], but post hoc testing revealed that this was driven by BL differences and variability during the PL drug session.

Varenicline Effects on Alcohol Responses After Controlling for Nausea

Because VAR increased ratings of feeling nauseated, analyses were repeated controlling for nausea. Controlling for nausea did not influence the previous findings, and in fact

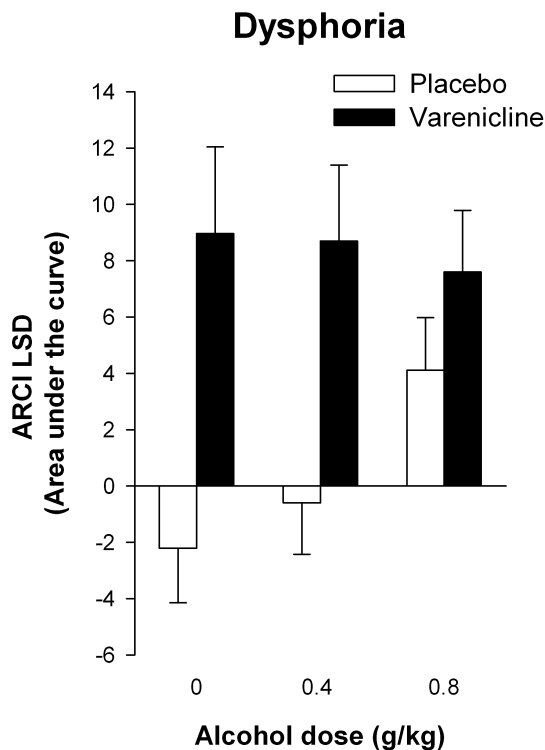


Fig. 3. Effects of varenicline (2 mg) and alcohol upon negative mood. Bars represent the mean area under the curve \pm SEM relative to precapsule baselines over the entire session.

strengthened the effects of VAR upon negative mood after drinking, that is, increased ARCI LSD after 0 and 0.4 g/kg alcohol only [Drug \times Drink: $F(2, 12) = 5.4, p = 0.02, \eta_p^2 = 0.5$].

DISCUSSION

VAR has been shown to reduce alcohol consumption in mice, rats, and humans (Fucito et al., 2011; Kamens et al., 2010a; McKee et al., 2009; Steensland et al., 2007; Wouda et al., 2011), and may do so by attenuating the positive

subjective effects or potentiating the negative subjective effects of alcohol. In this study, we examined the influence of acute pretreatment with VAR (2 mg) on subjective responses to alcohol in healthy social drinkers. We found that VAR increased the aversive effects of alcohol as indexed by ARCI LSD, an effect that was observed even after controlling for VAR-induced nausea. Thus, the mechanism by which VAR may reduce alcohol drinking behaviors is by increasing aversive subjective effects after consumption, thereby opposing the rewarding efficacy of alcohol and the likelihood of continued drinking behavior.

Our finding that VAR increased aversive subjective effects in a majority of subjects is consistent with both preclinical (Kamens et al., 2010b) and clinical studies (Fucito et al., 2011). Although our finding of increased negative mood (ARCI LSD) after VAR was only marginally significant after correction for multiple testing, power estimates indicated a medium size effect. VAR did not increase dysphoria or somatic effects (ARCI LSD) after the 0.8 g/kg dose of alcohol, perhaps because these effects of alcohol, as measured by overall AUC response, were already comparable to the effects of VAR alone.

These findings extend current clinical knowledge of the efficacy and tolerability of VAR among heavy drinkers to a non-nicotine-dependent sample who frequently smoke in the context of alcohol drinking. McKee and colleagues (2009) previously reported that VAR decreased alcohol consumption, craving, and positive subjective alcohol effects among heavier smokers than those enrolled in the current study. In addition, Fucito and colleagues (2011) showed that 2 mg VAR administered daily for 4 weeks increased sedative effects, decreased alcohol craving and resulted in fewer heavy drinking days among heavy smokers (a pack a day) undergoing treatment for smoking cessation. Thus, our findings demonstrate that while acute administration of VAR mildly increased ratings of nausea, the drug was generally well tolerated and may potentially reduce drinking among

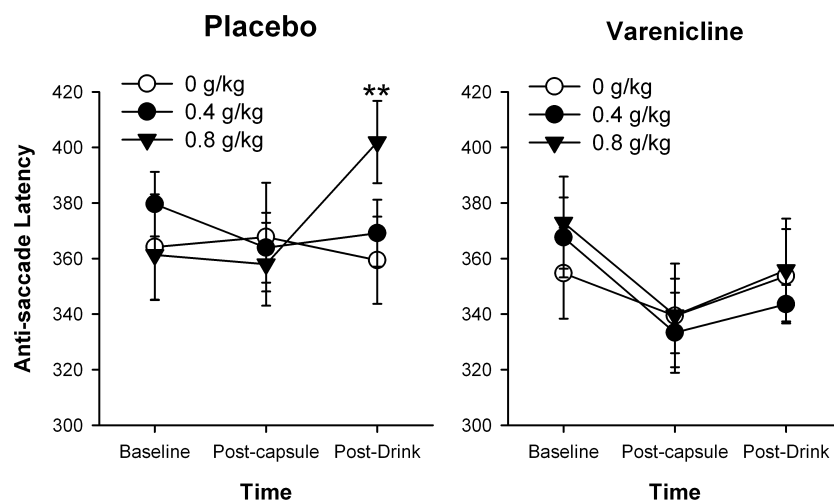


Fig. 4. Effects of varenicline and alcohol upon anti-saccade latency. Data points represent mean absolute scores \pm SEM at repeated times during the sessions.

moderate-to-heavy drinkers who are also nondependent social smokers. Furthermore, our data are consistent with animal and human studies showing that VAR potentiates the sedative-hypnotic effects of alcohol (Fucito et al., 2011; Kamens et al., 2010b) and our results suggest that, in nondependent smokers, the net effect of the nicotinic receptors activated by VAR may be increased aversive subjective effects.

To our knowledge, no previous studies have examined the effects of VAR on a sensitive and specific objective measure of alcohol's impairing effects, such as eye tracking performance. Nicotine has been shown to improve anti-saccade performance (Larrison et al., 2004; Rycroft et al., 2006) and produce minimal effects on pro-saccade and smooth pursuit tasks (Reilly et al., 2008). In our study, VAR decreased anti-saccade latency (i.e., like nicotine it improved anti-saccade performance) and also reduced alcohol-induced impairment of this measure. VAR did not, however, affect measures of pro-saccade (i.e., latency, velocity, or accuracy) or smooth pursuit (i.e., gain) performance. The anti-saccade task is a measure of response inhibition and volitional action that requires multiple cognitive processes, including sustained attention and working memory. Nicotine is known to enhance response inhibition, attention, and working memory (Heishman et al., 2010), which may contribute to its beneficial effect on anti-saccade performance. Thus, we may hypothesize that VAR counteracts the detrimental cognitive effect of alcohol by increasing attention and working memory through its agonist action on nicotinic receptors; however, more research will be needed in independent samples.

Our subjective and objective results suggest that there may be a specific interaction between VAR and alcohol, possibly mediated via nicotinic receptors. Although VAR produced some nausea, which may have complicated the interpretation, its interactions with alcohol were evident even after controlling for the acute effects of the drug on nausea ratings. Nicotinic receptors containing the $\beta 2$ subunit have been implicated in initial adverse subjective responses to alcohol in humans (Ehringer et al., 2007), the sedative-hypnotic effects of alcohol (Kamens et al., 2010b), in drug-induced dopamine release in the nucleus accumbens (Coe et al., 2005; Ericson et al., 2009; Rollema et al., 2007) and in VAR-induced attenuation of alcohol consumption in animals (Butt et al., 2004; Hendrickson et al., 2010; Owens et al., 2003). However, others suggest that other receptor subtypes are more specific to VAR's effect on alcohol consumption (Chatterjee et al., 2011; Jerlhag et al., 2006). Thus, the interactive effects of VAR and alcohol reported in this study are probably mediated by activity at nicotinic receptors; however, our results do not provide definitive insights into the specific subtype involved.

There were several limitations to the current study. First, the relatively small sample size meant that interactions of medium effect size did not meet significance after correction for multiple testing. Thus, although the findings are in line with previous studies and some were consistent across similar measures, for example, BAES sedation and ARCI LSD both measure negative drug effects, they should be interpreted with

caution. Second, the VAR dosing profile used in our study is different to other clinical studies. Others have administered VAR over a 1-week pretreatment phase with a titrated dosing schedule to reduce side effects prior to behavioral testing in the laboratory (Fucito et al., 2011; McKee et al., 2009) to avoid adverse effects such as nausea and vomiting (Faessel et al., 2006). Our study focused on single acute dose administration prior to behavioral testing and VAR did increase ratings of nausea, but these were relatively mild and controlling for nausea did not alter the main findings of the study. However, any interactions between VAR and alcohol, which are mediated by changes in nicotinic receptor populations, that is, numbers or subunit composition, as a result of repeated dosing during pretreatment would not have been measured as this was outside the scope of this study (Turner et al., 2011). Third, our study utilized a group of nondependent heavy drinking smokers and so the results may not generalize to other drinkers who are also nicotine-dependent. Nevertheless, our findings demonstrate the potential clinical efficacy of VAR among this particular subset of heavy drinkers who may not otherwise be considered for treatment with the drug. Finally, although we assessed "want more drug" after alcohol administration, we did not specifically examine "alcohol craving" as in prior research (McKee et al., 2009); therefore, we are unable to make direction comparisons on craving per se and its possible association to increased aversive effects of alcohol.

In conclusion, the findings of this study support those of earlier investigations that demonstrate effects of VAR upon subjective responses to alcohol. We have extended these findings by demonstrating in a group of light nondependent smokers that even acute doses of VAR increase the negative subjective effects of alcohol, which occur independently of increases in somatic complaints (i.e., nausea). Furthermore, we report that VAR offsets alcohol-induced impairments in eye movements, perhaps independently of its effect upon alcohol subjective responses. Thus, this study, combined with previous evidence, suggests that VAR may reduce alcohol drinking behaviors among light smokers by increasing the negative subjective effects of a low dose of alcohol, thus reducing the likelihood of a drinking episode becoming a binge.

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