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Nicotine increases alcohol self-administration in non-dependent male smokers

Sean P. Barrett [a,*], Matthew Tichauer [a], Marco Leyton [b], Robert O. Pihl [a,b]

[a] *Departments of Psychology McGill University, Montreal, Que., Canada H3A 1B1*
[b] *Psychiatry McGill University, Montreal, Canada*

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Abstract

Background: Alcohol and tobacco are commonly co-administered, yet little is known about the effects of acute nicotine administration on alcohol consumption in humans. This study sought to determine how nicotine delivered by tobacco smoke influences alcohol intake in humans using a double-blind placebo controlled repeated measures design.
Methods: During two randomized 120 min sessions 15 male occasional smokers smoked four nicotine-containing or four denicotinized cigarettes at 30 min intervals. Throughout the session, subjects could earn units of their preferred alcoholic beverage and glasses of water using a progressive-ratio (PR) task.
Results: Wilcoxon signed-rank tests indicated that nicotine increased alcohol self-administration in a significant proportion of participants ($P \leq 0.03$) without affecting water consumption ($P \geq 0.16$). A two-way ANOVA supported this observation further, and, compared to denicotinized cigarettes, the nicotine-containing cigarettes increased PR breakpoints for alcohol but not water, as reflected by a Cigarette × Beverage interaction ($P \leq 0.055$).
Conclusions: The present data suggest that acute nicotine administration increases alcohol consumption in at least a subset of smokers.

Keywords: Alcohol; Nicotine; Addiction; Self-administration; Polysubstance use; Progressive ratio

1. Introduction

The two most commonly abused substances in the general population, alcohol and nicotine, are frequently co-administered (e.g., Batel et al., 1995). The prevalence of tobacco smoking in alcoholics is thought to be as high as 90%, compared to less than 30% in the general population (e.g., Sobell et al., 1990; Romberger and Grant, 2004). Similarly, smokers are 50% more likely to drink regularly than adult non-smokers (Kozlowski and Ferrence, 1990). Some evidence suggests that these associations reflect an ability of ethanol and nicotine administration to increase motivation to obtain the other substance. In smokers, acute alcohol administration is consistently reported to increase cigarette self-administration (Griffiths et al., 1976; Mello et al., 1980; Keenan et al., 1990). In comparison, the converse association is less well understood. There are several reports that, in rodents, chronic or repeated nicotine administration increases alcohol consumption (Smith et al., 1999; Le et al., 2000, 2003; Clark et al., 2001; Soderpalm et al., 2000), but this effect has not been uniformly replicated, and decreased alcohol self-administration has also been reported (Sharpe and Samson, 2002). Similarly, acute nicotine administration has been reported to increase (Gauvin et al., 1993), decrease (Nadal et al., 1998), and have no effect on alcohol intake (Nadal and Samson, 1999). Such inconsistent findings may be related to differences in doses, administration regimens, or rodent strains (Le, 2002). The contribution of these factors to the co-administration of nicotine and alcohol in humans remains unknown; to our knowledge, the effect of nicotine on alcohol self-administration in humans has yet to be determined. In a previous investigation acute cigarette smoking was found to increase alcohol related responding in male social drinkers (Perkins et al., 2000). However, because this study did not have a placebo smoking

* Corresponding author. Present address: Dalhousie University, Life Sciences Centre, Department of Psychology, 1205 Dr. Penfield Ave., Halifax, Nova Scotia, Canada B3H 4J1 Tel.: +1 514 398 6119; fax: +1 902 494 6585.
E-mail address: Sean.Barrett@dal.ca (S.P. Barrett).

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condition it was not possible to determine the extent to which the findings resulted from a pharmacological effect of nicotine.

In the present study, we sought to determine how nicotine delivered by tobacco smoke influences alcohol administration in humans using a double-blind placebo controlled repeated measures procedure, in which cigarettes made of nicotine-containing or denicotinized tobacco were smoked throughout the course of a drinking session. Since nicotine withdrawal may affect alcohol craving and consumption in dependent smokers (Palfai et al., 2000; see also Cooney et al., 2003; Colby et al., 2004), the present protocol examined non-dependent occasional smokers to avoid this potential confound.

2. Methods

2.1. Participants

Fifteen non-dependent male 'occasional' smokers (80% Caucasian) between the ages of 18 and 30 (mean = 22.3 ± 1.8) were recruited from the community through advertisements placed in local community newspapers and on university websites. All were medically healthy, free from current or previous mental illness including past or present substance use disorders (including nicotine dependence) as determined by a semi-structured clinical interview using DSM-IV criteria (First et al., 1995), and all scored a 0 on the Fagerström test for nicotine dependence (Heatherton et al., 1991). None reported the use of illegal drugs in the 30 days prior to the study, none were daily users of tobacco and none had a history of social, occupational or legal problems involving alcohol as determined by the Michigan Alcoholism Screening test (Pokorny et al., 1972). All had reached the minimum age to legally consume alcohol and tobacco in Quebec Canada and all reported having smoked a minimum of four cigarettes throughout the course of a drinking session on at least one occasion during the preceding year without experiencing any adverse consequences. On average participants reported consuming cigarettes on 2.7 ± 1.6 days and alcohol on 2.3 ± 0.8 days per week. Average daily consumption on days when the substance was used was 5.4 ± 1.6 cigarettes per day and 5.9 ± 2.1 drinks per day. Participants were informed that the study involved smoking two different brands of tobacco but not that one of the sessions used denicotinized cigarettes. Following a description of the study, all participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by a McGill University Research Ethics Committee.

2.2. Cigarettes

Prior to the study participants were asked to identify the brand(s) of cigarettes that they smoked in order to ensure their unfamiliarity with the specific brands of tobacco used during the testing sessions. Participants were informed that on each test day that they would be required to smoke four cigarettes over a 2-h period and that on each test day that a different brand of tobacco would be used. All cigarettes contained 65 g of tobacco, and were prepared to appear identical. The 'denicotinized' cigarettes were prepared using *Quest 3* tobacco (Vector Tobacco Inc., USA), and provided maximum nicotine yield of 0.05 mg and a tar yield of 10 mg. The 'nicotine' containing cigarettes were prepared using *Player's Light* tobacco (Imperial Tobacco Limited, Montreal Canada) and they provided nicotine and tar yields of 1.2 and 12 mg, respectively. This tobacco was selected for its relatively high nicotine to tar ratio and its relatively similar average tar yields to the denicotinzed tobacco.

2.3. Alcoholic beverages

Prior to the study sessions, each participant identified a preferred alcoholic beverage. The beverage could consist of any 80-proof liquor with a non-alcoholic mixer; the same beverage was to be consumed on both days. Choice of beverage was restricted to 80-proof liquors due to the high variability in the alcohol contents of commercially available brands of beer, wines and coolers. Participants were informed that on each test day they would be required to consume a minimum of one standard drink containing 12 g of 80-proof alcohol (38 ml) and that the maximum dose of alcohol that could be consumed on any day was 72 g or the equivalent of six-full standard drinks.

2.4. Subjective state

Participants were administered visual analogue scales (VAS) at baseline and immediately following the completion of each cigarette on each test day. Items were rated on a ten cm line labelled with the integers 1–10 and anchored with the words "least" and "most". Items included in the VAS were 'high', 'stimulated', 'energetic', 'anxious', 'sedated', 'intoxicated', 'want alcohol', 'like cigarette', 'crave cigarette', and 'crave alcohol'. Similar scales have been widely used to collect information about subjective drug effects in humans (e.g., Fischman and Foltin, 1991) and this method of data collection has been demonstrated to have acceptable psychometric properties (Bond and Lader, 1974).

2.5. Design

The research protocol was comprised of two test sessions. Each was conducted between 12 pm and 4 pm in the afternoon, was a minimum of 3 and a maximum of 14 days apart, was double blind, and was given in counterbalanced randomized order. In one condition subjects were required to smoke four 'nicotine' cigarettes and in the second condition four 'placebo' cigarettes were smoked. In both conditions, cigarettes were smoked at 30 min intervals throughout the

Table 1
Timeline of procedures during both self-administration sessions

Time of procedure	Tobacco and alcohol administration sessions
∼5 min after arrival	Breath alcohol and carbon monoxide analyses
∼10 min after arrival	Baseline VAS measure
∼12 min after arrival	Alcohol and water presentation
∼15 min after arrival	First cigarette followed by VAS subjective ratings
Immediately after VAS completion	Prime dose of alcohol
10 min after prime alcohol dose	Start of PR self-administration task
30 min after start of first cigarette	Second cigarette followed by VAS subjective ratings
60 min after start of first cigarette	Third cigarette followed by VAS subjective ratings
90 min after start of first cigarette	Fourth cigarette followed by VAS subjective ratings
120 min after start of first cigarette	End of PR self-administration task

VAS = visual analog scale. PR = progressive ratio.

first 90 min of the 120 min drinking session (t = 0, 30, 60, and 90 min). All participants were tested on separate days.

Participants arrived for each testing session having abstained from cigarettes for a minimum of 12 h, alcohol for a minimum of 24 h and food and caffeine for a minimum of 4 h (caffeine-free fluid intake was not restricted prior to the study). At this time they provided a breath alcohol sample using an alco-sensor III intoximeter (Thomas Security, Montreal, Canada) and a reading of 0.000 g of alcohol per 210 l of breath was required to confirm abstinence. Abstinence from tobacco was confirmed with a breath carbon monoxide analyzer (Vitalograph Breath CO, Lenexa, KS), using a maximum cutoff of five parts per million.

A timeline outlining the sequence of procedures is presented in Table 1. After completing baseline measures participants were comfortably seated in a chair in front of a glass containing 100 ml of water, a glass containing their preferred alcoholic beverage (containing 38 ml of 80-proof alcohol and 100 ml of mix) and a computer on a large table. They were told that after smoking their first cigarette of the day that they would receive one 'free' alcoholic drink but that all subsequent drinks of either type would have to be 'earned' using a computerized task (described below). Participants examined both of the drinks and were given instructions on how each could be earned. They were then told to smoke their initial cigarette. For each cigarette consumed they were instructed to inhale the smoke as well as to complete the cigarette to the filter. The pace and duration of the 'puffs' however was self-determined by the participant. Following the completion of their first cigarette participants were required to complete the VAS and then consume their 'free' alcoholic beverage within 10 min. The requirement for participants to administer this 'free' dose of alcohol was included in the protocol to normalize drinking in the laboratory, to ensure that alcohol was consumed on both test days and to enable comparisons with other studies examining alcohol self-administration in humans following a pharmacological manipulation (Modell et al., 1993; Perkins et al., 2000; Enggasser and de Wit, 2001; Petrakis et al., 2002; Leyton et al., 2004).

Immediately after consuming the 'free' dose of alcoholic, participants could begin using a computerized progressive ratio (PR) task to earn up to 10 mixed alcoholic drinks, each containing 6 g (19 ml) of alcohol and 50 ml of mix, and up to 10 100 ml drinks of water. To earn alcoholic beverages they would be required to repeatedly press the letters 'd' and 'r' a predetermined number of times, while water could be

Table 2
Number of water and alcohol units consumed during progressive ratio task in the nicotine and placebo cigarette conditions

Participant	Units of water consumed-nicotine	Units of water consumed-placebo	Difference in number of water consumed	Units of alcohol consumed-nicotine	Units of alcohol consumed-placebo	Difference in number of alcohol consumed
1	5	4	+1	8	5	+3
2	0	0	0	10	6.5	+3.5
3	0	0	0	10	10	0
4	4	3	+1	10	9	+1
5	0	0	0	10	8	+2
6	2	2	0	2	1	+1
7	0	10	−10	10	5	+5
8	7	9	−2	8	7	+1
9	6	6	0	8	6	+2
10	3	5	−2	0	0	0
11	0	1	−1	5	4	+1
12	4	3	+1	2	9.5	−7.5
13	5	6	−1	8	8	0
14	7	10	−3	7	6.5	+0.5
15	2	1	+1	10	8.5	+1.5

Difference values reflect changes in consumption over the two sessions (nicotine–placebo). Partially completed drinks were weighted as 1/2 units.

earned by pressing 'w' and 'a'. For each type of drink, the first earned beverage required 40 button presses. To earn subsequent drink of either kind the number of required button presses increased one-and-one-half times (i.e., 60, 90, 135, 203, 304, 456, 684 and 1026, 1538 clicks). Each type of drink required a total of 4536 button presses to reach the maximum amount allowed (software for this task is available upon request to M.L.). Each session lasted until the maximum number of alcohol or water drinks were earned or to a maximum of 2 h (excluding washroom breaks). While drinks could be earned and consumed at any time during the session, there was no requirement for participants to earn any drinks during the sessions and they were required to remain seated in the testing room until each session was completed. Each participant self-determined the rate of administration of all earned beverages, but new drinks of the same kind could not be earned until the previous drink had been completed. Upon completion of the PR task, participants were brought a meal and remained in the laboratory until their BAC reached 0.04. They were then safely escorted home by one of the researchers or by taxi.

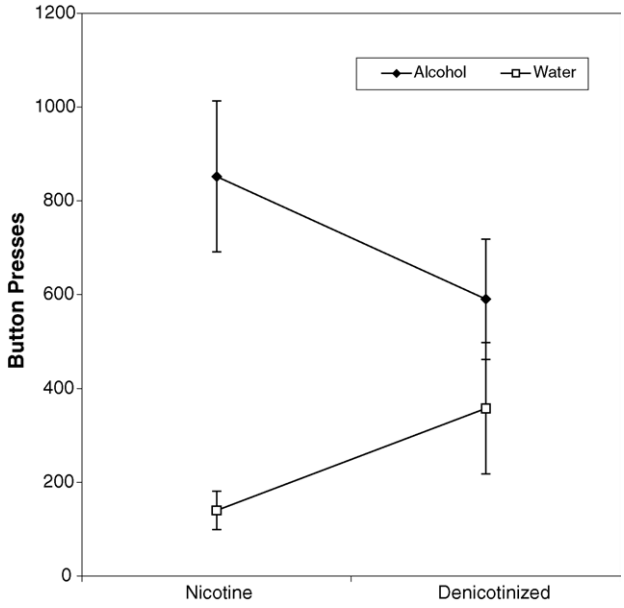

Fig. 1. Mean progressive ratio break points for number of button presses to earn alcohol and water drinks during the nicotine and denicotinized tobacco conditions. Vertical bars represent ±SEM. Analyses revealed overall increased responding for alcohol relative to water ($P \leq 0.01$) as well as a trend toward a relative preference for alcohol during the nicotine condition ($P \leq 0.055$).

3. Results

3.1. Alcohol and water self-administration

Because the behavioural PR data increase geometrically, the data were screened for normality. Using the Kolmogorov–Smirnov method, it was determined that each PR distribution was satisfactorily normal ($P > 0.05$) and this was confirmed through an inspection of the skewness and kurtosis of each variable (all absolute values < 2). To screen for outliers, Z-scores were calculated on the relative difference scores for PR responding in the two conditions (nicotine–denicotinized) and no outliers were identified (all absolute values < 3). Differences in the mean breakpoints for the number of button presses to earn alcohol and water drinks during the nicotine and placebo conditions were analyzed using a 2×2 ANOVA with drink type (water and alcohol) and cigarette type (nicotine-containing and denicotinized) as within-subjects factors. Fig. 1 presents the PR data for earned alcohol and water during the two smoking conditions. There was a significant main effect of drink type ($F_{1,14} = 8.79$, $P \leq 0.010$) reflecting increased responding for alcohol relative to water. Analyses also revealed a trend toward a drink × cigarette interaction ($F_{1,14} = 4.39$, $P \leq 0.055$) suggesting a greater relative preference for alcohol during the nicotine condition (Fig. 2).

Table 2 presents the number of water and alcohol units consumed by each participant on each test day. Because statistical outliers were identified (absolute Z score > 3) in the relative changes in water (participant 7) and alcohol consumption (participant 12) during the two test conditions, these data were analysed using non-parametric Wilcoxon signed-rank tests. The analyses revealed that a significant proportion of participants increased alcohol consumption in the nicotine condition relative to the denicotinized condition ($Z = -2.13$, $P \leq 0.03$), while water consumption was not systematically different in the two conditions ($Z = -1.41$, $P \geq 0.16$) (Fig. 3).

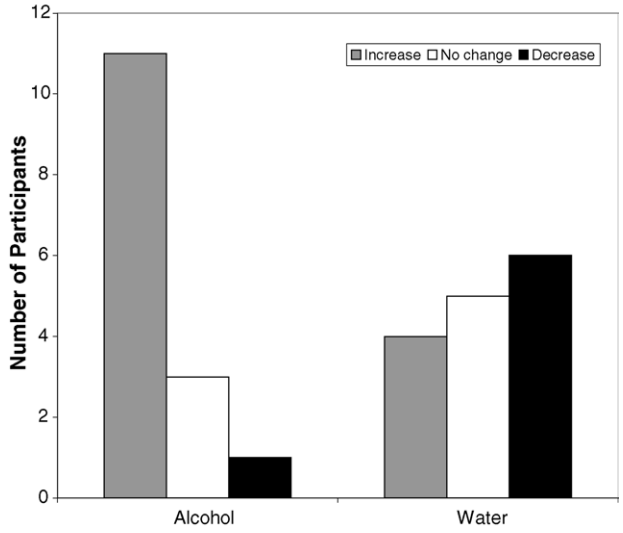

Fig. 2. Number of participants increasing, not changing, or decreasing their alcohol and water consumption during the nicotine administration test session. A significant proportion of participants increased alcohol consumption in the nicotine condition relative to the denicotinized condition ($P \leq 0.03$), while water consumption was not systematically different in the two conditions.

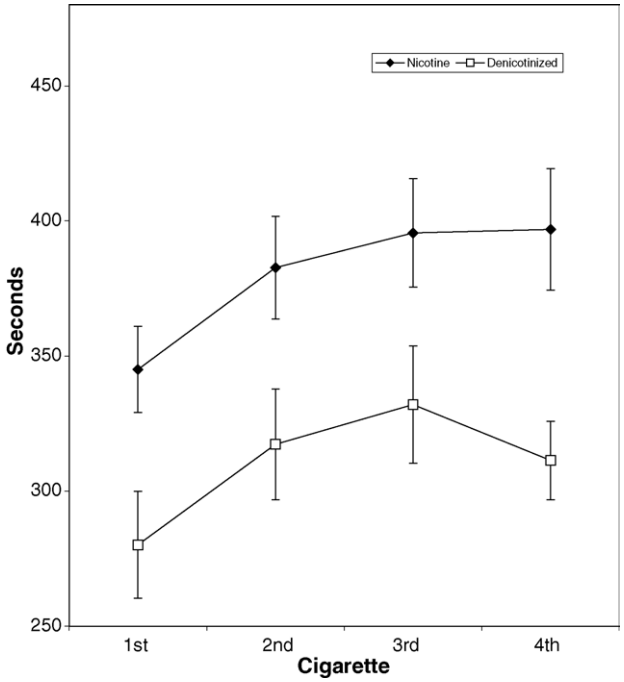

Fig. 3. Mean time to complete each nicotine-containing and denicotinized cigarette in seconds. Vertical bars represent ±SEM.

3.2. Subjective response to smoking

The subjective effects of the nicotine and placebo cigarettes prior to alcohol consumption were examined by comparing the relative changes from baseline in each VAS score following the first cigarette of each test day using paired samples *t*-tests. One subject did not provide a post-cigarette rating for 'high' on one of the test days limiting analyses for this variable to 14 participants.

Ingestion of the first nicotine cigarette was associated with significantly increased ratings of 'high' [$t(13) = 2.23$, $P \leq 0.044$], 'stimulated' [$t(14) = 2.55$, $P \leq 0.023$], 'sedated' [$t(14) = 3.06$, $P \leq 0.009$], and 'intoxicated' [$t(14) = 2.98$, $P \leq 0.010$] relative to the placebo cigarette. No systematic differences were evident for ratings of 'energetic', 'anxious', 'want alcohol', 'like cigarette', 'crave cigarette' or 'crave alcohol' ($P > 0.1$). Because simultaneous nicotine-induced increases in 'stimulated' and 'sedated' were not expected, bivariate correlations were performed among the variables significantly affected by nicotine administration. Nicotine-induced changes in 'stimulated' and 'sedated' were not related to each other [$r = -0.015$; $P \geq 0.96$], but each was positively associated with change in 'intoxicated' [stimulated-intoxicated: $r = 0.70$; $P \leq 0.004$; sedated-intoxicated: $r = 0.53$; $P \leq 0.043$], suggesting that there may have been differences in how the participants interpreted nicotine's intoxicating effects. Nicotine-induced change in 'high' was not significantly correlated with change in 'intoxicated' [$r = 0.44$; $P \geq 0.111$], 'sedated' [$r = 0.43$; $P \geq 0.128$] or stimulated [$r = 0.50$; $P \geq 0.067$]. Changes in none of these variables were related to overall nicotine related changes in alcohol consumption [$r < 0.2$; $P > 0.5$]. Relative differences in subjective responses following the initiation of alcohol consumption could not be meaningfully analysed because of substantial variability in both the rate and frequency of alcohol administration throughout the testing sessions.

3.3. Cigarette administration

In order to determine if the rates of self-administration for the nicotine-containing and denicotinized cigarettes significantly varied a 2×2 repeated measures ANOVA was performed using time to complete each cigarette (first, second, third, and fourth) and cigarette type (nicotine-containing and denicotinized) as within subjects factors. There were significant main effects for time of cigarette completion ($F_{3,42} = 11.77$, $P \leq 0.001$), reflecting the tendency for the first cigarette of each test day to be completed more quickly than subsequent cigarettes, as well as for cigarette type ($F_{1,14} = 21.91$, $P \leq 0.001$) reflecting slower administration of the nicotine-containing cigarettes. The cigarette type by time to completion interaction was not statistically significant ($P > 0.1$).

Because VAS ratings were collected immediately following the completion of each cigarette, we performed a series of post hoc stepwise regressions to determine if time to cigarette completion was associated with subjective state. For each cigarette, all corresponding subjective ratings were entered as potential predictors for the length of time of completion. For both the second ($r = 0.563$; $P < 0.029$) and third ($r = 0.544$; $P < 0.036$) nicotine-containing cigarettes the sole statistically predictor for time of cigarette completion was the respective 'intoxicated' rating, indicating that relatively high levels of intoxication were associated with a relatively slower pace of smoking. There was also a significant association between time of completion of the final 'denicotinized' cigarette and the corresponding 'like drink' rating ($r = 0.614$; $P < 0.015$), indicating that high levels of 'drink liking' were associated with a slower pace of smoking for this cigarette. No variables were found to be significantly associated with the time of completion of any of the other cigarettes ($P > 0.05$).

4. Discussion

In this study, nicotine administration via tobacco smoke increased alcohol consumption in a significant majority of the participants. While these findings are consistent with data demonstrating increased overall levels of alcohol consumption among smokers (e.g., Batel et al., 1995), to our knowledge this is the first placebo-controlled study to demonstration that nicotine acutely increases alcohol ingestion in humans.

Although the present study did not directly assess the mechanisms underlying nicotine's ability to potentiate alcohol self-administration, nicotine may increase alcohol ingestion through a neuropharmacological action. The appetitive

reinforcing properties of both drugs have been related to midbrain dopamine (DA) transmission (e.g., Di Chiara and Imperato, 1988), and evidence suggests that nicotine and alcohol may overlap in the mechanisms by which they promote DA release. In laboratory animals, both drugs appear to promote midbrain DA transmission through stimulation of nicotinic acetylcholine (NACh) receptors in the ventral tegmental area (e.g., Blomqvist et al., 1997; Soderpalm et al., 2000; Tizabi et al., 2002) and the blockade of NACh receptors decreases alcohol self-administration in animals (Blomqvist et al., 1996; Le et al., 2000) and alcohol drinking desire in humans (Chi and de Wit, 2003). Moreover, nicotine is also believed to enhance the DA response to other reinforcers by facilitating burst firing of the DA neurons (Rice and Cragg, 2004; Zhang and Sulzer, 2004) raising the possibility that nicotine increases alcohol responding by potentiating alcohol-related DA reinforcement. Finally, noradrenaline transmission has also been proposed to affect alcohol ingestion (Amit and Brown, 1982; Le et al., 2005), and nicotine increases noradrenaline release as well (e.g., Grenhoff and Svensson, 1989).

An alternative means by which nicotine may affect alcohol administration is through a pharmacokinetic interaction. Evidence suggests that nicotine alters mechanisms involved in hepatic alcohol metabolism (Schoedel and Tyndale, 2003) as well as rates of gastric emptying (Gritz et al., 1988), factors that might alter alcohol absorption and distribution. However, there is little direct empirical evidence to support this. Nicotine has failed to alter alcohol's pharmacokinetic properties in laboratory animals (Hisaoka and Levy, 1985; Collins et al., 1988) and evidence from human studies has been inconsistent (Perkins et al., 1995; Kouri et al., 2004). Thus, there is currently insufficient evidence to definitively exclude or support a pharmacokinetic explanation for our findings.

A relatively unexpected finding in the present study was that cigarette administration rates varied both within and between conditions. Nicotine-containing cigarettes were smoked at a slower rate than denicotinized tobacco, and for both types of cigarettes the first cigarette was smoked significantly faster than all others. Although the relatively faster pace of denicotinized tobacco administration is consistent with previous research indicating that smokers modify their 'puffing' behavior to achieve and maintain desirable nicotine levels (for review see Scherer, 1999), because changes in smoking rates were approximately equivalent in both conditions, it is unlikely that within session differences can be solely explained by attempts to optimize nicotine levels. An alternative explanation is that alcohol-related effects and/or intake may have influenced smoking rates following the initiation of drinking. This possibility appears to be consistent with post hoc findings that suggest the rates of administration of some cigarettes were associated with levels of intoxication (second and third nicotine cigarette) or drink liking (fourth placebo cigarette). While concurrent access to alcohol may have contributed to the variability in smoking rates, allowing participants to choose when they wanted to drink relative to tobacco administration was important to ensure the ecological validity of the findings.

The present results should be interpreted in light of the following methodological considerations. First, because we wished to control for potential confounding effects of nicotine withdrawal, participants were minimally nicotine dependent and the degree to which these results are applicable to heavier smokers remains unknown. Alternative designs to test the effects of nicotine on alcohol self-administration in dependent smokers are clearly needed. Second, the present protocol only tested men and it is possible that the findings may not extend to women. Evidence suggests that women are less sensitive to the pharmacological effects of nicotine than men (Perkins et al., 2002,1999) and that smoking may differentially affect alcohol consumption in men and women (Perkins et al., 2000). Additional research should be directed toward examining possible gender differences in alcohol–nicotine interactions. Third, since variability in the rate and frequency of alcohol self-administration was inherent in the research protocol, it was not possible to systematically assess the subjective effects associated with combined fixed doses of alcohol and nicotine. While previous research suggests that nicotine co-administration enhances several positive alcohol-related effects (Kouri et al., 2004; Perkins, 1995) as well as alcohol craving (Kouri et al., 2004) the present design did not allow us to determine how subjective effects were associated with changes in self-administration. It should be noted, however, that participants in the current study reported several discernable subjective effects of nicotine relative to placebo prior to alcohol ingestion including increased feelings of high, stimulation, and intoxication. Fourth, because the protocol imposed limits on the amount of alcohol consumed and the length of the drinking sessions it is possible that ceiling and floor limits may have influenced the magnitude of the observed effect. Indeed, in 5 of 11 cases where more alcohol was consumed during the nicotine than placebo condition, participants consumed the maximum possible dose during the nicotine session; among the three participants that ingested equal amounts of alcohol on both test days, one drank the minimum amount allowed on both days and a second consumed the maximum on both days. Nevertheless, despite this a significant majority of participants exhibited increased alcohol consumption during the nicotine condition. Finally although the sample size in this study was modest ($n = 15$), it was within the norms for investigations assessing within subject drug effects in humans and small sample size is typically associated with increased incidents of type II but not type I error.

In conclusion, to our knowledge, the present study is the first to demonstrate that nicotine administration via tobacco smoke increases alcohol self-administration in at least some smokers using a blinded placebo-controlled study. Because concurrent tobacco use may lead to alcohol dose escalation during drinking sessions, this practice may place some individuals at elevated risk for developing alcohol related problems. Future studies are needed to further delineate the effects

and consequences of nicotine and alcohol co-administration and to extend these findings to other groups of smokers.

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