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ORIGINAL INVESTIGATION

Pharmacological effects of naltrexone and intravenous alcohol on craving for cigarettes among light smokers: a pilot study

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Abstract
Rationale Although naltrexone has been widely researched in the context of drinking and smoking behaviors, with each substance studied separately, little is known about the effects of naltrexone on craving for cigarettes during alcohol intoxication.
Objectives The present study used a within-subjects double-blind placebo-controlled design to (1) examine the effects of alcohol, administered intravenously, on craving for cigarettes; (2) test the effects of naltrexone on cigarette craving during alcohol intoxication; and (3) examine the relationship between craving for alcohol and cigarettes across rising breath alcohol concentrations (BrACs).
Materials and methods Heavy drinking light smokers completed two counterbalanced intravenous alcohol challenge sessions, one after taking naltrexone (50 mg) for 3 days and one after taking a placebo for 3 days. During each session, participants reported on their craving for alcohol and cigarettes.
Results Analyses revealed a significant positive effect of BrAC on urge to smoke as well as a BrAC×Medication interaction. Specifically, the linear relationship between BrAC and urge to smoke was significantly weaker in the naltrexone condition, as compared to placebo. There was also a positive association between urge to drink and urge to smoke, and this relationship was moderated by BrAC.
Conclusions These findings demonstrate that the pharmacological effects of alcohol alone induce craving for cigarettes and that naltrexone blunts the progression of craving for cigarettes during alcohol intoxication. These results highlight the potential clinical utility of naltrexone for heavy drinkers trying to quit smoking.

Keywords Alcohol · Smoking · Naltrexone · Craving · Urge · Pharmacotherapy · Laboratory

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Alcohol and cigarettes are two of the most widely abused substances and are often used in combination. It was recently estimated that 6 in 10 adults in the USA are current drinkers and 1 in 4 are current smokers (Schoenborn et al. 2004). Levels of alcohol use are higher in smokers than nonsmokers, and the prevalence of smoking is higher in heavy drinkers as compared to nondrinkers (Rimm et al. 1995). Importantly, almost 20% of current smokers engage in hazardous drinking, consuming five or more drinks on one occasion at least once per month (Dawson 2000; Ockene and Adams 1995), compared to about 6.5% of nonsmokers (Dawson 2000). Moreover, just over 55% of those with an alcohol use disorder smoke compared to 22.5% of lifetime alcohol abstainers (Dawson 2000).

Given the strong association between tobacco and alcohol use, researchers have attempted to elucidate the mechanisms underlying this relationship. In laboratory studies, alcohol consumption is associated with increases in craving for cigarettes (Burton and Tiffany 1997; Kouri et al. 2004; Sayette et al. 2005), in a dose-dependent fashion

(Epstein et al. 2007; King and Epstein 2005). Interestingly, acute nicotine administration increased alcohol consumption among occasional smokers (Barrett et al. 2006), while intranasal nicotine enhanced alcohol's stimulant effects and attenuated its sedating effects (Perkins et al. 1995). More recently, a study has found that alcohol's effect on craving for smoking was partially mediated by its positive association with the self-reported stimulant effects of alcohol (Epstein et al. 2007); thus, increases in stimulation may account, in part, for alcohol's effects on cigarette craving and smoking. In short, these studies highlight the complex pharmacological interactions between both substances.

Alcohol may also increase the rewarding properties of smoking. Ethanol pretreatment was found to increase enjoyment from smoking (Glautier et al. 1996), increase satisfaction with smoking, the stimulant and calming effects of smoking, and relieve cigarette craving when individuals smoke nicotine-containing cigarettes compared to denicotinized cigarettes (Rose et al. 2002, 2004). Alcohol also offsets some of the effects of the nicotine antagonist mecamylamine, which reduces satisfaction with smoking (Rose et al. 2004). Importantly, studies have shown that heavy drinkers in smoking cessation treatment are at 5.1 times greater risk of lapsing back to smoking on drinking days compared to nondrinking days (Kahler et al. 2005). Collaboratively, these studies underscore the bidirectional nature of the relationship between alcohol and nicotine and suggest that understanding the pharmacological interactions between these substances has strong implications for the development of pharmacotherapies for comorbid alcohol and nicotine use disorders.

Naltrexone is a pure opioid receptor antagonist, which has been shown to have highest affinity for μ-opioid receptors (Littleton and Zieglgansberger 2003). Clinical trials have generally supported the efficacy of naltrexone as a pharmacotherapy for alcohol dependence. Studies have found that naltrexone reduces the occurrence of heavy drinking days (Balldin et al. 2003; Monti et al. 2001; Rubio et al. 2002), increases time to first relapse (Anton et al. 1999; Guardia et al. 2002), and reduces the number of drinking days (O'Malley et al. 1992; Volpicelli et al. 1992). More recently, a large multisite-controlled trial has found that naltrexone was an effective treatment for alcohol dependence when delivered in combination with a medically oriented behavioral intervention (Anton et al. 2006). There is also evidence suggesting that naltrexone may be an effective treatment for nicotine dependence for some smokers trying to quit (Byars et al. 2005; Covey et al. 1999), although two recent, larger studies of naltrexone for smoking cessation yielded mostly null results (O'Malley et al. 2006; King et al. 2006). The effects of naltrexone on craving for cigarettes during alcohol intoxication, however, are not well understood and warrant further investigation.

Laboratory studies of the effects of naltrexone on alcohol intoxication revealed that this pharmacotherapy dampens feelings of alcohol-induced stimulation (Drobes et al. 2004; Swift et al. 1994), reduces ratings of liking the alcohol (McCaul et al. 2001), decreases the latency to first and second drinks among social drinkers (Davidson et al. 1996), and reduces alcohol craving (Monti et al. 1999). Studies of naltrexone's effects on smoking behaviors indicated that naltrexone may modestly reduce reactivity to smoking cues (Hutchison et al. 1999; Rohsenow et al. 2007), reduce the reinforcing properties of smoking (Epstein and King 2004; King and Meyer 2000) and nicotine (Rukstalis et al. 2005), and reduce smoking in nontreatment seeking smokers (Lee et al. 2005; Rohsenow et al. 2003; Wewers et al. 1998), despite some exceptions and mixed findings (Epstein and King 2004; Rohsenow et al. 2007; Sutherland et al. 1995).

In summary, although naltrexone has been widely researched in the context of both drinking and smoking, little is known about the effects of naltrexone on craving for cigarettes during alcohol intoxication. Examining whether naltrexone attenuates the effects of alcohol on cigarette craving will provide important information about the potential effectiveness of naltrexone for smoking cessation among drinkers. The focus on light smokers, in turn, adds to the scant literature on this subgroup of smokers, who have recently been shown to experience a number of negative health consequences from smoking as little as one to four cigarettes per day (Bjartveit and Tverdal 2005). Additionally, prior studies have suggested that light and heavy smokers show similar levels of alcohol-induced craving for cigarettes (Shiffman et al. 1994).

In light of the existing literature, the goal of the present study was to examine the effects of intravenous alcohol and oral naltrexone on craving for cigarettes in a sample of nontreatment-seeking, heavy-drinking light smokers. Specifically, this study used a within-subjects double-blind placebo-controlled design to (1) examine the effects of intravenous doses of alcohol on craving for cigarettes in the absence of exteroceptive alcohol cues; (2) test the effects of naltrexone, as compared to placebo, on craving for cigarettes during alcohol intoxication; (3) examine the relationship between craving for alcohol and craving for cigarettes across rising levels of breath alcohol concentration (BrAC). Based on the existing literature, we hypothesized that intravenous alcohol would increase craving for cigarettes, even in the absence of exteroceptive alcohol cues. Moreover, we expected naltrexone to dampen the progression of craving for cigarettes during the ascending limb of BrAC, as compared to placebo. Finally, it was hypothesized that craving for alcohol and craving for cigarettes would be positively associated across rising levels of BrAC.

Materials and methods

Participants

Participants were ten (two women) nontreatment-seeking heavy drinkers who were also smokers and took part in a larger laboratory study of naltrexone (Ray and Hutchison 2007). This study was approved by the University of Colorado Human Research Committee, and all participants provided written informed consent. Inclusion criteria were (1) a score of 8 or higher on the alcohol use disorders identification test audit; Allen et al. 1997), indicating a heavy drinking pattern; (2) self-reported drinking frequency of three or more drinks (two for women) at least twice per week; and (3) no history of adverse reactions to venipuncture. All female subjects tested negative for pregnancy before the alcohol administration, and all subjects were required to have a BrAC of zero before each session. The average age of the sample was 21.8 (SD=1.55; range 21–26), and nine of the participants were Caucasian. The average number of drinks per drinking episode in the past year was 5.1 (SD=2.60; range=3–12), and the average drinking frequency in the past year was twice per week (ranging from three times per month to four times per week). The average number of cigarettes smoked per day during the past year of smoking was 5.15 (SD=5.25; range=1–15), and the average number of cigarettes smoked per day in the past week was 2.10 (SD=3.58; range=0–10).

Experimental procedures

Eligible participants were invited to the laboratory for the initial screening session where they provided a saliva sample for DNA analyses and completed a series of individual differences measures. Given that the larger trial (Ray and Hutchison 2007) had an emphasis on genetic factors, prospective genotyping was used to identify and oversample individuals who had at least one copy of the G allele of the A118G SNP of the OPRM1 gene. Although participants were recruited in the context of this pharmacogenetics trial, the allele frequency of the A118G SNP of the OPRM1 in the present study was 30% (three out of ten participants had one copy of the G allele), which is consistent with the allele frequency reported in unselected samples (e.g., 32% of the unselected screening sample had at least one copy of the G allele in Ray and Hutchison 2004) and suggest that the sample is not biased with regard to genotype. Before participating in the alcohol challenge, participants attended a physical examination at the General Clinical Research Center (GCRC) to ensure that they were in good physical health and were medically eligible to take part in the study. A total of 124 participants (39 women) were screened in the laboratory, 53 completed the physical exam, 7 of whom were ineligible for the study due to a medical reason, and 6 of whom decided not to participate in the trial, leaving us with 40 participants (12 women) who completed the larger laboratory trial, 10 of whom were smokers and who therefore were included in this study. All smokers in this study reported a light smoking pattern and no smokers were excluded.

During each experimental session (i.e., after naltrexone or placebo), participants were seated in a recliner chair and the intravenous was placed in their nondominant arm. Participants completed a baseline assessment before receiving any alcohol and subsequently completed identical assessment measures at each of the following points in BrAC: 0.02, 0.04, and 0.06. After the infusion procedure, participants were debriefed, given a meal, and asked to stay at the GCRC until their BrAC was below 0.02.

Alcohol administration

A number of studies have highlighted the importance of effectively controlling BrACs to reduce experimental variability in alcohol challenge studies (Li et al. 2001; O'Connor et al. 1998; Ramchandani et al. 1999). Therefore, the alcohol administration paradigm used in this study consisted of delivering alcohol intravenously, which effectively controls BrACs while also removing exteroceptive cues and emphasizing interoceptive cues. Based on procedures developed in our previous work (Ray and Hutchison 2004; Ray et al. 2006), the alcohol infusion sessions took place at the GCRC and were conducted by nurses under physician supervision using a 5% ethanol solution. An infusion nomogram was developed taking into account each participant's gender and weight. The formulas for determining target infusion rates were 0.166-ml/min×weight, in kilograms, for men and 0.126-ml/min×weight, for women. Participants started the intravenous alcohol administration at their target rate, and BrAC was monitored every 3 to 5 min. Upon reaching each target BrAC, participants' infusion rates were reduced to half, to maintain stable BrAC during testing, which took approximately 5 min at each time point. Consistent with our previous work, participants completed the alcohol infusion protocol, on average, in 66.53 min (SD=16.02) in the placebo condition and 68.78 (SD=17.34) on average, in the naltrexone condition. For details and a comparison of the infusion to oral alcohol, see Ray et al. (2007).

Medication procedures

Medication was a within-subjects factor, such that each participant completed one infusion session after taking naltrexone (50 mg) for 3 days and one session after taking a matched placebo for 3 days. Participants took the first medication (naltrexone 50 mg or placebo) for 3 days and completed the alcohol challenge on the third day of

medication intake. After the first session, participants were given the second medication and were tested again on the third day of medication usage. There was a wash out period of 7 days or more between the two medications. Active medication and placebo were delivered in counterbalanced order and using a double-blind design. Participants were instructed to report any side effects to the study physician. There were no dropouts as a result of medication side effects. Medication compliance was examined by packing the medication and placebo into capsules with 50 mg of riboflavin. Urine samples were collected before each ethanol infusion session and were analyzed for riboflavin content under an ultraviolet light (Del Boca et al. 1996). All samples tested positive for riboflavin content.

Measures

During the screening session, participants completed a battery of individual difference measures that included demographics, smoking, and drinking behaviors. During each ethanol infusion session, measures of urge to smoke and urge to drink were administered at baseline and at each target BrAC (i.e., 0.02, 0.04, and 0.06).

The *Urge Form* (*UF*) was used to assess urge to smoke and urge to drink. The UF is comprised of items assessing the urge to drink alcohol and smoke cigarettes; each item was rated on an 11-point Likert scale (range=0–10). At baseline, participants were asked "How strong is your urge to drink/smoke right now?" Responses were anchored by "No urge at all" and "Very strong urge." Urge to drink and urge to smoke were assessed by separate items. During the trial, the following question was used to assess urge to drink and to smoke: "What was the highest urge to drink/smoke that you felt during the time that the alcohol was infused?" These items had identical anchors and scale range. Mean urge to smoke, across BrACs, are shown in Fig. 1.

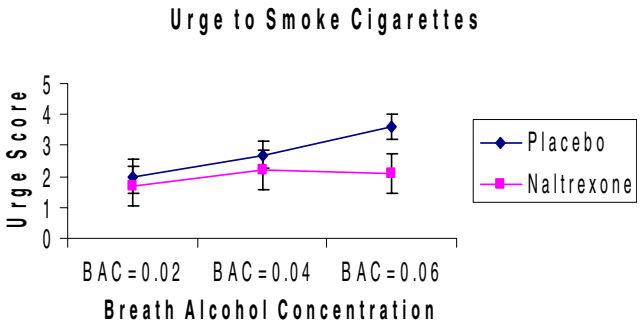

Fig. 1 Mean score on *urge to smoke cigarettes* and standard errors for the naltrexone and placebo conditions. Results revealed a significant BrAC×Medication interaction on urge to smoke, suggesting that naltrexone flattens the slope of craving for cigarettes during the ascending limb of BrAC, as compared to placebo

Alcohol use was evaluated by assessing drinking frequency and quantity using a variation of the measure used by White and Labouvie (1989). First, the instructions define one alcoholic drink as "one beer, one glass of wine, or one serving of hard liquor either by itself or in a mixed drink." Drinking frequency was measured with the item: "In the last year, how often did you drink alcohol on average?" Participants used a 12-point scale ranging from "I didn't drink any alcohol" to "daily." Drinking quantity was then measured with the item: "In the last year, when you drank alcohol, how many drinks did you consume on average on one occasion?"

Cigarette smoking was assessed using the smoking history questionnaire, which included multiple items about current and past smoking behaviors, such as "During the last year when you were smoking the heaviest, how many cigarettes did you smoke per day?" and "In the past week, how many cigarettes per day did you smoke?

Analytic strategy

A series of repeated measures mixed model analyses were conduced using PROC MIXED in SAS Statistical Software (SAS Institute 2003). The Mixed procedure represents a generalization of the standard linear model (GLM) procedure, such that the data are allowed to exhibit correlation and nonconstant variability. The mixed linear model, therefore, allows us to model not only the means of the data, but their variances and covariances as well. In this mixed linear model, Medication was a two level within-subjects factor (coded: Placebo=0 and Naltrexone=1), and BrAC was a three level within-subjects factor (coded: BrAC 0.02=1, BrAC 0.04=2, and BrAC 0.06=3). Given the small sample size, analyses in this study were restricted to examining the main effects of Medication, BrAC, and Medication×BrAC interactions on the dependent variable of urge to smoke cigarettes. Analyses of the relationship between urge to smoke and urge to drink were conducted by modeling urge to smoke as a function of urge to drink, BrAC, and their interaction separately during the placebo and naltrexone conditions. Urge to drink at each BrAC was modeled as a time-varying predictor of urge to smoke at that same assessment point. The interaction between BrAC and time-varying urge to drink was modeled to test whether the association between urge to drink and urge to smoke differed as a function of BrAC during the placebo condition.

Results

Pre-test comparisons

There was no significant effect of medication order on urge to smoke across BrACs, $F(1,9)=5.03$, $p=0.08$ and controlling

for Medication Order did not affect the results. There was no effect of Medication on urge to smoke at baseline, $F(1,9)<1.0$, $p=0.44$; therefore, the analyses presented herein focus on the three levels of BrAC (0.02, 0.04, 0.06). There were no significant differences in side effects as a function of medication condition. For details on compliance in this trial, see Ray and Hutchison (2007).

Effects of alcohol and naltrexone on urge to smoke cigarettes

The first step in conducting the repeated measures mixed model analysis assumed a main effect of Medication and a linear effect of BrAC on urge to smoke. Results revealed a significant linear effect of BrAC [$t(9)=10.49$, $p<0.0001$, $B=0.82$, SE=0.08], such that the urge to smoke increased in linear fashion across rising levels of breath alcohol. In this initial model, there was no support for a main effect of medication, $t(9)=-1.32$, $p=0.22$, $B=-0.44$, SE=0.33. The second step in the analysis consisted of adding the BrAC×Medication parameter to the model. Results revealed a main linear effect of BrAC, in the same direction as described above [$t(9)=5.43$, $p<.001$, $B=0.61$, SE=0.11]. The main effect of Medication in this model was not significant, $t(9)<1.0$, $p=0.84$, $B=0.08$, SE=0.38. However, there was a significant BrAC×Medication interaction on urge to smoke, $t(9)=-2.74$, $p<0.05$. The model coefficients indicated that the linear effect of BrAC on urge to smoke cigarettes was positive and significant when participants were taking placebo [$B=0.61$, SE=0.14] but was not significant when they were taking naltrexone [$B=0.27$, SE=0.28]. In summary, this interaction suggests that naltrexone flattens the slope of urge to smoke cigarettes during the ascending limb of alcohol intoxication, as compared to placebo (see Fig. 1). Finally, we have estimated the effect size of naltrexone vs placebo at each time point in BrAC; Cohen's d were: 0.19, 0.30, and 0.89, respectively, indicating a large effect of naltrexone vs placebo when BrAC reaches 0.06.

Relationship between urge to drink and urge to smoke

Analysis of the relationship between urge to drink and urge to smoke, during the placebo condition, revealed a positive and significant association between urge to smoke and urge to drink [$t(9)=2.49$, $p<0.05$, $B=0.45$, SE=0.18] such that higher urge to drink predicted higher urge to smoke cigarettes at the same assessment period (i.e., level of BrAC). In addition, there was a significant and positive main effect of BrAC on urge to smoke [$t(9)=2.98$, $p<0.01$, $B=1.14$, SE=0.38] paralleling the findings in our previous models. In addition, there was an urge to drink×BrAC interaction regarding urge to smoke cigarettes [$t(9)=-2.34$, $p<0.05$, $B=-0.19$, SE=0.08] indicating that the relationship between urge to drink and urge to smoke was strongest at lower levels of BrAC. This interaction is best illustrated by the correlation between urge to drink and urge to smoke, which was markedly higher when BrAC=0.02 ($r=0.73$;$R^2=0.53$; $p<0.05$), as compared to when BrAC=0.04 ($r=0.17$; $R^2=0.03$; $p=0.65$) or BrAC=0.06 ($r=0.18$; $R^2=0.03$; $p=0.96$; see Fig. 2). It is also noteworthy that naltrexone did not significantly reduce the urge to drink, compared to placebo, in this sample of smokers [$t(9)<1.0$, $p=0.86$]. Finally, we examined the relationship between urge to drink and urge to smoke in the naltrexone condition and found that the correlation was not significant at any time point in trial ($r=.08$, -0.21, -0.32; $p>0.10$). Therefore, it is unlikely that the increased urge to smoke was an indirect consequence of increased urge to drink.

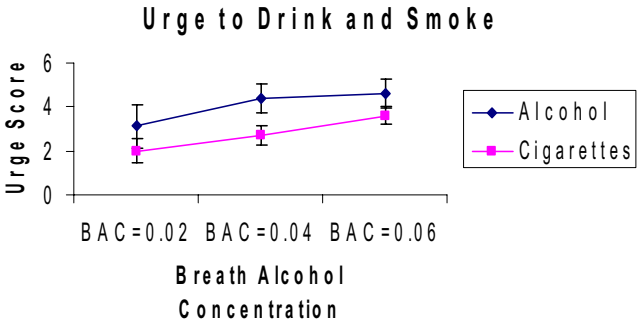

Fig. 2 Mean score on *urge to drink alcohol* and *urge to smoke cigarettes*, during the placebo condition, each presented with standard errors. Analysis revealed a positive association between urge to smoke and urge to drink, as well as a significant urge×BrAC interaction suggesting that the relationship was strongest at lower levels of BrAC

Discussion

The present study examined the effects of intravenous alcohol and naltrexone on craving for cigarettes in a sample of nontreatment-seeking, heavy-drinking, light smokers who participated in a larger laboratory study of naltrexone (Ray and Hutchison 2007). The first goal was to examine the effects of intravenous doses of alcohol on the craving for cigarettes. Although previous studies have shown that consuming alcohol increases the craving for cigarettes (e.g., Mello et al. 1980; Mitchell et al. 1995; Shiffman et al. 1994), this is the first study to examine alcohol's effects on craving for cigarettes in the absence of exteroceptive alcohol cues and based primarily on the pharmacological effects of alcohol. Results revealed that craving for cigarettes increased significantly across rising breath alcohol levels, suggesting that the pharmacological and interoceptive effects of alcohol are sufficient to elicit craving for cigarettes even in the absence of exteroceptive alcohol cues. This is important in terms of examining the direct pharmacological effects of alcohol. Furthermore, the

observed linear alcohol dose–response relationship was consistent with recent studies of the effects of alcohol administration on cigarette craving (Epstein et al. 2007; King and Epstein 2005).

The second study objective was to test the effects of naltrexone on craving for cigarettes during alcohol intoxication. Results indicated that naltrexone significantly decreased the linear progression of craving for cigarettes across the ascending limb of BrAC, as compared to placebo, suggesting that naltrexone may be helpful in reducing cigarette craving during alcohol intoxication, particularly at higher levels of BrAC. The finding that naltrexone reduces craving for cigarettes at higher levels of BrAC is consistent with previous studies showing that the effects of naltrexone on craving for alcohol and subjective intoxication may be alcohol-dose dependent (Anton et al. 2004; Drobes et al. 2004; McCaul et al. 2001). These findings expand on a previous placebo-controlled laboratory trial of naltrexone in which naltrexone was found to significantly reduce craving for cigarettes elicited by smoking cues (Hutchison et al. 1999). Given that heavy drinkers in smoking cessation treatment are at 5.1 times greater risk of lapsing back to smoking on drinking days compared to nondrinking days (Kahler et al. 2005), these findings highlight the potential clinical utility of naltrexone for heavy drinkers trying to quit smoking.

The third objective of this study was to test the relationship between craving for alcohol and craving for cigarettes across the ascending limb of alcohol intoxication. Craving for alcohol was significantly and positively associated with craving for cigarettes at a low level of alcohol intoxication (i.e., when BrAC=0.02); however, the relationship became nonsignificant as BrACs increased (i.e., when BrAC=0.04 and 0.06). The positive relationship between craving for alcohol and craving for cigarettes suggests that common mechanisms may be underlying craving for both substances (e.g., Davidson 2003). Nevertheless, the dose-dependent association between craving for alcohol and craving for cigarettes is intriguing and suggests that, at higher levels of BrAC, individuals begin to differentiate between craving for distinct substances, which is consistent with previous studies of the specificity of cue-reactivity among heavy drinkers and smokers (Strizke et al. 2004).

The present study must be interpreted in the context of its strengths as well as its limitations. Strengths include the high levels of control over BrACs, which is an important issue in alcohol administration studies (e.g., Li et al. 2001), the focus on the interoceptive and direct pharmacological effects of alcohol in the absence of exteroceptive cues, and the double-blind placebo-controlled within-subjects nature of the design, which markedly increased the statistical power to detect the effects of alcohol and naltrexone. Study limitations include the small sample size as well as the fact that our sample consisted of light smokers only; thus, these findings may not generalize to heavier smokers. Additionally, the intravenous alcohol administration provides high levels of control over BrACs and allows us to focus on the pure pharmacological effects of alcohol but is less externally valid as it differs from real-world drinking situations.

In conclusion, the present study is the first to examine whether the pharmacological effects of alcohol alone, in the absence of drinking and smoking cues, are sufficient to induce craving for cigarettes among heavy-drinking light smokers. Importantly, this pilot study provides preliminary evidence that naltrexone may be effective in reducing craving for cigarettes during alcohol intoxication. Future studies are needed to replicate and extend these findings, perhaps by examining heavy smokers and by adding exteroceptive alcohol and smoking cues. Ultimately, more studies will be necessary to determine the clinical utility of naltrexone in smoking cessation trials.

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The authors would like to state that the study described in this manuscript complied with the current laws of the USA.

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References

Allen JP, Litten RZ, Fertig JB, Babor T (1997) A review of research on the Alcohol Use Disorders Identification Test (AUDIT). Alcohol Clin Exp Res 21:613–619

Anton RF, Moak DH, Waid LR, Latham PK, Malcolm RJ, Dias JK (1999) Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. Am J Psychiatry 156:1758–1764

Anton RF, Drobes DJ, Voronin K, Durazo-Avizu R, Moak D (2004) Naltrexone effects on alcohol consumption in a clinical laboratory paradigm: temporal effects of drinking. Psychopharmacology 173:32–40

Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donavan DM et al (2006) Combined pharmacotherapies and behavioral interventions for alcohol dependence, the COMBINE study: a randomized controlled trial. JAMA 295:2003–2017

Balldin J, Berglund M, Borg S, Mansson M, Bendtsen P, Franck J et al (2003) A 6-month controlled naltrexone study: Combined effect with cognitive behavioral therapy in outpatient treatment of alcohol dependence. Alcohol Clin Exp Res 27:1142–1149

Barrett SP, Tichauer M, Leyton M, Pihl RO (2006) Nicotine increases alcohol self-administration in non-dependent male smokers. Drug Alcohol Depend 81:197–204

Bjartveit K, Tverdal A (2005) Health consequences of smoking 1–4 cigarettes per day. Tob Control 14:315–320

Burton SM, Tiffany ST (1997) The effect of alcohol consumption on craving to smoke. Addiction 92:15–26

Byars JA, Frost-Pineda K, Jacobs WS (2005) Naltrexone augments the effects of nicotine replacement therapy in female smokers. J Addict Dis 24:49–60

Covey LS, Glassman AH, Stetner F (1999) Naltrexone effects on short-term and long-term smoking cessation. J Addict Dis 18:31–40

Davidson RJ (2003) Affective neuroscience and psychophysiology: toward a synthesis. Psychophysiology 44:655–665

Davidson D, Swift R, Fitz E (1996) Naltrexone increase the latency to drink alcohol in social drinkers. Alcohol Clin Exp Res 20:732–739

Dawson DA (2000) Drinking as a risk factor for sustained smoking. Drug Alcohol Depend 59:235–249

Del Boca FK, Kranzler HR, Brown J, Korner PF (1996) Assessment of medication compliance in alcoholics through UV light detection of a riboflavin tracer. Alcohol Clin Exp Res 20:1412–1417

Drobes DJ, Anton RF, Thomas SE, Vornin K (2004) Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment seeking alcoholics and social drinkers. Alcohol Clin Exp Res 28:1362–1370

Epstein AM, King AC (2004) Naltrexone attenuates acute cigarette smoking behavior. Pharmacol Biochem Behav 77:29–37

Epstein AM, Sher TG, Young MA, King AC (2007) Tobacco chippers show robust increases in smoking urge after alcohol consumption. Psychopharmacology 190(3): 321–329

Glautier S, Clements K, White JA, Taylor C, Stolerman IP (1996) Alcohol and the reward value of cigarette smoking. Behav Pharmacol 7:144–154

Guardia J, Caso C, Arias F, Gual A, Sanahuja J, Ramirez M et al (2002) A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder: results from a multicenter clinical trial. Alcohol Clin Exp Res 26:1381–1387

Hutchison KE, Monti PM, Rohsenow DJ, Swift R, Colby SM, Gnys M, Niaura RS, Sirota AD (1999) Effects of naltrexone with nicotine replacement on smoking cue-reactivity: preliminary results. Psychopharmacology 142:139–143

Kahler CW, Resendes A, Monti PM, Ramsey SE, Abrams DA, Brown RA (2005) Alcohol use and smoking outcomes among heavy drinkers in smoking cessation treatment. In: Society for Research on Nicotine and Tobacco Annual Meeting, Prague, Czech Republic

King AC, Epstein AM (2005) Alcohol dose-dependent increases in smoking urge in light smokers. Alcohol Clin Exp Res 29:547–552

King AC, Meyer PJ (2000) Naltrexone alteration of acute smoking response in nicotine-dependent subjects. Pharmacol Biochem Behav 66:563–572

King A, de Wit H, Riley RC, Cao D, Niaura R, Hatsukami D (2006) Efficacy of naltrexone in smoking cessation: a preliminary study and an examination of sex differences. Nicotine Tob Res 8:671–682

Kouri EM, McCarthy EM, Faust AH, Lukas SE (2004) Pretreatment with transdermal nicotine enhances some of ethanol's acute effects in men. Drug Alcohol Depend 75(1):55–65

Lee YS, Joe KH, Sohn IK, Na C, Kee BS, Chae SL (2005) Changes of smoking behavior and serum adrenocorticotropic hormone, cortisol, prolactin, and endogenous opioids levels in nicotine dependence after naltrexone treatment. Prog Neuropsychopharmacol Biol Psychiatry 29:639–647

Li T, Yin S, Crabb DW, O'Connor S, Ramchandani VA (2001) Genetic and environmental influences on alcohol metabolism in humans. Alcohol Clin Exp Res 25:136–144

Littleton J, Zieglgansberger W (2003) Pharmacological mechanisms of naltrexone and acamprosate in the prevention of relapse in alcohol dependence. Am J Addict 12:3–11

McCaul ME, Wand GS, Stauffer R, Lee SM, Rohde CA (2001) Naltrexone dampens ethanol-induced cardiovascular and hypothalamic–pituitary–adrenal axis activation. Neuropsychopharmacology 25:537–547

Mello NK, Mendelson JH, Sellers ML, Kuehnle JC (1980) Effect of alcohol and marijuana on tobacco smoking. Clin Pharmacol Ther 27:202–209

Mitchell SH, de Wit H, Zacny JP (1995) Effects of varying ethanol dose on cigarette consumption in healthy normal volunteers. Behav Pharmacol 6:359–365

Monti PM, Rohsenow DJ, Hutchison KE, Swift RM, Mueller TI, Colby SM et al (1999) Naltrexone's effect on cue-elicited craving among alcoholics in treatment. Alcohol Clin Exp Res 23:1386–1394

Monti PM, Rohsenow DJ, Swift RM, Gulliver SB, Colby SM, Mueller TI et al. (2001) Naltrexone and cue exposure with coping and communication skills training for alcoholics: Treatment process and 1-year outcomes. Alcohol Clin Exp Res 25:1634–1647

Ockene JK, Adams A (1995) Screening and intervention for smoking and alcohol use in primary care settings: similarities, differences, gaps, and challenges. In: Fertig JB, Allen JP (eds) Alcohol and tobacco: from basic science to clinical practice. National Institutes of Health, Bethesda, MD, pp 281–294

O'Connor S, Morzorati S, Christian J, Li T (1998) Clamping breath alcohol concentration reduces experimental variance: Application to the study of acute tolerance to alcohol and alcohol elimination rate. Alcohol Clin Exp Res 22:202–210

O'Malley SS, Jaffe AJ, Change G, Schottenfeld RS, Meyer RE, Rounsaville B (1992) Naltrexone and coping skills therapy for alcohol dependence: a controlled study. Arch Gen Psychiatry 49:881–887

O'Malley SS, Cooney JL, Krishnan-Sarin S, Dubin JA, McKee SA, Cooney NL et al (2006) A controlled trial of naltrexone augmentation of nicotine replacement therapy for smoking cessation. Arch Intern Med 166:667–674

Perkins KA, Sexton JE, DiMarco A, Grobe JE, Scierka A, Stiller RL (1995) Subjective and cardiovascular responses to nicotine combined with alcohol in male and female smokers. Psychopharmacology 119:205–212

Ramchandani VA, Bolane J, Li TK, O'Connor S (1999) A physiologically-based pharmacokinetic (PBPK) model for alcohol facilitates rapid BrAC clamping. Alcohol Clin Exp Res 23:617–623

Ray LA, Hutchison KE (2004) A polymorphism of the mu-opioid receptor gene and sensitivity to the effects of alcohol in humans. Alcohol Clin Exp Res 28:1789–1795

Ray LA, Hutchison KE (2007) A double-blind placebo-controlled study of the effects of naltrexone on alcohol sensitivity and genetic moderators of medication response. Arch Gen Psychiatry, in press

Ray LA, McGeary J, Marshall E, Hutchison KE (2006) Risk factors for alcohol misuse: integrating heart rate response to alcohol, alcohol sensitivity, and personality factors. Addict Behav 31:1959–1973

Ray LA, Meskew-Stacer S, Hutchison KE (2007) The relationship between prospective self-rating of alcohol sensitivity and craving and experimental results from two alcohol challenge studies. J Stud Alcohol Drugs 68(3)379–384

Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC (1995) Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. Br Med J 310:555–559

Rohsenow DJ, Monti PM, Colby SM, Gulliver SB, Swift RM, Abrams DB (2003) Naltrexone treatment for alcoholics: effect on cigarette smoking rates. Nicotine Tob Res 5:231–236

Rohsenow DJ, Monti PM, Hutchison KE, Swift RM, MacKinnon SV, Sirota AD et al (2007) High dose transdermal nicotine and naltrexone: Effects on nicotine withdrawal, urges, smoking, and effects of smoking. Exp Clin Psychopharmacol 15(1):81–92

Rose JE, Brauer LH, Behm FM, Cramblett M, Calkins K, Lawhon D (2002) Potentiation of nicotine reward by alcohol. Alcohol Clin Exp Res 6:930–1931

Rose JE, Brauer LH, Behm FM, Cramblett M, Calkins K, Lawhon D (2004) Psychopharmacological interactions between nicotine and ethanol. Nicotine Tob Res 6:133–144

Rubio G, Manzanares J, Lopez-Munoz F, Alamo C, Ponce G, Jimenez-Arriero, MA, Palomo T (2002) Naltrexone improves outcome of a controlled drinking program. J Subst Abuse Treat 23:361–366

Rukstalis M, Jepson C, Strasser A, Lynch KG, Perkins K, Patterson F et al (2005) Naltrexone reduces the relative reinforcing value of nicotine in a cigarette smoking choice paradigm. Psychopharmacology 180:41–48

SAS Institute 2003. The SAS system for windows (version 8.2) SAS Institute, Cary, NC

Sayette MA, Martin CS, Wertz JM, Perrott MA, Peters AR (2005) The effects of alcohol on cigarette craving in heavy smokers and tobacco chippers. Psychol Addict Behav 19:263–270

Schoenborn CA, Adams PF, Barnes PM, Vickerie JL, Schiller JS (2004) Health behaviors of adults: United States, 1999–2001. Vital Health Stat 10(219):1–79

Shiffman S, Fischer LA, Paty JA, Gnys M, Hickcox M, Kassel JD (1994) Drinking and smoking: a field study of their association. Annals Behav Med 16:203–209

Strizke WGK, Breiner MJ, Curtin JJ, Lang AR (2004) Assessment of substance cue reactivity: advances in reliability, specificity, and validity. Psychol Addict Behav 18:148–159

Sutherland G, Stapleton JA, Russell MA, Feyerabend C (1995) Naltrexone, smoking behaviour and cigarette withdrawal. Psychopharmacology 120:418–425

Swift RM, Whelihan W, Kusnetsov O, Buongiorno G, Hsuing H (1994) Naltrexone-induced alterations in human ethanol intoxication. Am J Psychiatry 151:1463–1467

Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP (1992) Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 49:876–880

Wewers ME, Dhatt R, Tejwani GA (1998) Naltrexone administration affects ad libitum smoking behavior. Psychopharmacology 140:185–190

White HR, Labouvie EW (1989) Towards the assessment of adolescent problem drinking. J Stud Alcohol 50:30–37