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Naltrexone and Alcohol Effects on Craving for Cigarettes in Heavy Drinking Smokers

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Naltrexone has been extensively studied for the treatment of alcohol use disorder. However, less is known about the effects of naltrexone on smoking outcomes in the context of alcohol use among East Asian individuals who have been suggested to differ in response to alcohol and to naltrexone. The present study is a secondary analysis that used a double-blind placebo-controlled design ($n = 31$) to examine the (a) effects of alcohol on basal craving for cigarettes, (b) effects of naltrexone on cigarette craving and alcohol craving during alcohol administration, and (c) relationship between craving for alcohol and cigarettes. Heavy drinking smokers of East Asian descent completed two counterbalanced intravenous alcohol administration sessions, one after taking naltrexone (50 mg) for five days and one after taking a placebo for five days. Self-reported subjective craving for cigarettes and for alcohol was recorded during each experimental session. Craving for cigarettes and alcohol increased significantly throughout the intravenous alcohol administration. A significant breath alcohol concentration (BrAC) \times Medication interaction revealed that naltrexone blunted cigarette craving during alcohol administration, compared to placebo. Naltrexone significantly reduced craving for alcohol during alcohol administration in this group of heavy drinking smokers. Alcohol craving significantly predicted cigarette craving, however this effect did not vary across rising alcohol administration or by medication. These findings demonstrate that naltrexone reduces the urge to smoke and to drink during alcohol administration. Clinical studies are needed to further ascertain whether naltrexone may be of benefit to this distinct subgroup of heavy drinking smokers.

Public Health Significance

This study suggests that naltrexone reduces craving for cigarettes during alcohol administration. Craving for alcohol can predict craving for cigarettes in the human laboratory. These findings are consistent with the literature suggesting an adjunctive role for naltrexone in smoking cessation among individuals who drink alcohol regularly.

Keywords: smoking, alcohol, naltrexone, craving, pharmacotherapy

Tobacco and alcohol are two of the most commonly used substances. Results from the National Epidemiological Survey on Alcohol and Related Conditions—III (NESARC-III) highlights the large comorbidity between these two substances with robust asso-

ciations between Nicotine Use Disorder (NUD) and Alcohol Use Disorder (AUD) according to *DSM-5* criteria (Chou et al., 2016; Grant et al., 2015). Moreover, compared to nondrinkers, adults who drink heavily or meet criteria for an AUD are significantly

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ReJoyce Green conceptualized the manuscript, undertook the statistical analysis, and wrote the results and discussion section of the manuscript. All other authors assisted in contributing to various parts of the manuscript. Lara Ray designed the original study, obtained funding for the experiment, and contributed to writing the manuscript and its conceptualization. All authors have approved the final manuscript.

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Lara Ray receives study medication from Pfizer and Medicinova. None of the authors have any other conflicts of interest to disclose.

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more likely to report former tobacco use as well (McKee, Falba, O'Malley, Sindelar, & O'Connor, 2007). At the level of binge drinking, young adults who binge drink also smoke more heavily than nonbinge drinkers (Gubner, Delucchi, & Ramo, 2016). When examining smokers who called into a smoking quit line, 22.9% reported hazardous drinking, (Toll et al., 2012). The co-use of these substances does influence treatment, such that tobacco use during AUD treatment longitudinally predicts increased likelihood of alcohol dependence three years later (Weinberger, Platt, Jiang, & Goodwin, 2015).

Due to these high rates and impact co-use has on treatment outcomes, efforts have been aimed at understanding the mechanisms underlying the relationship between cigarettes and alcohol use. Laboratory studies have examined how the exposure or use of one substance may affect the use of the other substance through various paradigms including alcohol cue exposure (Dunbar, Shiffman, Kirchner, Tindle, & Scholl, 2014; Verplaetse & McKee, 2017) and alcohol self-administration (Verplaetse & McKee, 2017). Kahler and colleagues (2014) found that heavy drinkers smoked a cigarette faster following low and high-dose alcohol, in comparison to a placebo beverage. This effect was partially mediated by smoking urges, thereby highlighting the impact that craving for cigarettes following alcohol administration can have on subsequent smoking behavior. An ecological momentary assessment study similarly found that when participants consumed alcohol, they reported significantly increased levels of pleasure and decreased levels of subjectively feeling worse from their last cigarette (Piasecki et al., 2011). Evidence supporting cross-reinforcement and cross-tolerance as one possible mechanisms underlying this co-use pattern has been demonstrated (Oliver et al., 2013). Taken together, these studies underscore the bidirectional nature of the relationship between alcohol and cigarettes.

Few treatment options are available for heavy drinking smokers trying to quit smoking. Heavy drinkers have significantly lower rates of smoking cessation in part due to their inability to remain abstinent for more than 1-month following a smoking quit attempt (Kahler et al., 2009). While there exist FDA-approved medications for nicotine use and alcohol use, there have been no FDA approved medications that have been explicitly approved for treating both disorders simultaneously. Naltrexone is an opioid receptor antagonist with the highest affinity for the mu-opioid receptor that has been FDA approved for the treatment of AUD (Littleton & Ziegler, 2003) and is the top of the line pharmacotherapy treatment option for AUD that has shown effects in reducing alcohol consumption in human laboratory studies and clinical trials (Hendershot, Wardell, Samokhvalov, & Rehm, 2017; Maisel, Blodgett, Wilbourne, Humphreys, & Finney, 2013). Evidence is emerging that naltrexone may influence smoking outcomes by reducing cue-elicited withdrawal symptoms (Rohsenow et al., 2007) and reducing cigarette and alcohol consumption in comparison to placebo (A. King, Cao, Zhang, & Rueger, 2013). Naltrexone has also been found to have specific effects on reducing smoking urges and increase smoking abstinence among heavy drinking smokers in comparison to moderate-to-light drinkers or smokers who do not drink (Fridberg, Cao, Grant, & King, 2014), suggesting that naltrexone may serve of high benefit to heavy drinking smokers wanting to quit smoking. There is also evidence to suggest that naltrexone may serve as an effective adjunct treatment to Nicotine Replacement Therapy (NRT; O'Malley et al.,

2006) and varenicline, an FDA approved smoking cessation aid (Ray et al., 2014). Although a recent study by Roberts and colleagues (2018) found that naltrexone in addition to varenicline, an FDA approved medication for nicotine dependence, did not improve smoking outcomes in comparison to varenicline alone.

Despite these findings, there is overall mixed evidence that naltrexone may be a beneficial in treating smoking outcomes for heavy-drinking smokers (Fridberg et al., 2014; Kahler et al., 2017), particularly as a stand-alone treatment. In a sample of alcohol dependent daily smokers recently abstaining from alcohol, naltrexone was found to have no effect in reducing smoking in the context of alcohol (Rohsenow et al., 2003). Kahler and colleagues (2017) found that heavy drinking smokers reduced their cigarette use while in smoking cessation treatment, naltrexone did not improve smoking cessation outcomes nor reduce alcohol use. A meta-analysis of existing studies yielded mostly null results for effects of naltrexone as an adjunct to Nicotine Replacement Therapy (NRT) on long-term smoking abstinence (David, Lancaster, Stead, Evins, & Prochaska, 2013). Importantly, however, studies have since identified potential sex differences in the effects of naltrexone for smoking cessation and cessation-related weight gain (A. King et al., 2006; A. C. King et al., 2012). Taken together, these studies suggest that while the literature is mixed on naltrexone's efficacy for smoking cessation, certain subgroups of smokers, such as heavy drinkers or females, may indeed benefit from naltrexone, particularly as an adjunctive treatment for smoking cessation.

Despite an extensive literature on the effects of naltrexone on alcohol response and cessation in laboratory studies and clinical trials, less is known about the effects of naltrexone on craving for cigarettes during alcohol administration. Our group last examined this in Ray and colleagues (2007) and found naltrexone to reduce the progression of craving for cigarettes throughout alcohol administration in a small sample ($N = 10$) of light smokers. The present study expands this literature by examining the effects of intravenous alcohol and oral naltrexone on craving for cigarettes in a sample of nontreatment seeking heavy drinking smokers of East Asian descent. The present study is a secondary analysis of a larger clinical trial examining the pharmacogenetic effects of naltrexone on individuals of East Asian descent (Ray et al., 2018). The rationale behind including East Asian individuals in the larger clinical trial is that East Asian individuals are more likely to express the minor allele for the OPRM1 mu-opioid receptor gene (Arias, Feinn, & Kranzler, 2006) that has been suggested to moderate the effects of naltrexone for AUD (Cservenka, Yardley, & Ray, 2017; Ray, Bujarski, Chin, & Miotto, 2012).

As heavy and light smokers have been found to exhibit similar levels of alcohol-induced craving for cigarettes (Sayette, Martin, Wertz, Perrott, & Peters, 2005), our sample consisted of both daily and occasional smokers. Specifically, our aims were to examine: 1) the effects of alcohol on craving for cigarettes, 2) the effects of naltrexone on urge for cigarettes and alcohol during alcohol administration, 3) the relationship between craving for alcohol and cigarettes across rising breath alcohol concentrations (BrAC). Based on the existing literature, and particularly our previous study (Ray et al., 2007), we hypothesized that intravenous alcohol would increase craving for cigarettes, even in the absence of exteroceptive alcohol cues. Through only using intravenous and not including exteroceptive cues, this study design allows us to examine the direct effects of alcohol exposure with less interference from

expectancies or cue-induced effects. 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.

Method

Participants and Screening Procedures

This study was approved by the University of California Los Angeles Institutional Review Board (IRB# 13-000736 Optimizing Naltrexone for Individuals of Asian Descent). All participants provided written informed consent after receiving a full explanation of the study. This study aimed to conduct secondary analysis of a larger trial examining pharmacogenetic effects of naltrexone on subjective response to alcohol in individuals of East Asian descent (Ray et al., 2018). Inclusion criteria for that study were as follows: (a) East-Asian ethnicity (i.e., Chinese, Korean, Japanese, or Taiwanese); (b) between the ages of 21 and 55; (c) score of 8 or higher on the Alcohol-Use Disorders Identification Test (Allen, Litten, Fertig, & Babor, 1997), indicating a heavy drinking pattern. Exclusionary criteria included current major depression with suicidal ideation, lifetime psychotic disorder, lifetime substance use disorder (other than cannabis use disorder).

Initial assessment of the eligibility criteria was conducted through a telephone interview. Eligible participants were then invited to the laboratory for in-person screening. Upon arrival, participants read and signed an informed consent form and provided a saliva sample for DNA analyses. Participants were required to have a BrAC of 0.00g/dl and to test negative on a urine drug test for all drugs, except for marijuana. All female participants were required to test negative on a pregnancy screen. Participants then completed a series of individual differences measures and a diagnostic interview. The following individual differences measures were administered during the in-person screening visit: (1) Timeline follow-back (Sobell, Sobell, Klajner, Pavan, & Basian, 1986) was administered in a face-to-face interview format to assess frequency and quantity of alcohol use over the past 30-days; (b) Fagerström Test of Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991) assessed nicotine dependence; (c) Smoking History Questionnaire assessed for their smoking history; and (d) Beck-Depression Inventory-II (Beck, Steer, & Brown, 1996) assessed for depressive symptomology. Participants were also administered the Clinical Institute of Withdrawal Scale (CIWA) during their initial screening visit (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989). Participants scoring higher than 10 on the CIWA, indicating clinically significant withdrawal, were excluded from the study.

Eligible participants following the in-person screening visit attended a physical examination and medically eligible individuals were then randomized to receive either naltrexone (50 mg/day) or matched placebo first. A total of 77 participants (26 women) were enrolled, randomized, and completed at least one experimental infusion as part of the larger study. Of these 77 individuals, 31 identified as either daily or occasional smokers and were included in this analysis. Of these 31 smokers, 28 completed both infusion sessions, one after taking placebo and one after taking naltrexone. For the three smokers who only completed one alcohol

infusion session, two completed their one infusion while on placebo and one completed the infusion on naltrexone.

Alcohol Administration and Medication Procedures

Participants completed two experimental sessions, one after taking naltrexone for 5 days and one after taking a matched placebo for 5 days (minimum 7-day wash-out period between conditions). This study was double-blind and medication was delivered in a counterbalanced fashion. During each experimental session, participants completed one alcohol infusion. Participants were not required to test negative for THC during the alcohol infusion sessions. Overall, 71% of participants tested negative for THC immediately prior to both infusion sessions. Participants were seated in a recliner chair and the i.v. was placed in their nondominant arm. After completing the baseline assessment, participants received intravenous doses of alcohol and completed identical assessment measures at BrACs of 0.02, 0.04, and 0.06g/dl. After the infusion procedure was finished, participants were given a meal and asked to stay in the lab until their BrAC was below 0.02g/dl. Craving for cigarettes and alcohol was assessed via the Urge Form (UF; Ray et al., 2007) which asks with identical questions for urge to smoke and drink: "How strong is your urge to smoke/drink right now?". This was rated on an 11-point Likert scale with responses anchored at "No Urge At All" to "Very Strong Urge".

Active medication and placebo capsules were packaged with 50 mg of riboflavin allowing for medication compliance to be examined via urine samples collected immediately prior to each infusion session. Analyzed under ultraviolet light, all samples tested positive for riboflavin content. All participants tested negative for drugs (except marijuana) and women tested negative for pregnancy prior to the experimental session. Participants were allowed to smoke a cigarette immediately prior to the alcohol infusion procedures to mitigate cigarette-induced craving. During the placebo condition, 10 participants chose to smoke a cigarette immediately prior to the infusion whereas nine participants did so during the naltrexone condition.

Data Analytic Plan

Analyses were conducted using a multilevel mixed modeling framework (Singer, 1998) in SAS University Edition Version 9.4 with PROC MIXED. The analyses examined the effects of *Medication*, a two-level within-subjects factor (Placebo vs. Naltrexone, coded 0 and 1), *BrAC*, a four-level within-subjects factor (BrAC = 0.00, 0.02, 0.04, 0.06g/dl, coded 0–3) and their interaction on craving for cigarettes and craving for alcohol assessed with the Urge Form (UF). To examine the relationship between craving for alcohol and craving for cigarettes, craving for cigarettes was predicted as a function craving for alcohol, BrAC, medication, and their interaction. Initial mixed models included the following covariates: an indicator of drinking frequency from the TLFB (number of drinking in the days past 30 days), sex, THC test (i.e., negative at both infusions, positive at one infusion, or positive at both infusions), and smoking status (daily vs. occasional). Since genotype for the Asn40Asp single nucleotide polymorphism (SNP) of the mu opioid receptor (OPRM1) gene has been shown to alter response to naltrexone in the context of alcohol use (Anton

et al., 2008; Ray et al., 2012). However, some studies have found no pharmacogenetic effect of naltrexone (Oslin et al., 2015; Schacht et al., 2017). OPRM1 genotype was included as a covariate in all models. Consistent with the literature, OPRM1 status was grouped for individuals who were Asp40 carriers versus Asn40 homozygotes. In efforts to further validate the primary results, all analyses also controlled for alcohol metabolizing genes ADLH2 and ADH1B which can dramatically affect responses to alcohol administration, particularly in individuals of East Asian ancestry. In no case was the significance of our primary outcomes affected by the inclusion or exclusion of any of the aforementioned covariates. Final models reported in the results section below do not include nonsignificant covariates from the initial models. Significant covariates within each model are reported below.

Results

Demographic characteristics of the study sample are presented in Table 1. Notably, this sample consisted of occasional ($n = 19$) and daily ($n = 12$) smokers. Occasional smokers had a mean FTND score of 0.05 ($SD = 0.23$) and daily smokers had a mean FTND score of 2.67 ($SD = 2.39$). These scores indicate that occasional smokers did not have nicotine dependence, while daily smokers had low severity nicotine dependence. A series of Fisher's exact tests, nonparametric tests accounting for small cell size (Fisher, 1922), were conducted to examine differences between naltrexone and placebo on 24 possible side effects from the medication as indicated by the Systematic Assessment for Treatment Emergent Effects (Jacobson, Goldstein, Dominguez, & Steinbook, 1986; Levine & Schooler, 1986) checklist. Results indicated that there were no significant differences in side effects experienced between the two medication conditions for this sample ($p \geq .06$). In regard to the medication blind, participants were asked to report which medication they believed they were taking at the end of each alcohol infusion session. During the placebo condition, 83% of participants correctly guessed they were receiving placebo. While on naltrexone, 59% correctly guessed they were receiving naltrexone.

Table 1
Sample Characteristics

Variable ^a	Smokers ($n = 31$)
Age	27.65 (6.54)
Sex (Male/Female) (n)	22/9
Ethnicity (n)	
Chinese	8
Japanese	4
Korean	19
OPRM1 status (AA/AG & GG) (n)	13/18
Smoking status (occasional/daily) (n)	19/12
Smoking days ^b	14.94 (13.02)
Cigarettes per smoking day ^b	4.95 (4.66)
Drinking days ^b	14.74 (7.53)
Drinks per drinking day ^b	5.53 (3.10)

^a Standard deviation appear within parentheses for continuous variables. ^b Assessed by the 30-Day Timeline Follow Back (TLFB) Interview.

Effects of Alcohol and Naltrexone on Urge to Smoke Cigarettes

Analyses revealed a significant main effect of BrAC ($b = 0.55$, $SE = 0.08$, $p < .01$) such that craving for cigarettes increased across rising BrAC levels. Medication also exerted a significant main effect ($b = -0.52$, $SE = 0.17$, $p < .001$) such that naltrexone reduced craving for cigarettes. There was a significant BrAC \times medication interaction ($b = -0.49$, $SE = 0.15$, $p < .01$) such that Naltrexone significantly reduced craving for cigarettes across rising BrAC levels as compared to placebo (see Figure 1). The only significant covariate included was smoking status, namely regular versus occasional smoker ($p < .01$).

Effects of Alcohol and Naltrexone on Urge to Drink

Analyses revealed a significant main effect of BrAC ($b = 0.47$, $SE = 0.08$, $p < .01$) indicating that urge for alcohol increased across rising BrAC levels. There was a significant main effect of medication ($b = -0.45$, $SE = 0.19$, $p = .02$) with participants having less urge for alcohol while on Naltrexone in comparison to placebo. The medication \times BrAC interaction was not significant ($b = -0.26$, $SE = 0.16$, $p = .11$; Figure 2). No covariates were significant in these models (p 's > 0.12).

Relationship Between Urge to Drink and Urge to Smoke

Analysis of the relationship between urge to drink and urge to smoke revealed a significant main effect of craving for alcohol ($b = 0.40$, $SE = 0.06$, $p < .01$), indicating a coupling of alcohol and cigarette craving. However, there was no BrAC \times craving for alcohol interaction ($b < 0.01$, $SE = 0.05$, $p = .99$) or medication \times craving for alcohol interaction ($b = -0.04$, $SE = 0.15$, $p = .79$) suggesting that the effect of alcohol craving on cigarette craving does not differ across rising BrAC levels nor is it moderated by medication. The only significant covariate in these models was smoking status, namely whether participants were regular or occasional smokers (p 's < 0.01).

Discussion

The current study examined the effects of alcohol administration and naltrexone on cigarette craving in a sample of nontreatment seeking heavy drinking smokers of East Asian descent who participated in a larger laboratory study of naltrexone (Ray et al., 2018). Specifically, this study aimed to replicate and extend upon a previous study by our group (Ray et al., 2007), examining the effects of naltrexone on cigarette craving in a small sample of 10 light smokers. The first objective was to examine how intravenous alcohol administration may affect cigarette craving. Results demonstrated that cigarette craving increased across rising BrAC supporting our previous finding (Ray et al., 2007) that the pure pharmacological effects of alcohol can elicit craving for cigarettes even in the absence of external cues. This finding is largely consistent with a host of studies demonstrating that alcohol administration increases cigarette craving among smokers (Epstein, Sher, Young, & King, 2007; Peloquin, McGrath, Telbis, & Barrett, 2014; Piasecki et al., 2011).

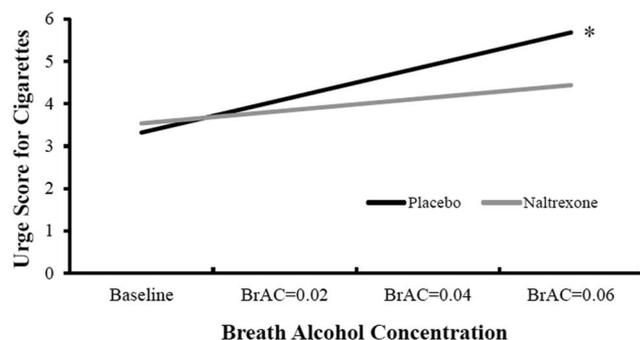


Figure 1. Predicted values of urge to smoke across rising breath alcohol concentration level (BrAC). Asterisk indicates significant medication \times BrAC interaction.

Our second aim was to examine the effects of naltrexone on craving for cigarettes during alcohol administration. Results revealed that in comparison to placebo, naltrexone blunted cigarette craving across rising BrAC levels. Specifically, naltrexone appears to be most effective in reducing craving for cigarettes at higher levels of BrAC, which are more likely to be reached by heavy drinkers. These results also align with previous studies demonstrating naltrexone to reduce smoking urges (A. King et al., 2006; A. C. King et al., 2012) as well as our own findings in the human laboratory (Ray et al., 2007). Taking into consideration the greater likelihood of experiencing a smoking lapse while drinking (Kahler et al., 2012), the pattern of our results suggest that naltrexone may serve to reduce cigarette craving for smokers who are also heavy drinkers. Additionally, there was a significant main effect of alcohol administration on craving for alcohol with heavy drinking smokers reporting greater craving for alcohol at higher alcohol administration levels. This is noteworthy as the primary results from this trial, which included both smokers and nonsmokers, did not detect an effect of naltrexone in reducing urge to drink (Ray et al., 2018). In other words, the present findings in a small sample comprised exclusively of smokers, leads us to speculate that the co-occurrence of smoking and drinking may magnify the effects of naltrexone. This is consistent with a recent clinical trial indicating that the effects of naltrexone as an AUD treatment were stronger among individuals who were also smokers (Anton et al., 2018).

On the other hand, there are a series of studies and meta-analyses that have also found have null effects of naltrexone on smoking outcomes (David et al., 2013; Kahler et al., 2017; Roberts et al., 2018; Rohsenow et al., 2003). One possible reason for these differences could be due to various mediators of naltrexone's effects on smoking outcomes that have yet to be examined. King and colleagues (2012), for instance have found sex differences in naltrexone efficacy on smoking cessation and weight outcomes, which may in part be due to differential hormonal response (Lovallo et al., 2012; Smith et al., 2006). Another potential mediator may be nicotine metabolite ratio (NMR), which is an indicator of the liver enzyme CYP2A6, a major nicotine and cotinine metabolizing gene, and a genetically informed biomarker of nicotine clearance (Lerman et al., 2015; Rubinstein, Benowitz, Auerback, & Moscicki, 2008). Response to smoking-cessation treatment may vary depending on NMR (Benowitz, 2010). Lerman and colleagues (2006) sampled 480 treatment-seeking smokers and found

NMR predicted efficacy of transdermal nicotine, such that higher metabolite ratios were associated with lower nicotine concentrations and greater craving after one week of treatment. Lerman and colleagues (2015) have also found slow metabolizers to respond better with nicotine patch, whereas normal metabolizers responded better to varenicline. By contrast, however, a recent study suggests that NMR does not significantly moderate the effectiveness of varenicline and nicotine replacement therapy (Shahab, Bauld, McNeill, & Tyndale, 2018). In light of this burgeoning yet mixed data regarding smoking pharmacotherapy, further investigation may be warranted to examine NMR's potential role in moderating naltrexone's effects on smoking cessation.

The third aim of this study was to examine the relationship between craving for alcohol and cigarettes across rising BrAC levels. There was a positive relationship between cigarette craving and alcohol craving demonstrating that as craving for alcohol increases, craving for cigarettes also increases. However, there was no interaction between alcohol craving and BrAC level suggesting that the effect of alcohol on cigarette craving does not differ across each timepoint in the rising BrAC curve. These results suggest that within each respective BrAC timeframe, craving for cigarettes and craving alcohol are significantly associated with each other. There was also no evidence of naltrexone interacting with craving for alcohol in predicting craving for cigarettes, suggesting that naltrexone did not significantly alter the predictive relationship of craving for alcohol on craving for cigarettes in this sample. Considering the increasing evidence for similar neurobiological underpinnings of cigarette and alcohol-use, specifically with convergence through the endogenous opioid and acetylcholine systems (Drews & Zimmer, 2010; Spanagel, 2009), the complementing increases in cigarette craving and alcohol craving add further support to the linkage between these two systems at a pharmacological level.

This study must be interpreted in light of its strengths and limitations. Strengths include double-blind placebo-controlled within-subjects design and the intravenous administration of alcohol to increase control over BrAC timepoints. An additional strength is that this study extends beyond previous studies that use primarily Caucasian samples by demonstrating naltrexone effects on smoking outcomes in a sample of individuals of East Asian descent. Limitations include the relatively small sample size and relatively low nicotine dependence status of our subset of smokers.

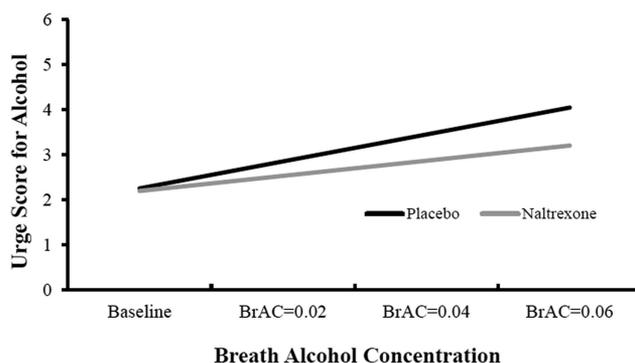


Figure 2. Predicted values of urge to drink across rising breath alcohol concentration level (BrAC).

Additionally, while our East Asian sample is a strength in extending beyond Caucasian samples, it also limits the generalizability of our findings (Cservenka et al., 2017). However, the magnitude of our results despite the overall lower nicotine dependence severity of our sample implies that these effects are detectable even among less heavy smokers, and these effects may grow in magnitude when applied to a greater nicotine dependent sample. Future studies should examine these effects in heavier smokers, as well as heavier drinkers considering that at higher levels of BrAC corresponding more closely with binge drinking episodes, there is a greater likelihood of relapse where the examining the effects of naltrexone in this context would be crucial.

In conclusion, the present study examined the effects of intravenous alcohol administration and naltrexone on craving for cigarettes and alcohol, and the association between cigarette and alcohol craving during alcohol administration. Considering the high frequency with which these substances are used within the same time-period, examining their effects in combination is crucial for advancing our understanding of what pharmacotherapies may serve to benefit this sizable subgroup of smokers. The present results indicated that alcohol increases craving for cigarettes and for alcohol, and that naltrexone reduced craving for cigarettes and for alcohol across rising BrAC levels. The association between alcohol craving and cigarette craving in turn remained significant across levels of rising BrAC. Clinical studies are needed to further ascertain whether naltrexone may be of benefit to this distinct subgroup of heavy drinking smokers.

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