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ORIGINAL INVESTIGATION

Varenicline, low dose naltrexone, and their combination for heavy-drinking smokers: human laboratory findings

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Abstract
Rationale Heavy-drinking smokers constitute a sizeable and hard-to-treat subgroup of smokers, for whom tailored smoking cessation therapies are not yet available.
Objectives The present study used a double-blind, randomized, 2×2 medication design, testing varenicline alone (VAR; 1 mg twice daily), low dose naltrexone alone (L-NTX; 25 mg once daily), varenicline plus naltrexone, and placebo for effects on cigarette craving and subjective response to alcohol and cigarettes in a sample (n=130) of heavy-drinking daily smokers (≥10 cigarettes/day).
Methods All participants were tested after a 9-day titration period designed to reach a steady state on the target medication. Testing was completed at 12 h of nicotine abstinence, after consuming a standard dose of alcohol (target breath alcohol concentration=0.06 g/dl) and after smoking the first cigarette of the day.
Results The combination of VAR+L-NTX was superior to placebo, and at times superior to monotherapy, in attenuating cigarette craving, cigarette and alcohol "high," and in reducing ad-lib consumption of both cigarettes and alcohol during the 9-day medication titration period.
Conclusions These preliminary findings indicate that clinical studies of the combination of VAR+L-NTX for heavy drinkers trying to quit smoking are warranted and may ultimately improve clinical care for this sizeable and treatment-resistant subgroup of smokers.

Keywords Naltrexone · Varenicline · Heavy drinker · Smoker · Human lab · Craving

Introduction

There is a strong positive association between cigarette smoking and alcohol use, both at the epidemiological (Anthony and Echeagaray-Wagner 2000) and pharmacological (Dani and Harris 2005) levels. Approximately 20–25 % of all regular smokers are also heavy drinkers (Dawson 2000; Toll et al. 2012). Heavy-drinking smokers experience more negative health consequences, such as deficits in brain morphology and functional impairments (Durazzo et al. 2007) and greater risk for various cancers (Ebbert et al. 2005) than individuals who are either smokers only or drinkers only. Alcohol use, in turn, is thought to trigger lapses in smoking cessation. Greater alcohol use is associated with lower odds of quitting smoking (Hymowitz et al. 1997; Kahler et al. 2010; Toll et al. 2012), and it is estimated that abstinent smokers are five times as likely to experience a smoking lapse during drinking episodes than at other times (Kahler et al. 2010). Although heavy-drinking smokers constitute a distinct subpopulation with a unique clinical profile and treatment needs (Dani and Harris 2005; Littleton et al. 2007), there are no available treatments tailored to heavy-drinking smokers, and efforts to develop novel treatment approaches for this group are warranted.

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It may be possible to optimize smoking cessation treatments for heavy-drinking smokers through the combination of effective pharmacotherapies for smoking and drinking. Varenicline, an α4β2 nicotinic acetylcholine receptor (nAChRs) partial agonist and α7 nAChR full agonist, is an effective smoking cessation aid (Gonzales et al. 2006). Its mechanisms of action stem from the stimulation of dopamine release while competing for nAChR binding, thereby preventing the full agonist action of nicotine (Coe et al. 2005). Through these mechanisms, varenicline reduces craving and withdrawal and attenuates the rewarding effects of smoking (Ashare et al. 2012; Brandon et al. 2012; Glover and Rath 2007; Tonstad 2006; Zierler-Brown and Kyle 2007). In clinical trials, varenicline was more effective as a smoking cessation agent than bupropion (Gonzales et al. 2006), nicotine replacement therapy (Mills et al. 2012), and placebo (Gonzales et al. 2006; Jorenby et al. 2006; Nides et al. 2006; Oncken et al. 2006; Williams et al. 2007). While varenicline has been advanced as a first-line treatment for nicotine dependence (Fiore et al. 2008), abstinence rates of 43 % at 12 weeks and 25 % at one-year follow-up (Cahill et al. 2011) suggest that there is a clear opportunity to improve upon these clinical outcomes, particularly among hard-to-treat subgroups, such as heavy-drinking smokers. Additionally, recent studies found that varenicline reduces alcohol self-administration in the laboratory (McKee et al. 2009) and alcohol craving (Fucito et al. 2011) and consumption (Fucito et al. 2011; Mitchell et al. 2012) in smoking cessation trials. Varenicline, therefore, is a medication of interest for its ability to both treat nicotine dependence and attenuate alcohol craving and alcohol consumption.

Naltrexone, in turn, is an opioid receptor antagonist with efficacy for the treatment of alcoholism (Anton et al. 2006). Naltrexone pharmacotherapy, at a standard dose of 50 mg/day, has been found to reduce the following: relapse rates (Heinala et al. 2001; Latt et al. 2002; Volpicelli et al. 1992), the number of drinking days (O'Malley et al. 1992; Volpicelli et al. 1992), the frequency of heavy-drinking days (Balldin et al. 2003; Monti et al. 2001; Rubio et al. 2002), and drinks per drinking episode (Chick et al. 2000; Guardia et al. 2002; Morris et al. 2001; O'Malley et al. 1992) while increasing time to first relapse (Anton et al. 1999; Guardia et al. 2002; Kiefer et al. 2003). In the large, multi-site, COMBINE Study, naltrexone (at a dose of 100 mg/day) was superior to placebo in terms of percent days abstinent, when delivered in combination with medical management (Anton et al. 2006), thus representing a first line of treatment for alcoholism. Furthermore, when combined with counseling and nicotine patches, adjunctive naltrexone increased cigarette smoking quit rates relative to placebo, but only among participants with higher levels of depressive symptoms (Walsh et al. 2008) and among women (Byars et al. 2005; King et al. 2006). Three other studies found support for the use of naltrexone as an augmentation to varying levels of nicotine replacement therapy (i.e., nicotine patch), namely 21 mg/24 h for 4 weeks (Krishnan-Sarin et al. 2003), 21 mg/24 h for 6 weeks (O'Malley et al. 2006), and decreasing doses from 21 mg/24 h to 7 mg daily over the course of 4 weeks (King et al. 2012). In contrast, one study did not support combining naltrexone with bupropion (Toll et al. 2008). Further, one study found that naltrexone may preferentially decrease both smoking and drinking among smokers who are also heavy drinkers (King et al. 2009). No studies to date have tested the combination of varenicline and naltrexone for smoking cessation.

Together, these studies underscore the reciprocal effects of varenicline and naltrexone on both smoking and drinking outcomes and suggest that combining these medications for heavy-drinking smokers may be a viable and promising alternative to monotherapy. The present study used a double-blind, randomized, 2×2 medication design, testing varenicline alone (1 mg twice daily), low dose naltrexone alone (25 mg once daily), varenicline plus low dose naltrexone (1 mg twice daily and 25 mg once daily, respectively), and placebo for their effects on cigarette craving and subjective response to alcohol and cigarettes in a sample of heavy-drinking, daily smokers (n=130). The 25-mg dose of naltrexone was selected based on a study by O'Malley et al. (2009) comparing three doses of naltrexone (25, 50, and 100 mg/day) as augmentation to nicotine replacement therapy for smoking cessation, which found naltrexone effects in reducing hazardous drinking at 25 mg/day (O'Malley et al. 2009). All participants were tested after a 9-day titration period designed to reach a steady state on the target medication dosage. The primary objective of this study was to use a behavioral pharmacology approach to evaluate the combination of varenicline and a low dose of naltrexone on craving and subjective responses to cigarettes and alcohol. It was hypothesized that the combination of varenicline and a low dose naltrexone would exceed the effects of monotherapy and placebo in attenuating cigarette craving and the reinforcing effects of cigarettes among heavy-drinking, daily smokers.

Method

Participants

A community-based sample of daily smokers was recruited via online and print advertisements in the Los Angeles area. Inclusion criteria were as follows: (1) age between 21 and 55 years; (2) endorsement of smoking 10 or more cigarettes per day; and (3) current status of heavy drinking according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines (NIAAA 1995): for men, >14 drinks per week or ≥5 drinks per occasion at least once per month over the past 12 months; for women, >7 drinks per week or ≥4

drinks per occasion at least once per month. Exclusion criteria were the following: (1) more than 3 months of smoking abstinence in the past year; (2) self-reported use of cocaine, methamphetamine, heroin, or other illicit drugs (other than marijuana) in the previous 60 days or positive urine toxicology screen at assessment visit; (3) lifetime history of psychotic disorders, bipolar disorders, or major depression with a suicidal ideation; (4) current symptoms of moderate depression (or higher), indexed by a score ≥20 on the Beck Depression Inventory-II (BDI-II) (Beck 1996); and (5) medical ineligibility determined by a physical exam and laboratory tests, suggesting that the participant would be unable to tolerate study procedures.

A total of 427 individuals (79 % male) were screened in person, and 130 individuals (67 % male) were randomized to the following medication conditions: (a) varenicline alone (VAR, n=34), (b) naltrexone alone (L-NTX alone, n=35), varenicline + naltrexone (VAR + L-NTX, n=31), and placebo (PLAC, n=30). A total of 120 individuals completed the laboratory assessment visit, 30 in each medication condition. Details on study enrollment are provided in the CONSORT diagram flow available in the Supplementary Materials.

Screening measures and medication administration

Interested individuals called the laboratory and completed a telephone-screening interview. Individuals who were deemed eligible came to the laboratory for in-person screening. After receiving a full explanation of study procedures and providing written, informed consent, participants completed the screening visit. The following measures were administered during the screening visit: (a) a demographics questionnaire; (b) the Beck Depression Inventory-II (BDI-II) administered at screening to identify and exclude individuals with current feelings of active suicidality and those with moderate to severe symptoms of depression; (c) frequency and quantity of alcohol/drug use; (d) a Smoking History Questionnaire to collect detailed history of nicotine use and quit attempts; (e) the Fagerstrom Test of Nicotine Dependence (FTND) to assess nicotine dependence (Heatherton et al. 1991); (f) the Wisconsin Smoking Withdrawal Scale (WSWS) to measure nicotine withdrawal symptoms (Welsch et al. 1999); and (g) the Time Line Follow Back (TLFB) to assess cigarette and alcohol use over the past 30 days (Sobell et al. 1986). Carbon monoxide (CO) levels and a urine cotinine test were used to verify the self-reported smoking pattern. Participants were required to have a breath alcohol concentration (BrAC) of 0.00 g/dl at the beginning of each visit.

Participants deemed eligible following the in-person screening completed a physical exam and clinical labs. Individuals who passed the physical exam were then randomized to one of the four medication conditions. Participants then took the study medication for 9 days and completed the laboratory study visit on medication day 9. The participants were titrated on varenicline as follows: days 1–2, 0.5 mg per day; days 3–5, 0.5 mg twice per day; and days 6–9, 1 mg twice per day. Naltrexone was administered at 25 mg per day for a period of 9 days. Placebo pills were matched to the active medications in number of pills and packaging. Study medications were packed into opaque capsules with 50 mg of riboflavin, and compliance with taking the medication was monitored by testing a urine sample for riboflavin content at each testing session by examining it under an ultraviolet light (Del Boca et al. 1996). Participants were given a 24-h telephone number to call the physician to discuss side effects, and physician office hours were available as needed. All procedures were approved by the Institutional Review Board of the University of California, Los Angeles.

Procedures & measures

Participants were required to abstain from cigarettes for 12 h prior to the testing session, and expired CO levels of less than 10 ppm (or below 50 % of initial screening value) were required to verify overnight smoking abstinence. After testing at baseline (i.e., 12 h of abstinence), participants received a loading dose of alcohol designed to reach a target BrAC of 0.060 g/dl, calculated using published guidelines (Brick 2006). The target BrAC level was selected on the basis of previous studies by our group showing that at this dose, heavy drinkers report significant changes in the subjective effects of alcohol and alcohol craving (Ray and Hutchison 2004; 2007), including increases in cigarette craving (Ray et al. 2007). The alcohol administration was not blinded, such that both participants and experimenters were aware that alcohol was being consumed; however, participants did not have access to their BrAC recordings until the study was complete. Upon reaching the target dose (30 min post-alcohol administration, on peak BrAC), participants completed post-alcohol assessments. After that, participants smoked the first cigarette of the day in the laboratory and completed assessments immediately after smoking that first cigarette. Participants smoked their own cigarette and no smoking instructions were provided. Pre- and post-cigarette CO levels were recorded.

During the experimental sessions, the following measures were administered at baseline (i.e., 12 h of abstinence), post-drinking, and post smoking: (a) Craving—cigarette craving was assessed with three single items, "How hard it would be to refuse a cigarette?", "All I want right now is a cigarette," and "Do you want another cigarette?" (the latter item was only administered after smoking was allowed), each rated on a 10-point Likert scale (where 0=no craving and 10=highest craving); (b) Mood—the Profile of Mood States (POMS-Short) was used to assess changes in mood at abstinence, post-drinking, and post smoking (McNair 1971) as studies by our group found it to be sensitive to alcohol intoxication effects

(Ray et al. 2009; Ray et al. 2010b); (c) After alcohol administration, participants reported on "alcohol high" using a 10-point Likert scale, and "cigarette high" was recorded; the item consisted of "How high (as in drug high) do you feel?", this item is consistent with a previous work in alcohol administration and medication studies (Ray and Hutchison 2007; Volpicelli et al. 1995); and (d) The short form of the Systematic Assessment for Treatment Emergent Events (SAFTEE) (Jacobson et al. 1986; Levine and Schooler 1986) was administered at the experimental session. In addition to the repeated questionnaires, participants reported on their use of cigarettes and alcohol over the 9-day titration period using the Time Line Follow Back (TLFB) interview (Sobell et al. 1986). No biomarker (e.g., CO, cotinine) was available for verification of self-reported cigarette and alcohol use during the titration period as participants did not return to the laboratory during that time.

Power analyses

Power analyses for the final study sample of $n=120$ completers were conducted in G*Power 3:1 (Faul et al. 2009). Specifically, we conducted a sensitivity analysis to determine the minimum effect size that could be reliably detected in the planned two-group comparison (VAR + L-NTX vs. PLAC and vs. each monotherapy) setting an alpha level of $p<0.05$, a two-tailed t test, and an independent group mean comparisons where each group has an $n=30$. Results indicated that the study sample afforded an 80 % power to detect an effect size in the magnitude of Cohen's $d=0.73$ or greater, which approximates a large effect size (Cohen 1992). On the basis of this sensitivity analysis as well as the novelty of the pharmacotherapy combination, we decided against p value correction in order to protect against type-II error and to inform future studies in the field.

Statistical analyses

A series of planned univariate ANCOVAs (equivalent to independent t tests with a covariate) between medication groups were performed with alpha set at $p<0.05$. Omnibus tests were not conducted as the overall effect of group (i.e., across all four medication groups) on each outcome is not of interest. Analyses of medication effects post-drinking included baseline (i.e., at 12h abstinence) as a covariate; post-smoking analyses controlled for post-drinking scores in the same manner; thus, the medication groups were compared on means adjusted for the previous time point. This sequential approach prevented redundancy in the results. Fisher's exact tests (Fisher 1922) were used to compare the medication groups on the SAFTEE. A number of covariates were examined, including age, cigarettes per day, drinks per drinking day, and FTND score. All analyses were conducted using SAS statistical software v9.3.

Results

There were significant medication group differences (Fisher's exact test, $p<0.05$) on the following side effects (frequencies provided): abdominal pain or cramps (VAR $n=3$, L-NTX $n=7$, VAR + L-NTX $n=11$, PLAC $n=4$), nausea or vomiting (VAR $n=14$, L-NTX $n=5$, VAR + L-NTX $n=18$, PLAC $n=2$), decreased appetite (VAR $n=6$, L-NTX $n=11$, VAR + L-NTX $n=6$, PLAC $n=2$), difficulty staying awake (VAR $n=2$, L-NTX $n=4$, VAR + L-NTX $n=6$, PLAC $n=0$). There were no serious adverse events during the study. Given the medication effects on nausea, which in turn could influence the subjective ratings of craving and mood (O'Malley et al. 2000), analyses were repeated controlling for nausea, and the results were maintained. Likewise, controlling for age, cigarettes per day, drinks per drinking day, FTND score, and smoking and drinking levels during the 9-day titration period did not alter the results reported below.

All urine samples tested positive for riboflavin, and all participants had a BrAC of 0.00 g/dl at each visit. Participants were compliant with the required 12 h of abstinence such that the average CO level was 14.67 ppm (SD=10.5) at the initial evaluation and 6.50 ppm (SD=6.0) following abstinence. After being allowed to smoke in the laboratory, CO levels rose to an average of 11.04 ppm (SD=8.2), yet there was no effect of the medication group on post-smoking CO level, after controlling for baseline CO level (ps>0.10). Peak BrAC post alcohol was 0.067 g/dl (SD=0.024), consistent with the intended target BrAC. The medication groups differed significantly on age [F (3,128)=4.53, $p<0.01$], but were comparable on all other demographic, smoking, and alcohol use measures (ps>0.10) (Table 1).

Craving and mood effects in the laboratory

Baseline (a 12-h smoking abstinence) effects There were no significant medication effects at 12 h of nicotine abstinence (i.e., baseline). Specifically, there were no medication group differences on nicotine withdrawal (WSWS) (ps>0.28), cigarette craving (ps>0.36), alcohol craving (ps>0.21), vigor (ps>0.19), tension (ps>0.08), and positive (ps>0.20) and negative (ps>0.29) moods.

Post-alcohol effects Means, standard errors, analyses of medication effects post-alcohol administration, and controlling for baseline scores (at 12 h of abstinence) are presented in Table 2. As shown in Fig. 1a, the combination of VAR + L-NTX was superior to placebo, L-NTX alone, and VAR alone in attenuating the craving for cigarettes. Individuals on the

Table 1 Demographic information, smoking behavior, and alcohol use by medication condition among study completers (n=120)

Variable	Medication condition			
	VAR n=30	L-NTX n=30	VAR + L-NTX n=30	PLAC n=30
Age	34.60	30.23*	29.77[a]	38.10
Sex (% male)	66.67	70.00	56.67	70.00
Ethnicity (%)				
-Caucasian	35.71	43.33	37.93	58.62
-African Am.	39.29	33.33	27.59	17.24
-Asian	0.00	10.0	20.69	3.45
-Latino	17.86	6.67	10.34	17.24
-Native Am.	7.14	6.67	3.45	3.45
Education (years)	13.80	13.23	13.97	14.24
Cigarettes per day	14.27	14.01	14.34	14.78
FTND score	3.63	3.63	3.63	4.00
Alcohol drinks per drinking day	6.43	6.31	7.22	6.19
Drinking days per month	21.73	21.60	19.30	20.20

[a] Significant difference from PLAC at p<0.05 (no other between medication group differences observed)

combination reported being better able to resist smoking a cigarette after receiving alcohol. The combination of VAR + L-NTX attenuated alcohol "high" more strongly than placebo and monotherapy (Fig. 1b). The study medications affected the mood-altering effects of alcohol administration, such that, after alcohol administration, L-NTX alone was associated with a more negative mood compared to placebo and VAR + L-NTX, more tension compared to the VAR + L-NTX and VAR alone, and a less positive mood compared to VAR alone. VAR alone was associated with higher ratings of vigor after alcohol consumption than PLAC or L-NTX alone.

Post-cigarette effects Means, standard errors, and analyses of medication effects after cigarette smoking and controlling for post-alcohol scores are presented in Table 3. As shown in Fig. 2a, the combination of VAR + L-NTX attenuated craving for cigarettes, compared to placebo, on the following items: "All I want right now is a cigarette" and "How much would you like another cigarette?" VAR alone or L-NTX alone did not differ from placebo on measures of cigarette craving post smoking. The combination of VAR + L-NTX attenuated ratings of "high" post cigarette compared to placebo and to L-NTX alone (Fig. 2b). L-NTX alone was significantly

Table 2 Adjusted means and standard errors for post-alcohol effects by medication group controlling for baseline scores (at 12 h of abstinence)

Variable	Medication condition			
	VAR	L-NTX	VAR + L-NTX	PLAC
Craving				
- Cigarette	8.14 (0.43)	7.93 (0.42)	6.88 (0.42)*[a,b]	7.88 (0.43)
- Alcohol	17.31 (1.72)	15.95 (1.67)	15.65 (1.73)	15.71 (1.71)
Alcohol high	5.58 (0.43)	5.55 (0.43)	4.29 (0.44)*[a,b]	5.50 (0.44)
Mood				
- Positive	3.23 (0.12)[c]	2.91 (0.12)[c]	3.15 (0.12)	2.91 (0.12)
- Negative	1.24 (0.08)[c]	1.72 (0.07)**[b,c]	1.29 (0.08)[b]	1.39 (0.08)
- Tension	1.33 (0.08)*[c]	1.72 (0.08)[b,c]	1.44 (0.08)[b]	1.59 (0.08)
- Vigor	2.88 (0.13)*[,c]	2.54 (0.12)[c]	2.74 (0.12)	2.53 (0.12)

All results are for analyses controlling for baseline ratings

*p<0.05; significant difference from PLAC

**p<0.01

[a] Significant difference between VAR + L-NTX vs. VAR alone

[b] Significant difference between VAR + L-NTX vs. L-NTX alone

[c] Significant difference between L-NTX alone vs. VAR alone

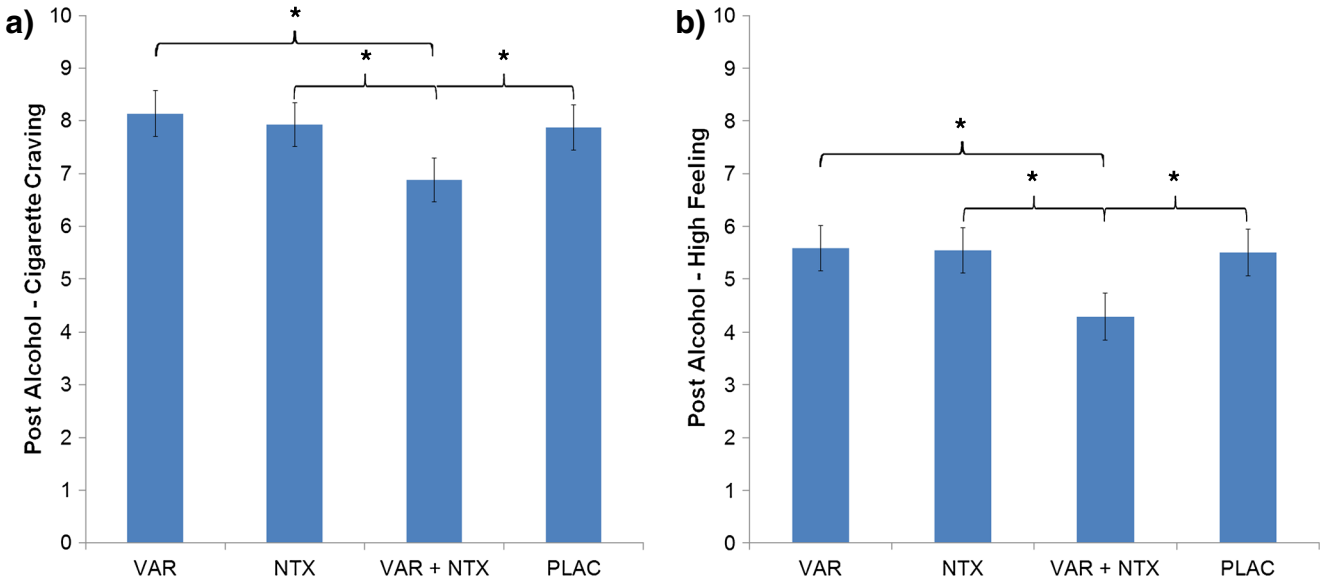

Fig. 1 Adjusted means and standard error of the mean for ratings post-alcohol administration (controlling for baseline) for cigarette craving (**a**) and alcohol "high"(**b**). Significant group differences are indicated by an *asterisk* for $p<0.05$ and *double asterisk*s for $p<0.01$

different from placebo in attenuating the positive mood post cigarette and was associated with a more negative mood than placebo, VAR only, and the combination of VAR + L-NTX.

Smoking and drinking effects in the natural environment

As for the question of whether study medication altered smoking (i.e., cigarettes per day) and drinking (i.e., drinks per drinking day) during the 9-day titration period, the combination of VAR + L-NTX and L-NTX alone were associated with fewer drinks per drinking day than placebo (Fig. 3a). The combination was also associated with fewer cigarettes per day during the titration period than placebo and L-NTX alone (Fig. 3b). These analyses controlled for drinks per drinking day and cigarettes per day, respectively, during the 30 days prior to medication randomization.

Discussion

The present study tested whether a combination of effective medications for smoking cessation (VAR) and for alcohol

Table 3 Adjusted means and standard errors for post-cigarette effects by medication group controlling for post-alcohol scores

Variable	Medication condition			
	VAR	L-NTX	VAR + L-NTX	PLAC
Craving				
- Cigarette	3.00 (0.45)	3.52 (0.45)	3.65 (0.46)*	3.91 (0.46)
- Alcohol	14.68 (1.21)	13.44 (1.21)	14.44 (1.23)	16.34 (1.23)
Cigarette high	4.36 (0.45)	5.06 (0.45)	3.39 (0.45)**[b]	5.19 (0.46)
Mood				
- Positive	2.79 (0.10)	2.94 (0.10)**	2.84 (0.10)	3.17 (0.10)
- Negative	1.51 (0.08)[c]	1.35 (0.08)*[b,c]	1.45 (0.08)[b]	1.40 (0.08)
- Tension	1.68 (0.08)	1.50 (0.08)	1.61 (0.08)	1.48 (0.08)
- Vigor	2.38 (0.11)	2.63 (0.10)	2.54 (0.10)	2.70 (0.10)

All results are for analyses controlling for post-alcohol ratings

*$p<0.05$; significant difference from PLAC

**$p<0.01$

[a] Significant difference between VAR + L-NTX vs. VAR alone

[b] Significant difference between VAR + L-NTX vs. L-NTX alone

[c] Significant difference between L-NTX alone vs. VAR alone

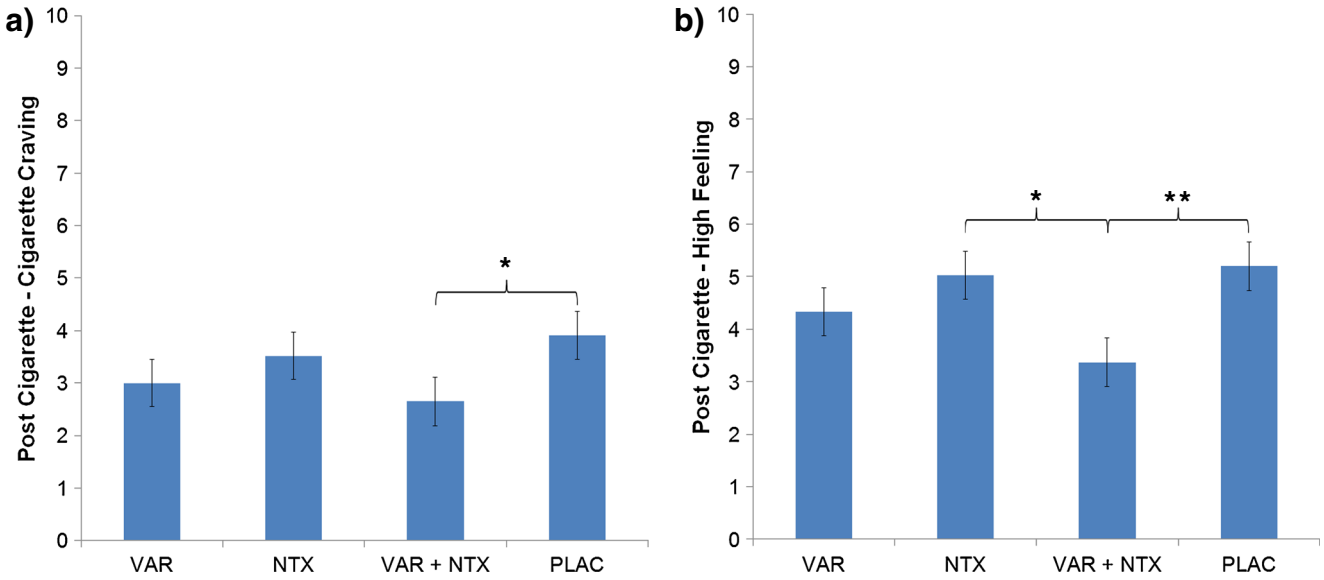

Fig. 2 Adjusted means and standard error of the mean for post-smoking ratings (controlling for post-alcohol ratings) of cigarette craving (**a**) and cigarette "high" (**b**). Significant group differences are indicated by an *asterisk* for $p<0.05$ and *double asterisk*s for $p<0.01$

misuse (L-NTX) would be superior to monotherapy and placebo on subjective measures of mood and cigarette craving among heavy-drinking smokers. There were no differences across medication groups on baseline (i.e., 12 h of nicotine abstinence) mood and craving. This was contrary to recent findings, including our own, demonstrating that varenicline attenuates tonic craving for cigarettes compared to placebo (Brandon et al. 2012; Ray et al. 2014). However, following alcohol administration, an interesting pattern of medication effects emerged. This assessment period is particularly useful in understanding alcohol use as a trigger for smoking among heavy-drinking smokers. The findings that the combination of VAR + L-NTX was superior to placebo and also to VAR alone in attenuating craving for cigarettes after alcohol might have potential clinical implications. Specifically, it seems possible to improve upon the current first line of treatment for smoking cessation, varenicline, by augmenting it with L-NTX, in heavy drinkers trying to quit.

The combination of VAR + L-NTX attenuated "alcohol high" more strongly than placebo and monotherapy. Recent studies found that VAR potentiates the aversive effects of alcohol (Childs et al. 2012) and reduces alcohol self-administration (McKee et al. 2009) compared to placebo, and perhaps these

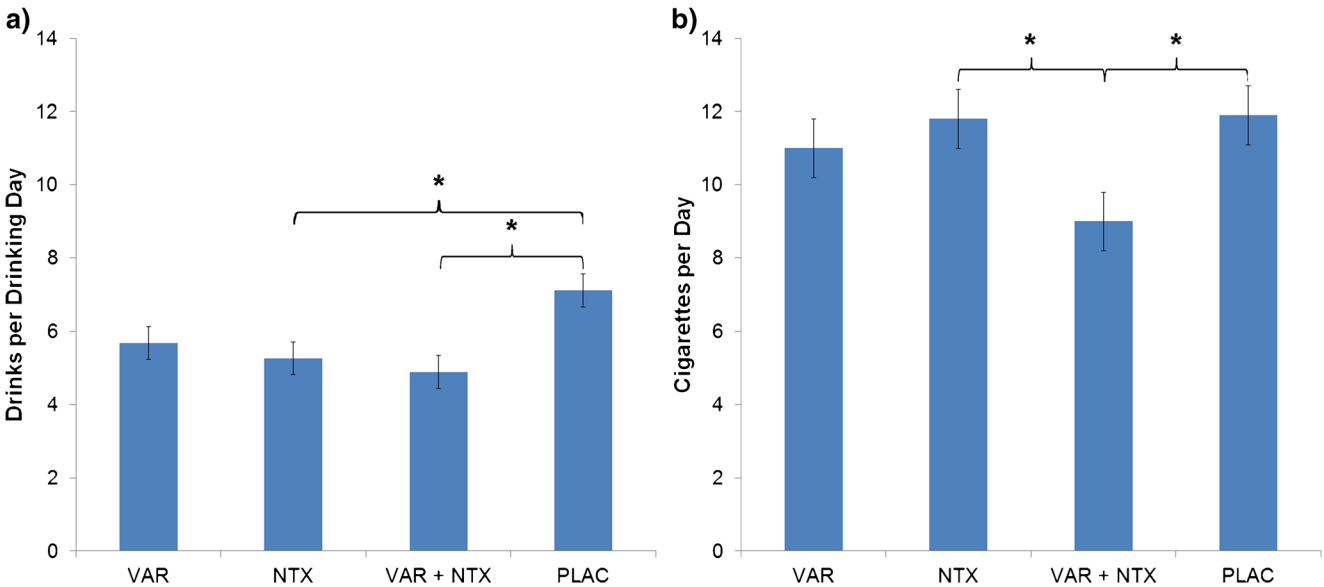

Fig. 3 Adjusted means and standard error of the mean for drinks per drinking day (**a**) and cigarettes per day (**b**) during the 9-day titration period after controlling for pre-randomization ratings of drinks per drinking day and cigarettes per day, respectively. Significant group differences are indicated by an *asterisk* for $p<0.05$ and *double asterisk*s for $p<0.01$

effects may be harnessed by the combination of VAR + L-NTX. Analyses of mood variables suggested that L-NTX alone was superior to placebo and often to the other treatments in blocking the positive mood-altering effects of alcohol. This observation is consistent with the available literature suggesting that naltrexone's primary mechanism of action for alcohol misuse is attenuation of the rewarding effects of alcohol (King et al. 1997; Ray et al. 2010a; Volpicelli et al. 1995).

Next, we evaluated the effects of medication upon smoking the first cigarette of the day. This is clinically relevant as craving for the first cigarette of the day is a strong indicator of nicotine dependence (Haberstick et al. 2007), and smokers often report the first cigarette of the day to be the most difficult cigarette to give up. The combination of VAR + L-NTX attenuated cigarette "high" more strongly than placebo and L-NTX alone. The combination also reduced cigarette craving over placebo, as indexed by ratings of desire for another cigarette. Mood variables suggested that L-NTX alone was blocking the effects of the first cigarette of the day on positive mood as well as increasing negative mood. This finding is consistent with our earlier work suggesting that naltrexone was superior to placebo in attenuating craving for cigarettes during alcohol exposure (Ray et al. 2007). Importantly, while studies have noted that naltrexone-precipitated nausea may impact, and even explain, clinical outcomes (O'Malley et al. 2000), all results survived controlling for nausea at the time of testing. Further, the 9-day titration period along with the low dose of naltrexone compares well to other acute dosing regimens for laboratory studies of naltrexone (e.g., Anton et al. 2004; O'Malley et al. 2002; Ray and Hutchison 2007).

Perhaps most intriguing, the combination of VAR + L-NTX was associated with reduced drinks per drinking day and cigarettes per day during the 9-day titration period compared to placebo, and with respect to cigarettes smoked per day, the combination was also superior to L-NTX monotherapy. While analyses of the brief period of medication titration should be interpreted with caution, the overall pattern of results from the human laboratory component suggest that the combination of VAR+L-NTX may be useful to heavy-drinking smokers by attenuating the rewarding effects of cigarettes and alcohol. Of note, controlling for smoking and drinking behavior during the 9-day titration period did not alter the results of laboratory testing reported herein. Thus, a clinical trial of VAR + L-NTX among heavy drinkers trying to quit smoking appears warranted.

These findings must be interpreted in the context of the study strengths and limitations. Strengths include the randomized, double-blind, placebo-controlled design. The well-phenotyped sample of community heavy drinkers, who smoke daily, is also a strength. Limitations include the non-treatment-seeking nature of the sample, as studies have shown that treatment-seeking status may impact the results of pharmacotherapy studies for nicotine dependence (Perkins et al. 2006). The single-item assessment of craving and "high" are also not ideal as scales of cigarette craving with stronger psychometric properties are available. The alcohol administration procedure was not placebo-controlled and was not blinded, such that expectancy effects may have influenced responses to the self-report measures of the effects of alcohol and nicotine. The uncorrected nature of the results should also be considered as preliminary. While sensitivity analyses suggested that only medium to large effect sizes (Cohen's $d \geq 0.73$) were detectable in this study, there is also the potential for type-I error given multiple comparisons.

In this study, we selected a 25-mg/day dose of naltrexone on the basis of literature indicating this was a promising adjunctive dosage (O'Malley et al. 2009); however, since this study began, multiple reports have favored a 50-mg/day dose of naltrexone over the low dose of 25 mg/day used in this study. In particular, a clinical trial by Toll et al. (2010) found that naltrexone at 25 mg/day was not significantly different from placebo (Toll et al. 2010). Further, recent smoking cessation trials of naltrexone at 50 mg/day have shown a benefit of naltrexone over placebo on quit rates as well as post-cessation weight gain (King et al. 2012; King et al. 2013). In addition, it has been demonstrated that the standard 50-mg dose of naltrexone produces near complete inhibition of the mu-opioid receptor (Weerts et al. 2008), and as such, the low dose used in this study is unlikely to produce such blockade. Thus, future studies of naltrexone in combination with varenicline should consider the standard dose of 50 mg/day as opposed to the low-dose naltrexone implemented in this study.

In order to properly interpret the clinical significance of these results, it is important to consider the context in which alcohol use and cigarette smoking co-occur. While the alcohol dosing (target BrAC=0.06 g/dl) was selected to produce significant changes in the subjective effects of alcohol and alcohol craving (Ray and Hutchison 2004; 2007), including increases in cigarette craving (Ray et al. 2007), smoking occurs across levels of alcohol dosing. To that end, a recent study demonstrated that a low dose of alcohol (target BrAC= 0.03 g/dl) was sufficient to produce robust cigarette craving among alcohol and cigarette co-users (Oliver et al. 2013). A similar pattern was found in an ecological momentary assessment study, recording cigarette craving and subjective effects after one standard drink. (Piasecki et al. 2011). Thus, the dose of alcohol used in this study may exceed the dose necessary to activate the alcohol-nicotine cross-craving and cross-reinforcement patterns observed in heavy-drinking smokers. Further, lower doses of alcohol may be more representative of typical alcohol consumption patterns (e.g., 1–2 drinks per episode). Importantly, one must also consider the instances where alcohol consumption is most likely to trigger a smoking lapse. Kahler et al. (2010) found that while a moderate drinking episode (1–4 drinks for men and 1–3 drinks for women) was associated with four times greater risk of a smoking lapse than non-drinking, a heavy-drinking episode (5+ drinks for

men and 4+ drinks for women) was associated with more than double the risk of lapsing compared with moderate drinking and more than eight times greater risk compared to non-drinking. These findings suggest that higher alcohol doses may be even more informative about drinking episodes with higher likelihood of precipitating a smoking lapse among heavy-drinking smokers trying to quit cigarettes. Hence testing medication effects at higher alcohol doses may be ultimately more informative about their ability to prevent alcohol-precipitated smoking lapses.

In summary, these results advance medication development for heavy-drinking smokers by suggesting that the combination of VAR + L-NTX may be superior to placebo, and at times superior to monotherapy, in attenuating cigarette craving, cigarette and alcohol "high," and reducing ad-lib consumption of both cigarettes and alcohol during the titration period. While preliminary, these findings suggest that clinical studies of this combination for heavy drinkers trying to quit smoking appear warranted and may ultimately improve clinical care for a sizeable and hard-to-treat subgroup of smokers.

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