Distress Tolerance and Craving for Cigarettes Among Heavy Drinking Smokers

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ABSTRACT. Objective: Heavy drinking smokers experience significant difficulties with smoking cessation. Craving is closely tied to relapses during cessation attempts, and alcohol consumption increases cigarette craving among heavy drinking smokers. To date, however, few moderators of the relationship between craving and relapse have been identified. Individuals' capacity for distress tolerance predicts smoking cessation outcomes and may be connected to craving. Relatedly, pharmacotherapies like varenicline and naltrexone reduce cigarette and alcohol cravings, respectively. No studies have examined the interrelationships among distress tolerance, craving, and pharmacotherapy effects. This study therefore examines distress tolerance as a moderator of the relationship between overnight abstinence-induced cigarette craving and subsequent alcohol- and cigarette-induced changes in craving among heavy drinking smokers. This study also examines the impact of varenicline and naltrexone on these relationships. **Method:** A total of 120 non–treatment-seeking heavy drinking smokers were randomized and titrated to one of the following conditions: (a) placebo, (b) varenicline, (c) naltrexone, or (d) varenicline + naltrexone. Participants then completed a laboratory paradigm after overnight abstinence that included consumption of alcohol (target .06 g/dl breath alcohol concentration) and one cigarette. Craving was assessed as abstinence-induced (Time 1), alcohol-induced (Time 2), and cigarette-induced (Time 3). **Results:** Within varenicline + naltrexone, low distress tolerance individuals exhibited higher increases from abstinence- to alcohol-induced cigarette craving relative to high distress tolerance individuals. Across medications, low distress tolerance individuals reported flatter decreases from abstinence- to cigarette-induced cigarette craving relative to high distress tolerance individuals. **Conclusions:** Distress tolerance may differentially predict alcohol-induced cigarette craving when titrated to pharmacotherapy, as well as moderate decreases in craving after cigarette consumption. Future exploration of the identified interactive effects could elucidate specific conditions in which cravings are more proximally related to abstinence-induced smoking. (*J. Stud. Alcohol Drugs, 79,* 918–928, 2018)

ALTHOUGH CIGARETTE SMOKING in the United States has declined in recent years, 15.1% of U.S. adults report regular smoking, that is, smoking at least 100 cigarettes during their lifetime and smoking at minimum several days a week (Center for Behavioral Health Statistics and Quality, 2016). Frequent co-use of alcohol and cigarettes may contribute to this persistently high prevalence of smoking. Approximately 20%–25% of regular smokers report heavy levels of drinking, defined as more than 7 drinks per week or 4 or more drinks per occasion at least once per month in the past year for women, and more than 14 drinks per week or 5 or more drinks per occasion at least once per month for men (Dawson, 2000; National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2005; Toll et al., 2012). Such heavy drinking smokers constitute a high-risk subpopulation who exhibit difficulties in smoking cessation and alcohol cessation. Increased alcohol use is associated with failed smoking cessation attempts (Cook et al., 2012; Hughes & Kalman, 2006; Kahler et al., 2009), and heavy drinking smokers are less likely to moderate or sustain abstinence during alcohol cessation attempts (Baltieri et al., 2009; Fucito et al., 2012).

Identifying factors that contribute to lapse and relapse in heavy drinking smokers may be important to improve smoking cessation outcomes in this population (Roche et al., 2016). Within both the alcohol and smoking literature, there is evidence that craving, or persistent urge or desire for a substance, is one of the greatest risk factors for unsuccessful cessation attempts. Craving can occur at a stable basal level and also be induced through drug priming (Shiffman, 2005). Individuals report increases in cigarette craving in response to direct consumption of alcohol (Bossert et al., 2013; Dunbar et al., 2014; Ray, 2011), although cigarette craving quickly decreases after consumption of a cigarette because of satiation effects (Rose et al., 2003; Schlagintweit & Barrett, 2016). Such craving episodes have been characterized in qualitative smoking studies as emotionally distressing events and associated with other consummatory behavior such as eating food and drinking alcohol (Sayette et al., 2005; Shiffman et al., 1997; 1996). Such substance-induced cravings are associated with increased risk for relapse during cessation attempts in clinical trials and naturalistic studies (Adinoff, 2004; Businelle et al., 2013) and with increased cigarette and alcohol consumption in experimental studies (Dunbar et al., 2014; Schlagintweit & Barrett, 2016). Pharmacological and behavioral treatments for smoking cessation have therefore focused on the reduction of craving (Conklin et al., 2013; Drobes et al., 2003; Ray et al., 2012; Young et al., 2014).

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Another construct potentially related to craving and cessation outcomes is distress tolerance, a stable yet malleable individual difference factor conceptualized as individuals' respective capacities to endure negative affect or aversive psychological or physical states (Brown et al., 2005). Low distress tolerance may be a risk factor for smoking cessation because of a lower threshold for tolerating aversive internal states that frequently occur during cessation. Abstinent smokers with low distress tolerance are more likely to engage in smoking behaviors that reduce such experiential distress and thereby are at greater risk for relapse (Baker et al., 2004; Johnson et al., 2009; Zvolensky et al., 2010). Higher distress tolerance predicts greater duration of smoking abstinence and longer time to lapse during cessation attempts (Brandon et al., 2003; Brown et al., 2009; Hajek, 1991; Hajek et al., 1987; Perkins et al., 2010). Distress tolerance measures differentiate smokers with previous successful quit attempts from those without such a history (Brown et al., 2002). Yet, distress tolerance has not been investigated in heavy drinking smokers, and it is unclear how this measure relates to smoking behavior in this sizeable subgroup of smokers.

A limited number of studies have examined the interactive relationship between distress tolerance and craving. These studies have identified that low distress tolerance, relative to high distress tolerance, predicts stronger negative affect and higher cigarette cravings on study-assigned quit dates in smokers during an unassisted quit attempt (Abrantes et al., 2008). Smokers with low distress tolerance may also be more sensitive to contexts that induce craving during abstinence; in an ecological momentary assessment study of treatment-seeking smokers, increases in cigarette craving during a cessation attempt were associated with daily stressors, and this relationship was stronger for individuals with low, relative to high, distress tolerance (Volz et al., 2014). As ecological momentary assessment studies corroborate the impact of recent alcohol use on smoking cravings during quit attempts (Businelle et al., 2018), distress tolerance may modulate craving during a cessation attempt as well as reactions to acute craving inductions. To date, however, no studies have examined the relationship between distress tolerance and changes in smoking- or alcohol-induced cigarette craving. Elucidation of this relationship may be important for heavy drinking smokers, as they are in particularly high risk for relapse because of alcohol-induced cigarette craving.

There are ongoing efforts within the treatment literature to build on distress tolerance and craving for smoking cessation. Several novel behavioral therapies have been developed to target distress tolerance directly among smokers; such therapies are well accepted and moderately efficacious (Bloom et al., 2016; Brown et al., 2013; Farris et al., 2016). Within the pharmacotherapy literature, varenicline, a partial agonist of the alpha4beta2 nicotinic acetylcholine receptor, is a widely prescribed smoking cessation medication and reduces cigarette cravings during cessation attempts (Jorenby et al., 2006; Ray et al., 2013). Naltrexone is an opioid receptor antagonist that improves alcohol cessation outcomes and attenuates alcohol craving (Anton et al., 2006; Helstrom et al., 2016). A combination of varenicline and naltrexone to treat both alcohol and smoking behaviors is posited to be an optimal smoking cessation treatment for heavy drinking smokers (Ray et al., 2014). This combination therapy was superior to varenicline alone and naltrexone alone in reducing neural activation underlying smoking cue-induced craving (Ray et al., 2015). A recent study, however, found no differences between monotherapy and combination therapy on alcohol-induced cigarette smoking among heavy drinking smokers, although both therapies' effects were superior to placebo (Roberts et al., 2018). Notably, although these medications' effects on substance craving are well documented, virtually no studies have explored their effects on the relationship between distress tolerance and craving. It is possible that pharmacotherapy's craving reductions benefit individuals with low distress tolerance who would otherwise be more sensitized to acute craving inductions (Brown et al., 2005). Examination of these relationships may therefore elucidate whether distress tolerance is a potential predictor of pharmacotherapy response in heavy drinking smokers.

In sum, there are multiple gaps in the literature regarding the relationships among distress tolerance and craving induced by abstinence and consumption of substances (i.e., alcohol, cigarettes), as well as potential impacts of pharmacotherapy on such relationships. To address these gaps, the current study used a randomized, double-blind, placebo-controlled experimental paradigm to study the relationship between distress tolerance and cigarette craving induced by alcohol and cigarette consumption after overnight (i.e., 12 hours) abstinence. This secondary analysis derives from a laboratory study (Ray et al., 2014) in which non–treatment-seeking heavy drinking smokers were randomly assigned to one of the following four medication conditions: (a) placebo (PLAC), (b) varenicline (VAR), (c) naltrexone (NTX), and (d) varenicline plus naltrexone (VAR + NTX). Participants were titrated to their assigned medication for 9 days and came to the laboratory for testing on Day 9 upon completing 12 hours of overnight abstinence. The primary study aim was to test whether distress tolerance interacted with abstinence-induced craving to predict subsequent alcohol-induced and cigarette-induced craving for cigarettes. We hypothesized that individuals with low distress tolerance, relative to those with high distress tolerance, would exhibit higher increases from abstinence- to substance-induced cravings. The second aim was to examine whether there were differences in this relationship across medication conditions (PLAC, VAR, NTX, VAR + NTX), to determine if monotherapy and/or combination therapies alter the relationships among distress tolerance and abstinence- and substance-induced craving. Although exploratory, we hypothesized that within PLAC,

VAR, and NTX, distress tolerance would moderate the relationship between abstinence and substance-induced craving, such that individuals with low relative to high distress tolerance would exhibit higher increases in alcohol-induced craving and steeper declines in cigarette-induced craving. Consistent with recent work from our group suggesting that combination VAR + NTX is more beneficial than monotherapies for smoking cessation among heavy drinking smokers (Ray et al., 2014, 2015), we anticipated that abstinence-induced cigarette craving would not be associated with alcohol-induced or cigarette-induced cigarette craving in VAR + NTX, and that distress tolerance would not moderate this relationship.

Method

Participants and procedures

The non–treatment-seeking sample for this secondary analysis (N = 120) comes from a study examining effects of pharmacotherapies on subjective response to cigarettes and alcohol (Ray et al., 2014). This larger study recruited community-based daily smokers through advertisements in the Los Angeles metropolitan area. Eligibility criteria were (a) between 21 and 55 years old; (b) smoking 10 or more cigarettes per day; (c) current heavy drinking, per NIAAA guidelines (NIAAA, 2005); 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 include (a) longer than 3 months of smoking abstinence in the past year; (b) self-reported use of illicit drugs other than marijuana in the past 60 days or positive urine toxicology screen at baseline; (c) history of psychotic disorders, bipolar disorders, or major depression with suicidal ideation; (d) current symptoms of moderate to severe depression, indicated by a Beck Depression Inventory-II score ≥20 (BDI-II; Beck et al., 1996); and (e) medical ineligibility based on a physical exam and laboratory tests. In all, 427 individuals completed this baseline screening process, of which 130 were randomized to one of four medication conditions and 120 completed the protocol. Ten randomized participants were excluded because of failure to pick up medication or failure to show up to the experimental visit. Study procedures are depicted in Figure 1.

Screening procedures

Interested individuals completed an initial phone interview to assess smoking and drinking patterns, as well as psychiatric and medical conditions. Individuals eligible after this interview completed an in-person screening visit. After providing informed consent, participants completed (a) demographics questionnaire; (b) breath-holding task, a distress tolerance assessment discussed further below; (c) Smoking History Questionnaire; (d) Fagerström Test of Nicotine Dependence (Heatherton et al., 1991); (e) Alcohol Dependence Scale (Skinner & Allen, 1982); and (f) Timeline Follow Back (TLFB) to assess cigarette and alcohol use over the past 30 days (Sobell & Sobell, 1992). Self-reports of current smoking were verified with breath carbon monoxide (CO) levels and a urine cotinine test (≥100 ng/mL). Participants were also required to have a breath alcohol concentration (BrAC) of .00 g/dl at the beginning of all study visits. Participants eligible after this in-person screening completed a physical exam and clinical labs.

Medication procedures

Medically eligible participants were randomized to one of four medication conditions, as follows: (a) varenicline alone (VAR, 2 mg/day, n = 34), (b) naltrexone alone (NTX, 25 mg/day, n = 35), (c) varenicline + naltrexone (VAR + NTX, n = 31), and (d) placebo (PLAC, n = 30). All medications were packed with 50 mg riboflavin into opaque capsules; medication compliance was assessed by testing participant urine samples for riboflavin content under ultraviolet light (Del Boca et al., 1996). In addition, placebo pills were matched to the active medications in number of pills and packaging. The study physician provided a 24-hour number to address any side effects or medical issues. Participants took the study medication for 9 days and completed a laboratory experimental visit on medication Day 9 (upon completing 12 hours of CO-verified smoking abstinence). All procedures were approved by the University of California, Los Angeles, Institutional Review Board.

Experimental visit

Participants were required to abstain from cigarettes for 12 hours before the experimental visit. Abstinence was bioverified via expired CO levels of less than 10 ppm (or below 50% of initial screening value) and BrAC of .00 g/dl. After completing verification procedures after 12 hours of abstinence, participants completed cigarette craving measures (described further below) as well as the Minnesota Nicotine Withdrawal Scale (Hughes & Hatsukami, 1986).

Participants then received a loading dose of alcohol designed to reach a target BrAC of 0.060 g/dl, calculated using standardized guidelines (Brick, 2006). The target BrAC level was selected from previous studies demonstrating that at this dose, heavy drinkers report significant changes in cigarette (Ray et al., 2007) and alcohol craving (Ray & Hutchison, 2007). This alcohol administration procedure was unblinded; participants and coordinators were aware that the consumed liquid was alcohol. Participants, however, did not know their BrAC recordings until the study was ongoing. Once participants reached the peak BrAC (30 minutes after admin-

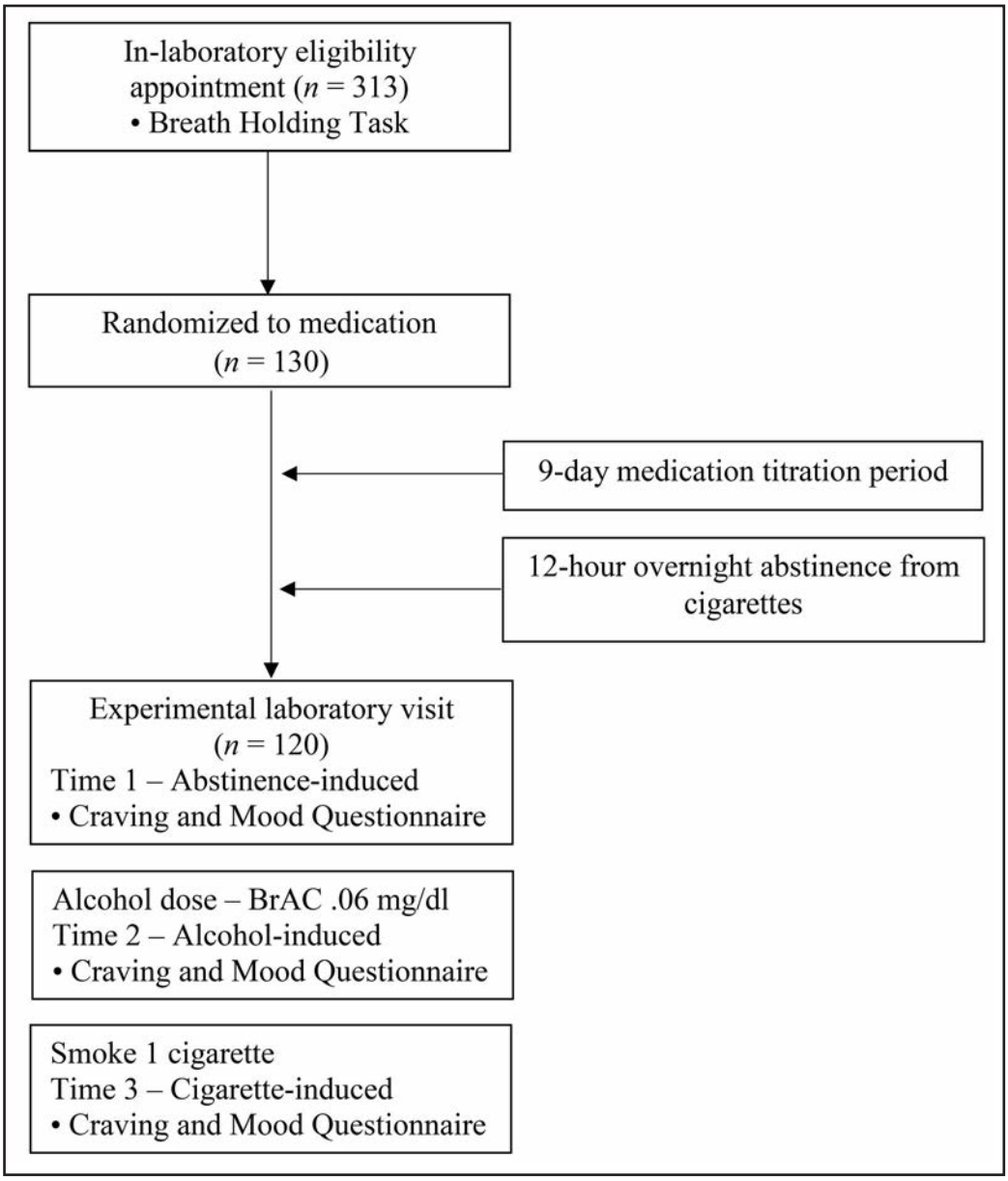

FIGURE 1. Study flowchart. BrAC = breath alcohol concentration.

istration), they completed assessments of alcohol-induced cigarette craving.

After completing alcohol-induced assessments, participants smoked the first cigarette of the day in the laboratory. Participants smoked their own cigarette and no smoking instructions were provided. Participants then completed assessments of cigarette-induced cigarette craving.

During the experimental session, the cigarette craving was assessed in the following time points: abstinence-induced (Time 1), alcohol-induced (Time 2), and cigarette-induced (Time 3). Craving was assessed with the Craving and Mood Questionnaire (CMQ), a five-item scale assessing cigarette urge, craving, and desire (Shiffman et al., 1998); the CMQ demonstrates good internal consistency and is sensitive to cue inductions (Hutchison et al., 1999).

Distress tolerance task

During the baseline screening visit, participants completed the breath-holding task, a validated behavioral index of physical distress tolerance previously used in smoking research (Brown et al., 2002; MacPherson et al., 2008). For this task, participants are asked to take a deep breath and hold it for as long as they can. They are asked to indicate to the study coordinator when they begin to feel uncomfortable by holding up a sign. They are then instructed to continue

Table 1. Sample characteristics

Variable	Medication condition			
	VAR (n = 30)	NTX (n = 30)	VAR + NTX (n = 30)	PLAC (n = 30)
Age	34.6 (11.05)	30.23 (8.51)[a]	29.77 (9.44)[a]	38.10 (9.64)
Sex (% female)	33.33	30	43.33	30
Race/ethnicity (%)				
White	35.71	43.33	37.93	58.62
African American	39.29	33.33	27.59	17.24
Asian	0	10	20.69	3.45
Latino/a	17.86	6.67	10.34	17.24
Native American	7.14	6.67	3.45	3.45
Education (no. of years)	13.80 (3.15)	13.23 (9.90)	13.97 (3.00)	14.24 (3.92)
Fagerström Test for Nicotine Dependence	3.09 (1.68)	3.37 (1.78)	3.39 (1.38)	3.48 (1.72)
Minnesota Nicotine Withdrawal Scale (overnight abstinence-induced)	15.00 (5.67)	15.67 (4.99)	14.70 (5.71)	14.63 (5.13)
Alcohol Dependence Scale	11.35 (5.76)	12.63 (8.02)	14.97 (8.43)	11.21 (6.59)
TLFB cigarettes per day	14.27 (4.76)	14.01 (5.94)	14.34 (6.73)	14.78 (6.39)
TLFB alcohol drinks per drinking day	6.43 (4.24)	6.31 (3.89)	7.22 (3.55)	6.19 (3.30)
TLFB drinking days per month	21.73 (8.15)	21.60 (7.81)	19.30 (7.50)	20.20 (8.45)
Breath-holding duration (seconds)	19.61 (14.41)	13.67 (11.57)	13.76 (9.63)	15.37 (14.90)
Craving measures				
Abstinence-Induced Craving and Mood Questionnaire	32.59 (13.75)	31.93 (13.22)	28.53 (15.26)	31.03 (15.60)
Alcohol-Induced Craving and Mood Questionnaire	37.33 (12.68)	37.87 (10.73)	35.24 (14.88)	35.80 (14.05)
Cigarette-Induced Craving and Mood Questionnaire	16.37 (12.66)	18.30 (13.71)	13.90 (12.56)	19.77 (14.55)

Notes: Unless indicated, descriptives are reported as M (SD). VAR = varenicline; NTX = naltrexone; VAR + NTX = varenicline plus naltrexone; PLAC = placebo; no. = number; TLFB= Timeline Followback. [a]Significant difference from placebo at $p < .05$.

holding their breath for as long as they can past this point of discomfort. Level of distress tolerance is assessed as the latency between the initial point of discomfort and the point at which they can no longer tolerate holding their breath. Lower breath holding latency is associated with unsuccessful smoking cessation outcomes, include relapse (Brown et al., 2005).

Analytic plan

As the distribution of breath holding duration was positively skewed (skewness = 1.53), we conducted a square root transformation of this variable. Study aims were tested using multiple regression analyses. To assess whether distress tolerance predicts post-overnight experiences, the first model examined the effect of breath holding duration (BH) on abstinence-induced cigarette craving and abstinence-induced withdrawal (Minnesota Nicotine Withdrawal Scale). To test primary study aims, cigarette craving at Time Point 2 and 3 (i.e. alcohol induced, cigarette induced) were examined as dependent variables in separate models. Each model included main effects of BH, abstinence-induced smoking craving, and medication (a four-level categorical variable) in Level 1; the three two-way interactions of these three variables in Level 2; and the three-way interaction (BH × abstinence-induced craving × medication) in Level 3. Cigarette-induced craving reduction analyses covaried for alcohol-induced craving increases, consistent with previous repeated-measures studies to prevent redundant results (Ray et al., 2014; Sayette et al., 2005). Because this is an exploratory study, we used an uncorrected alpha threshold of .05 for all post hoc analyses.

Results

Sample characteristics and overnight abstinence-induced craving

Demographic, behavioral, and smoking variables are presented in Table 1. Other than average age, there were no significant differences between medication groups on any of these variables (ps > .25). In addition, there were no significant group differences in abstinence-induced, alcohol-induced, or cigarette-induced cigarette craving. All participants were able to sustain bioverified overnight abstinence, and medication compliance was verified for participants' respective assignments. There were no differences in distress tolerance among participant dropouts and study completers, $t(128) = .08$, $p = .93$.

The average breath holding duration was 15.20 s (SD = 12.94), indicating that participants, on average, were able to endure holding their breath for 15 seconds from the time at which they began to feel discomfort. There were no significant overall group differences across medication conditions on square root–transformed breath holding duration, F(3,

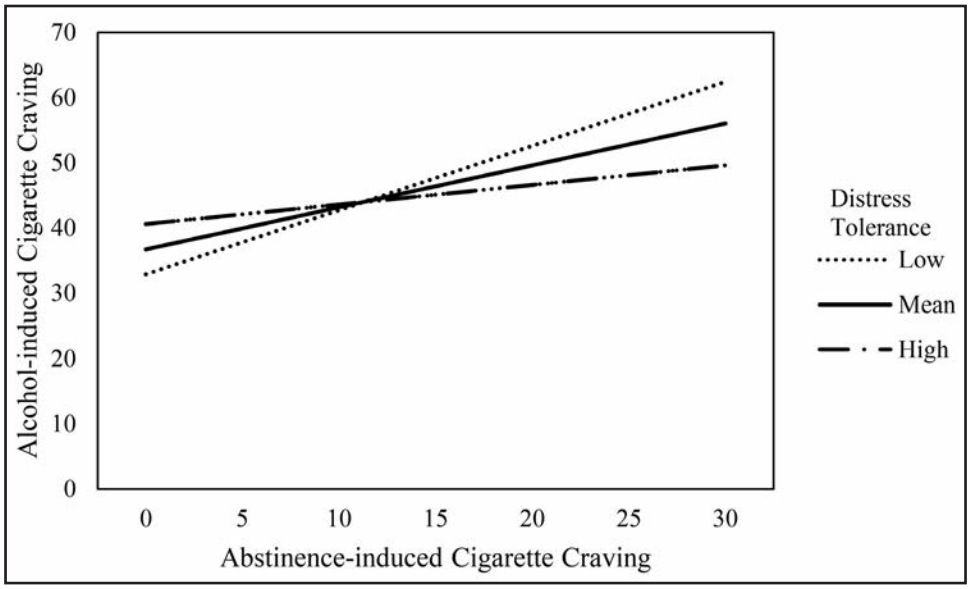

FIGURE 2. Interaction of breath holding and abstinence-induced cigarette craving on alcohol-induced cigarette craving in the varenicline + naltrexone (VAR + NTX) condition. Low and high breath holding represent -1 and +1 *SD,* respectively, from the mean.

116) = 1.66, p = .18. BH was not associated with either 90-day TLFB cigarettes per day or total Fagerström Test of Nicotine Dependence score (ps > .38). BH was also not predictive of either abstinence-induced cigarette craving, *B* (*SE*) = -0.95 (0.76), p = .22, or withdrawal, *B* (*SE*) = 0.23 (0.29), p = .42.

Paired sample *t* tests were used to verify experimental manipulation of craving. Across medications, there were increases from abstinence-induced cigarette craving, Time 1: *M* (*SD*) = 30.77 (14.37); to alcohol-induced craving, Time 2: *M* (*SD*) = 36.52 (13.08), $t(119) = -5.60$, $p < .001$. Additionally, there was a significant reduction from alcohol-induced craving to cigarette-induced craving, Time 3: *M* (*SD*) = 17.18 (13.42), $t(119) = 14.82$, $p < .001$. These results are consistent with previous studies on substance-induced changes in craving (Bossert et al., 2013; Schlagintweit & Barrett, 2016).

Alcohol-induced craving

There were significant positive predictive effects of abstinence-induced cigarette craving, *B* (*SE*) = 0.57 (0.70), $p < .001$; and BH, *B* (*SE*) = 1.82 (0.55), p = .001; on alcohol-induced cigarette craving increases. There was no main effect of medication (p = .53). In the second level, there was a significant interactive effect of BH × abstinence-induced cigarette craving, *B* (*SE*) = -0.13 (0.04), p = .001, such that abstinence-induced cigarette craving more strongly predicted increases in alcohol-induced craving for those lower in distress tolerance. There was a significant effect of BH × medication, *B* (*SE*) = 1.17 (0.48), p = .02, although simple main effects of BH within each medication group were not significant (ps > .13). The effect of abstinence-induced cigarette craving × medication was nonsignificant (p = .64).

Last, the three-way interaction of BH, abstinence-induced craving, and medication was significant, *B* (*SE*) = -0.12 (0.04), p = .001. Post hoc analyses were subsequently conducted to examine predictive effects of BH × abstinence-induced cigarette craving on alcohol-induced craving increases within each of the medication groups. Analyses revealed a significant interactive effect of BH and abstinence-induced craving, *B* (*SE*) = -0.24 (0.09), p = .009, on alcohol-induced craving within the VAR + NTX group. In this group, abstinence-induced cigarette craving more strongly predicted alcohol-induced cigarette craving increases among individuals with low distress tolerance relative to those with higher distress tolerance (Figure 2). This overall model explained a significant amount of variance within VAR + NTX, adjusted R^2 = .65, $F(3, 26) = 18.30$, $p < .001$. In contrast, these interactive effects were nonsignificant in the other medication conditions, PLAC: *B* (*SE*) = -0.13 (0.10), p = .18; VAR: *B* (*SE*) = 0.05 (0.08), p = .54; NTX: *B* (*SE*) = -0.11 (0.08), p = .16. These three medication conditions also demonstrated a significant predictive effect of abstinence-induced cigarette craving (ps < .001), but a nonsignificant effect of BH (ps = .13–.92) on alcohol-induced cigarette craving increases. Using a computational tool developed by Preacher and colleagues (2006), simple slope analyses indicated that within VAR + NTX, abstinence-induced cigarette craving significantly predicted alcohol-induced craving increases among individuals with low (-1 *SD*) distress tolerance, *B* (*SE*) = 0.99 (0.15), $p < .001$. In contrast, this relationship was nonsig-

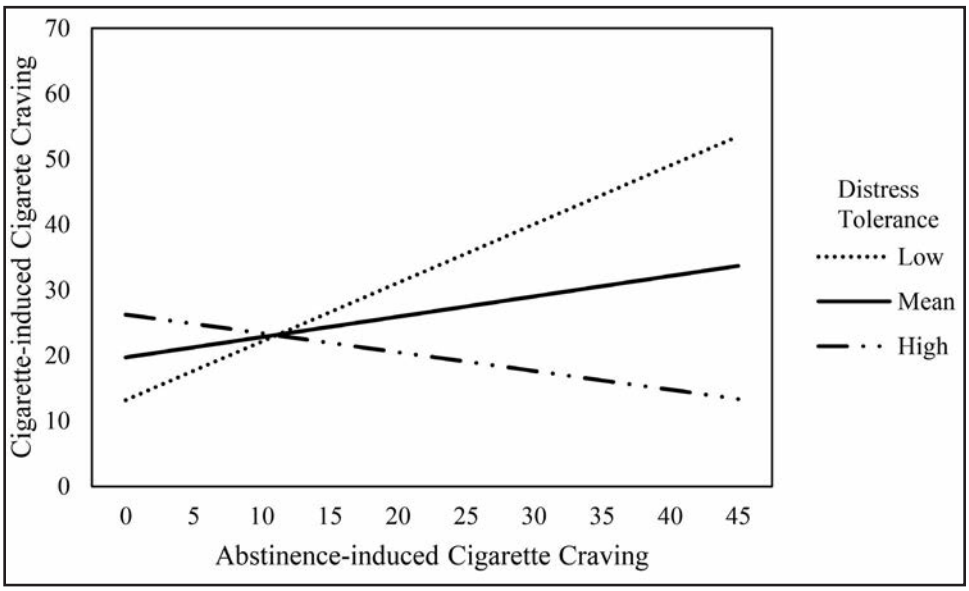

FIGURE 3. Interactive effect of breath-holding and abstinence-induced cigarette craving on cigarette-induced cigarette craving. Low and high breath holding represent -1 and +1 *SD,* respectively, from the mean.

nificant among individuals with high (+1 *SD*) distress tolerance, *B* (*SE*) = 0.41 (0.22), $p = .11$.

Cigarette-induced craving

There was a significant positive predictive effect of abstinence-induced cigarette craving on cigarette-induced cigarette craving reduction, *B* (*SE*) = 0.26 (0.08), $p = .003$. There was no main effect of either BH, *B* (*SE*) = 1.01 (0.75), $p = .18$; or medication, *B* (*SE*) = 0.66 (1.07), $p = .54$; on this outcome. In the second level, there were no significant abstinence-induced craving × medication, *B* (*SE*) = 0.08 (0.06), $p = .30$; or BH × medication effects, *B* (*SE*) = 1.00 (0.64), $p = .12$. There was, however, a significant abstinence-induced craving × BH effect, *B* (*SE*) = -0.13 (0.06), $p = .02$; such that after we controlled for alcohol-induced cigarette craving increases, abstinence-induced cigarette craving more strongly predicted cigarette-induced cigarette craving decreases among individuals with low distress tolerance relative to those with higher distress tolerance (Figure 3.). The three-way interaction of BH, abstinence-induced craving, and medication was nonsignificant, *B* (*SE*) = -0.02 (0.05), $p = .67$. This overall model explained a significant amount of variance, adjusted $R^2 = .10$, $F(7, 112) = 3.19$, $p = .006$.

To ensure that the analyses were not driven by severity of addiction or nicotine withdrawal, analyses with statistically significant findings were repeated to incorporate Fagerström Test of Nicotine Dependence and Minnesota Nicotine Withdrawal Scale scores as covariates. All significant results remained significant when these covariates were included in these models. Additionally, inclusion of age as a covariate did not change these results.

Discussion

This secondary analysis of a laboratory study (Ray et al., 2014) examined the predictive effects of distress tolerance and overnight abstinence-induced cigarette craving on subsequent substance-induced craving changes in heavy drinking smokers randomized to one of four medications. We first examined the relationship between abstinence-induced cigarette craving and distress tolerance assessed at a previous time point; breath holding was not predictive of overnight abstinence-induced cigarette craving or withdrawal. This result, although produced from a different design, contrasts a previous study that identified a negative relationship between distress tolerance and cigarette craving during individuals' quit day (Abrantes et al., 2008). Of note, this previous study used categorical composite scores (low, average, and high) from tasks assessing physical (breath holding and carbon monoxide challenge task) and cognitive (mirror tracing and timed serial adding task) distress tolerance to predict craving. Recent reviews of the distress tolerance literature have delineated such dimensions of distress tolerance as possibly distinct (Leyro et al., 2010); it is therefore possible that tasks assessing primarily physical distress tolerance alone do not reliably predict overall craving after brief abstinence, but additional replication studies are warranted.

Regarding substance-induced craving, individuals across medication conditions demonstrated increases in cigarette craving after consumption of alcohol. Within the varenicline

+ naltrexone condition, heavy drinking smokers with low, relative to high, distress tolerance exhibited a higher increase from overnight abstinence-induced to alcohol-induced cigarette craving. It is notable that although these effects were limited to this combination therapy group, individuals in the three other medication conditions demonstrated a similar predictive relationship between overnight abstinence-induced cigarette craving and increases in alcohol-induced craving, regardless of distress tolerance capacity. Monotherapies, including varenicline and naltrexone, have been shown to reduce background levels of cigarette craving (Gonzales et al., 2006; Hutchison et al., 1999; Jorenby et al., 2006) and demonstrate mixed results in reducing cue-induced cigarette craving (Brandon et al., 2011; Ferguson & Shiffman, 2009; Franklin et al., 2011; Fridberg et al., 2014; Ray et al., 2014; Rohsenow et al., 2007). Previous work by our group has demonstrated that varenicline plus naltrexone reduces smoking topography intensity in heavy drinking smokers relative to monotherapies and placebo (Roche et al., 2015) and attenuates anterior cingulate cortex activation when viewing cigarette cues relative to naltrexone and placebo (Ray et al., 2015). In contrast to study hypotheses, it is therefore possible that synergistic benefits of combination therapy provide more benefit to individuals with higher levels of distress tolerance relative to those with low distress tolerance; for high distress tolerance individuals, overnight abstinence-induced cigarette craving is less affected by alcohol consumption when titrated to this combination therapy. Such a disrupted relationship is particularly relevant for heavy drinking smokers, as smoking lapses are four times as likely to occur on drinking days for heavy drinking smokers during a cessation attempt (Kahler et al., 2010). These exploratory analyses warrant future replication in larger samples; if corroborated, these results may suggest that low distress tolerance individuals titrated to varenicline plus naltrexone, as well as those receiving monotherapy regardless of distress tolerance capacity, may benefit from additional interventions such as adjunctive psychoeducation of coping methods to anticipate increases in alcohol-induced craving. It may also suggest that high distress tolerance alone is not sufficient to buffer against increases in alcohol-induced cigarette cravings when titrated to monotherapy or placebo.

Across medication conditions, consumption of a cigarette resulted in a reduction in cigarette craving, consistent with prior findings (Rose et al., 2003; Schlagintweit & Barrett, 2016). There was also an interactive effect of distress tolerance and abstinence-induced cigarette craving on cigarette-induced cigarette craving; those with low distress tolerance, relative to those with high distress tolerance, exhibited flatter craving reductions from abstinence-induced to cigarette-induced craving after controlling for increases because of alcohol consumption. These results suggest that although distress tolerance does not directly predict craving intensity after overnight abstinence or craving response to alcohol or cigarette consumption, individuals with low distress tolerance and high levels of post-overnight abstinence craving may fail to observe reductions in craving after smoking a cigarette. Thus, relative to those with moderate to high distress tolerance, heavy drinking smokers with low distress tolerance may be at risk to smoke more cigarettes during an alcohol-induced smoking lapse in an attempt to reduce alcohol-augmented cigarette cravings. Such an elevated risk is important to address in smoking cessation attempts, as ecological momentary assessment studies have found that the number of cigarettes smoked during a lapse is predictive of the rate of full relapse (Shiffman et al., 2006).

The overall results of this study corroborate the examination of trait factors like distress tolerance in craving research. Specifically, distress tolerance may differentially predict alcohol-induced cigarette craving when titrated to smoking cessation medications, as well as moderate decreases in craving after cigarette consumption. Within the larger craving literature, studies have identified a close relationship between craving and relapse across multiple substances (Hendershot et al., 2011; Moore et al., 2014), but systematic reviews acknowledge that there is a dearth in understanding potential moderators of this relationship (Leventhal & Zvolensky, 2015; Veilleux & Skinner, 2015; Wray et al., 2013). Additionally, although the present study did not directly examine the prospective relationship between craving and smoking, there is evidence that, post-brief abstinence, low distress tolerance individuals demonstrate greater ad libitum smoking and different dimensions of craving are predictive of ability to resist smoking and number of cigarettes smoked in a laboratory model of smoking lapse (Roche et al., 2014). Future exploration of the identified interactive effect of distress tolerance and abstinence-induced craving could elucidate specific conditions in which cravings are proximally related to abstinence-induced smoking.

There were several important study limitations. These results, particularly regarding three-way interactions on alcohol-induced cigarette craving, are preliminary given the small sample size and uncorrected significance threshold. Participants were non–treatment-seeking smokers and may not be generalizable to all smokers, as treatment-seeking status affects smoking pharmacotherapy studies (Perkins et al., 2006). This experimental study incorporated a programmed smoking lapse in the laboratory; additional research is necessary to understand the paradigm's generalizability to smoking lapse in the real world. Commercially available cigarettes vary in levels of nicotine and other tobacco constituents (Eldridge et al., 2015), and participants were not provided standardized instructions when they smoked the first cigarette of the day; future studies may benefit from standardized procedures and cigarettes that allow for precise control of tobacco exposure. Additionally, we assessed distress tolerance at one time point before abstinence. Although distress tolerance is a moderately stable trait over time (Kiselica et al., 2014), there

is evidence that distress tolerance can decrease during smoking abstinence among adults (Cosci et al., 2015) and during alcohol abstinence among heavy drinking youth (Winward et al., 2014). Future studies that examine distress tolerance and craving may benefit from repeated assessments. This study also used alcohol and cigarette consumption without a comparison to a neutral control condition. The paradigm was administered solely after medication titration without a baseline comparison, and it is possible that the primary findings are driven by randomization and not medication effects. Consideration of these limitations may strengthen future study designs and reduce potential sources of bias (Kühn & Gallinat, 2011).

This study extends the distress tolerance and craving literature to identify an interactive effect of breath holding and abstinence-induced cigarette craving on subsequent alcohol and smoking-induced craving, such that low distress tolerance individuals with high levels of abstinence craving may fail to have reductions in craving after smoking a cigarette. This study provides exploratory data on pharmacological effects that may specifically affect alcohol-induced cigarette cravings after abstinence. The study findings corroborate the importance of assessing traits such as distress tolerance as moderators of substance-induced craving and provide an empirical basis to explore additional relationships among craving and smoking behavior.

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