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Combined varenicline and naltrexone treatment reduces smoking topography intensity in heavy-drinking smokers

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ABSTRACT

Heavy drinking smokers constitute a distinct sub-population of smokers for whom traditional smoking cessation therapies may not be effective. Recent evidence suggested that combined varenicline (VAR) and naltrexone (NTX) therapy may be more efficacious than either monotherapy alone in reducing smoking and drinking-related behavior in this population. The manner in which individuals smoke a cigarette (i.e., smoking topography) may be predictive of smoking cessation outcomes, yet the effects of smoking pharmacotherapies on puffing behavior have not been thoroughly examined. Therefore, the current double-blind medication study examined the effects of VAR alone (1 mg BID), low dose NTX alone (25 mg QD), the combination of VAR + NTX, and placebo on smoking topography measures in heavy drinking, non-treatment seeking daily smokers (n = 120). After a 9-day titration period, participants completed a laboratory session in which they smoked their first cigarette of the day using a smoking topography device following 12 h of nicotine abstinence and consumption of an alcoholic beverage (BrAC = 0.06 g/dl). The primary measures were puff count, volume, duration, and velocity and inter-puff interval (IPI). Independent of medication group, puff velocity and IPI increased, while puff volume and duration decreased, over the course of the cigarette. The active medication groups, vs. the placebo group, had significantly blunted puff duration and velocity slopes over the course of the cigarette, and this effect was particularly evident in the VAR + NTX group. Additionally, the VAR + NTX group demonstrated lower average IPI than the monotherapy groups and lower average puff volume than all other groups. These results suggest that smoking pharmacotherapies, particularly the combination of VAR + NTX, alter smoking topography in heavy drinking smokers, producing a pattern of less intense puffing behavior. As smoking topography has been predictive of the ability to quit smoking, future studies should examine how smoking pharmacotherapies' effects on puffing behavior relate to smoking cessation outcomes.

1. Introduction

Heavy drinking smokers represent a prominent and distinct subgroup of substance users who often present unique treatment challenges (Dani and Harris, 2005; Littleton et al., 2007). Levels of alcohol use are higher in smokers than non-smokers, and the prevalence of smoking is higher in heavy drinkers compared with non-drinkers (Dawson, 2000). Because of this, heavy drinking smokers experience more health consequences, including impaired brain morphology and function (Durazzo et al., 2007) and greater risk for various cancers (Ebbert et al., 2005), than those who only drink or smoke. The co-use of these substances also has clinical importance, as greater alcohol use is associated with decreased odds of quitting smoking and smokers are four times more likely to have a smoking lapse during drinking episodes (Hymowitz et al., 1997; Kahler et al., 2008, 2010). Thus, while there are currently no pharmacological treatments tailored to heavy drinking smokers, recent work in this population has focused on developing medications that can reduce both alcohol and cigarette consumption (Fridberg et al., 2014; Ray et al., 2014a).

There is evidence that varenicline (VAR) and naltrexone (NTX), both alone and in combination, may reduce smoking behavior and alcohol consumption and, therefore, hold promise as a treatment for heavy drinking smokers. Varenicline is a front-line treatment for smoking cessation and in heavy drinking smokers has been shown to reduce the number of cigarettes smoked and alcoholic beverages consumed per day, while also attenuating alcohol craving (Fucito et al., 2011; McKee et al., 2009; Mitchell et al., 2012). Naltrexone (50 mg) is FDA-approved for the treatment of alcohol dependence but has also shown some promise as an adjunct treatment for smoking cessation (King et al., 2006, 2012). Of note, NTX may be primarily effective among heavy drinking smokers by preferentially reducing alcohol consumption and smoking urge while also improving smoking quit rates in comparison with non-heavy drinking smokers (Fridberg et al., 2014;

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King et al., 2009a; O'Malley et al., 2009). Finally, recent evidence from our group suggests that the combination of VAR and low dose NTX (25 mg) may be more effective in reducing cigarette craving, smoking behavior, and alcohol consumption than either medication alone (Ray et al., 2014a). Although the early evidence on combined VAR + NTX therapy as a targeted treatment for heavy drinking smokers is promising, additional studies are needed to replicate and extend these preliminary results by identifying biobehavioral mechanisms by which combined therapy may provide advantages over traditional monotherapies.

The manner in which an individual smokes a single cigarette, i.e., smoking topography, is an objective and reliable index of smoking intensity and reinforcement (Perkins et al., 2012). Importantly, preliminary evidence suggests that smoking topography measures may be more predictive of smoking cessation outcomes than other traditional measures of individual differences in smoking behavior, including severity of nicotine dependence and cigarettes per day (Strasser et al., 2004; Franken et al., 2006). For example, in a clinical trial comparing nicotine replacement therapies (NRTs) in heavy adult smokers, several pre-treatment smoking topography measures, including lower puff volume (capacity of each puff), lower puff velocity (flow rate of each puff), and higher interpuff interval (IPI; time between each puff), were predictive of greater abstinence rates independent of treatment group (Strasser et al., 2004). Similarly, in a NRT trial in adolescent smokers, lower puff volume at baseline was associated with better treatment outcomes (Franken et al., 2006). Finally, greater puff volume and longer puff duration at pretreatment baselines were related to poorer cessation outcomes in female smokers treated with NRT, but not those receiving VAR (McClure et al., 2013). Therefore, it appears that individuals with a less "intense" pattern of smoking/puffing behavior during a single cigarette, as indexed by a lower average puff volume, velocity, and duration and higher IPI, may have greater odds of maintaining abstinence during a quit attempt (McClure et al., 2013).

Despite the potentially meaningful association between smoking topography and smoking cessation outcomes, few studies have examined the effects of pharmacotherapies on smoking topography. In non-treatment seeking daily smokers, NTX, but not buproprion, significantly reduced puff count compared with placebo (Rukstalis et al., 2005). Conversely, two other studies of non-treatment seeking smokers reported that neither VAR nor bupropion treatment directly affected any individual smoking topography measure (McKee et al., 2012; Ashare et al., 2012); although, VAR was found to reduce a measure of daily smoking behavior that was comprised from an individual's cigarettes per day and total puff volume (Ashare et al., 2012). While smoking topography is a reliable index of an individual's smoking intensity and may be related to cessation outcomes, additional research is needed to determine whether topography measures are sensitive to the effects of smoking pharmacotherapies.

In sum, smoking topography measures, particularly puff volume and duration, may be predictive of smoking cessation outcomes. However, the effects of smoking pharmacotherapies on smoking topography remain unclear, particularly among hard-to-treat subgroups such as heavy drinking smokers. While there is early, but mixed, evidence suggesting that particular measures of smoking topography may be sensitive to VAR and NTX monotherapy (Rukstalis et al., 2005; McKee et al., 2012; Ashare et al., 2012), no studies have examined the combined effects of these medications on puffing characteristics. Therefore, the goal of this study was to examine whether VAR (1 mg/twice daily), low dose NTX (25 mg), and their combination affect smoking topography (vs. placebo) in heavy drinking smokers. Based on a prior study in this sample that found VAR + NTX combined therapy was more effective than VAR or NTX monotherapy and placebo in reducing cigarette craving, as well as daily smoking and drinking behavior (Ray et al., 2014a), we hypothesized that VAR and NTX treatment, both alone and in combination, will produce a less intense pattern of puffing behavior over the course of a single cigarette compared with placebo (i.e., a lower puff volume, velocity, and duration and higher IPI) and also that the combination of VAR and NTX will be more effective than either monotherapy alone in producing these changes.

2. Methods

2.1. Participants & screening procedures

The study was approved by the Institutional Review Board of the University of California, Los Angeles and was conducted in accordance with the Declaration of Helsinki. Detailed methodology of the general experimental and screening procedures has been previously published elsewhere (Ray et al., 2014a,b). A community-based sample of non-treatment seeking, daily smokers was recruited via online and print advertisements in the Los Angeles area. Participants were reminded at multiple points throughout the recruitment and screening processes that this was not a treatment study. Interested individuals called the laboratory and completed a telephone-screening interview to determine initial eligibility. Potential participants were eligible if they: (1) were between 21 and 55 years of age; (2) reported smoking 10 or more cigarettes per day and did not report more than 3 months of smoking abstinence in the past year; (3) fit the criteria for heavy drinking according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines (Health and Services, 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; (4) were of good general health; (5) were not currently pregnant or planning to become pregnant during the course of the study; (6); did not report use of cocaine, methamphetamine, heroin or other illicit drugs (other than marijuana) in the previous 60 days; and (7) reported no history of psychotic disorders, bipolar disorders, or major depression with suicidal ideation in their lifetime.

Individuals who met the initial eligibility requirements were invited to the laboratory for in-person screening, in which they provided informed consent. The in-person screening also consisted of a general physical examination by the study physician and the completion of several questionnaires, which included the Beck Depression Inventory (BDI-II; Beck et al., 1996), demographic and lifetime substance use history questionnaires, the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al., 1991), the Wisconsin Smoking Withdrawal Scale (Welsch et al., 1999), and the Time Line Follow Back to assess cigarette and alcohol use over the past 30 days (Sobell et al., 1986). Participants were asked to abstain from drinking alcohol for 24 h prior to the in-person screening visit, which was confirmed by breathalyzer. Urine drug screens and pregnancy tests were also performed. Individuals who passed the physical exam, had a BDI score <20 (no current symptoms of moderate depression or higher), had a breath alcohol concentration (BrAC) of 0.000 g/dl, and tested negative for drug use and pregnancy were randomized to a medication condition. Finally, expired carbon monoxide (CO) levels were collected at the screen in order to later verify overnight abstinence prior to the experimental session, as described below.

A total of 427 individuals (79% male) were screened in person, and 130 individuals (67% male) were randomized in a double-blind fashion to one of the following medication conditions: (a) VAR alone ($n = 34$), (b) NTX alone ($n = 35$), VAR + NTX ($n = 31$), and placebo ($n = 30$). A total of 120 individuals completed the study (n = 30 in each group), however 11 individuals had smoking topography data that could not be analyzed due to instrumentation error, leaving the final group sizes as follows: VAR = 29, NTX = 28, VAR + NTX = 25, and placebo = 27.

2.2. Experimental procedures & smoking topography measures

Participants took the study medication on a daily basis for 9 days and subsequently completed an experimental session on day 9. The participants were titrated on VAR 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