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Interplay Between Cigarette and Alcohol Use: Etiological and Treatment Approaches

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Interplay Between Cigarette and Alcohol Use: Etiological and Treatment Approaches

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Psychology

by

ReJoyce Denise Green

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ABSTRACT OF THE DISSERTATION

Interplay Between Cigarette and Alcohol Use: Etiological and Treatment Approaches

by

ReJoyce Denise Green

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2022

Professor Lara A. Ray, Chair

Background: Previous studies have highlighted a robust bidirectional relationship between alcohol and cigarette use. Co-use of these substances impacts treatment outcomes, as there are no FDA approved medications for the co-use of cigarettes and alcohol. The combination of 2 FDA approved medications for smoking cessation (varenicline) and alcohol use disorder (naltrexone) have shown promise as a treatment option for heavy drinking smokers.

Methods: The dissertation project examined both etiology and treatment of the unique subgroup of heavy drinking smokers. Chapter 1 (etiology) utilized a behavioral economics framework in a sample of non-treatment seeking heavy drinking smokers to examine demand for each substance using a hypothetical purchase task in which participants indicate how much of a substance they would consume at varying prices. Chapters 2 and 3 (treatment) consisted of a community sample of treatment-seeking heavy drinking smokers who completed a 12-week randomized clinical trial comparing varenicline plus placebo versus varenicline plus naltrexone for smoking cessation and

drinking reduction. Chapter 2 examined the impact of sex hormones in response to pharmacotherapy for female heavy drinking smokers. Chapter 3 examined whether drinking outcomes mediated the relationship between pharmacotherapy and smoking outcomes.

Results: Results from Chapter 1 (etiology) revealed cross-substance relationships, with use of one substance predicting greater demand of the opposite substance. Notably, we found a stronger effect of nicotine use on demand for alcohol than vice versa. Results from Chapter 2 (treatment) showed no interaction of sex hormones and pharmacotherapy on smoking outcomes. However, greater ratio of progesterone to estradiol was associated with greater percent days abstinent from alcohol for females assigned to the varenicline plus naltrexone condition. Results from Chapter 3 (treatment) indicated that drinking outcomes did not mediate the relationship between pharmacotherapy and smoking outcomes. However, throughout the active medication phase and follow-up phase there was a significant relationship between drinking and smoking outcomes.

Conclusion: These studies use a translational framework combining pharmacology, experimental psychology, and biomarkers of sex differences to address clinical implications of the co-use of cigarettes and alcohol. These studies advance a precision medicine approach whereby the complementarity between smoking and drinking can be clinically targeted.

The dissertation of ReJoyce Denise Green is approved.

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This dissertation is dedicated to my mother Luci, grandmother Joyce, and brother Israel for their unwavering support in my graduate pursuits. I am beyond grateful for their constant encouragement in all phases of my career.

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LAR designed the study. RG conducted study analysis, with the assistance of JM and MK. All authors contributed to the conceptualization of the manuscript and interpretation of the data. RG and LAR drafted the manuscript. All authors revised the manuscript and provided their approval of the current version submitted for publication. All authors agree to be accountable for all aspects of the work, including its accuracy and integrity.

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Introduction

Bidirectional Relationship Between Cigarette Smoking and Alcohol Use

Cigarettes and alcohol are two of the most commonly used recreational substances. The 2018 National Health Interview Survey (NHIS) reported 19.7% using any tobacco product, including 13.7% using cigarettes and 3.2% using e-cigarettes (Creamer et al., 2019). Of those using cigarettes, the prevalence of cigarette use was higher among men (15.6%) than women (12.0%) (Creamer et al., 2019). The National Epidemiological Survey on Alcohol Related Conditions – III (NESARC-III) found that the 12-month prevalence of Diagnostic and Statistical Manual – 5 (DSM-5) nicotine use disorder was 20.0%, while the prevalence of lifetime DSM-5 nicotine use disorder was 27.9% (Chou et al., 2016). In reference to cessation efforts, results from the NHIS revealed a significant increase in the prevalence of smoking quit attempts from 52.8% in 2009 to 55.1% in 2018, as well as a significant increase in successful quit attempts from 6.3% in 2009 to 7.5% in 2018 (Creamer et al., 2019). The impact of these high rates of cigarette use can be seen in the health consequences. The World Health Organization (WHO) recently estimated that tobacco use contributed to more than 7 million deaths per year (WHO, 2017).

Cigarette smoking has been linked with a variety of diseases including cardiovascular and respiratory diseases (Ambrose & Barua, 2004; Hikichi, Mizumura, Maruoka, & Gon, 2019; USDHHS, 2014), gastrointestinal diseases (Chu et al., 2013; Li et al 2014), and numerous cancers with lung cancer being among the leading causes of cancer-related mortality (Saba, Halytskyy, Saleem, & Oliff, 2017; USDHHS, 2014) that contribute to these high rates of morbidity and mortality. Cigarette smokers die approximately ten years earlier than non-smokers and cigarette smoking cessation prior to the age of 40 has been estimated to reduce risk of death

by approximately 90% (Jha et al., 2013). In addition, to direct acute and chronic health consequences, smoking exerts a large economic burden with an estimated $130 billion due to direct medical healthcare and $130 billion due to lost work productivity resulting from premature death (USDHHS, 2014; Xu, Bishop, Kennedy, Simpson, & Pechacek, 2015).

Alcohol use rates to remain high with recent estimates from the 2019 National Survey on Drug Use and Health (NSDUH) that 25.8% of adults in the U.S. reported engaging in binge drinking over the past month (USDHHS, 2019). Binge drinking was defined as 5 or more alcoholic beverages for men, and 4 or more alcoholic beverages for women on the same occasion at least one day in the past month. For DSM-5 alcohol use disorder (AUD), NESARC-III found a 12-month prevalence of 13.9% and lifetime prevalence of 29.1% (Grant et al., 2015). As with cigarettes, excessive alcohol consumption has been linked with a host of health consequences. Excessive alcohol use over an extended period of time has been associated with liver disease and cirrhosis (Szabo, 2015), as well as increasing the risk for cancers including mouth, liver, and breast cancer (WHO, 2019). The economic burden caused by alcohol misuse was estimated in 2010 to reach $249 billion in the United States alone, with an estimated three-quarters of the cost due to binge drinking (Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015). The high rates of use across cigarettes and alcohol contribute to an array of health consequences that consequently result in a large economic burden.

While alone these two substances are consumed at high rates, they are often used concurrently. In comparison to those who have never smoked, daily, occasional, and former smokers are all at greater risks of engaging in hazardous drinking (McKee, Falba, O'Malley, Sindelar, & O'Connor, 2007). Daily and occasional smokers were also more likely to meet diagnostic criteria for a DSM-IV alcohol abuse or dependence diagnosis (McKee et al., 2007). A

study of smokers who called into a smoking quit line found that 23% had reported hazardous drinking (Toll et al., 2012). Those who reported hazardous drinking also had significantly lower smoking cessation rates at a 1-week follow up than those who reported moderate alcohol consumption (Toll et al., 2012). This frequent pattern of co-use of alcohol and nicotine results in multiplicative health consequences for oral cancer (Blot et al., 1988; Talamini et al., 2002) and individuals who co-use are more likely face mortality from tobacco-related diseases than alcohol-related diseases (Hurt et al., 1996). Previous reports have found smokers with an alcohol diagnosis are more likely to have more severe nicotine dependence (Marks, Hill, Pomerleau, Mudd, & Blow, 1997). This can also be seen across the smoking trajectory, as smokers with past or current alcohol related problems are less likely to quit smoking across their lifetime (Hughes & Kalman, 2006).

These high rates of use, coupled with the multiplicative adverse health consequences, suggest the presence of a bidirectional relationship between cigarettes and alcohol. Due to this robust bidirectional relationship, efforts have been made to understand the underlying neurobiological mechanisms perpetuating co-use between these substances. Prior studies have established this mesolimbic dopamine pathway as a pathway that plays a key role in mediating the subjective experience of reward, as well as reward seeking, for natural rewards and substances of abuse (Di Chiara, 1997; Holden, 2001; Weiss, Lorang, Bloom, & Koob, 1993). This mesolimbic dopamine pathway originates with a cluster of neurons in midbrain region known as the ventral tegmental area (VTA) that project dopaminergic neurons into an area of the forebrain known as the nucleus accumbens (NAcc) (Funk, Marinelli, & Lê, 2006). Dopamine is released in the NAcc when stimulated by natural or artificial (i.e., substances of abuse) rewards

(Di Chiara, Diana, & Spano, 2014). The mesolimbic dopamine pathway serves a central role in the rewarding effects of substances of abuse.

Multiple mechanisms have been proposed to explain the co-use of nicotine and alcohol. The two most prominent models to explain the co-use of nicotine and alcohol are: cross-reinforcement through the mesolimbic dopamine pathway and cross-tolerance through shared genetic and nicotinic acetylcholine receptor (nAChR) interactions (Adams, 2017). The first mechanism of comorbidity is cross-reinforcement which is defined as the ability of nicotine to increase the motivation to consume alcohol and vice versa due to a shared neurobiological mechanism (mesolimbic dopamine pathway) (Adams, 2017). Both nicotine and alcohol have been shown to activate the mesolimbic pathway. For nicotine, previous studies have shown nicotine self-administration to occur to activate the mesolimbic dopamine pathway through the VTA (Corrigall, Coen, & Adamson, 1994) and the activation of nAChRs may stimulate the VTA neurons to release dopamine in the NAcc (Exley et al., 2011; Gotti et al., 2010; Maskos et al., 2005). Alcohol has also been shown to affect the mesolimbic pathway through interacting with nAChRs that have been shown to increase the rewarding properties of alcohol (Blomqvist, Engel, Nissbrandt, & Soderpalm, 1993; Blomqvist, Ericson, Johnson, Engel, & Soderpalm, 1996), and alcohol self-administration has been linked with dopamine release in the NAcc (Doyon et al., 2003; Imperato & Di Chiara, 1986; Weiss et al., 1993). The second mechanism perpetuating co-use is cross-tolerance. Tolerance is defined as continued use of a fixed amount of a substance resulting in a suppression of the effect, thus a greater amount of the substance is needed to produce the same effect. Both alcohol and nicotine have been shown to lead to tolerance (Perkins, 2002; Suwaki et al., 2001). One hypothesized contributing factor to the build-up of cross-tolerance is the role of genetics. In the alcohol literature, individuals with a family

history of alcohol dependence may experience a blunted sensitivity to the effects of alcohol (Schuckit & Smith, 2001), thus leading to potentially greater alcohol consumption. Of note, current smokers have been shown to have a diminished intoxicating effect of alcohol in comparison to non-smokers or former smokers (Madden, Heath, Starmer, Whitfield, & Martin, 1995). A second hypothesis contributing to cross-tolerance is the role of nicotinic receptors, as alcohol has been shown to alter the function of several nAChR subtypes, and subsequently alter neurotransmitter transmission at these receptors (Cardoso et al., 1999; Narahashi, Aistrup, Marszalec, & Nagata, 1999; Narahashi et al., 2001). A previous study found that alcohol-induced impairments in coordination were reduced by nicotine via nAChR subtype function, specifically alpha-7 subtypes further suggesting the role of these receptors in cross-tolerance of nicotine and alcohol (Taslim & Saeed Dar, 2011). Taken together, these are two possible mechanisms of action whereby nicotine and alcohol continue to potentiate the rewarding effects of the opposing substance, while increasing use through cross-tolerance, resulting in the observed high rates of co-use.

Human laboratory studies serve as one methodological avenue by which some of these mechanisms of action have been examined in humans. Alcohol may increase the rewarding aspects of cigarette smoking as it has been associated with greater satisfaction of the cigarette (Glautier, Clements, White, Taylor, & Stolerman, 1996) and relief of craving a cigarette (Rose et al., 2004). Administering alcohol to those who co-use is associated with dose-dependent increases craving for cigarettes (Epstein, Sher, Young, & King, 2007; King & Epstein, 2005), and this effect may be mediated by the stimulating effects of alcohol (Epstein et al., 2007). Conversely, nicotine administration has been shown to increase alcohol consumption in both animal studies (Olausson, Ericson, Löf, Engel, & Söderpalm, 2001) and human studies (Barrett,

Tichauer, Leyton, & Pihl, 2006). Nicotine has also been shown to increase the sedative effects of alcohol (Acheson, Mahler, Chi, & de Wit, 2006). Notably, a majority of studies have focused on the effect of alcohol on nicotine use and less research thus far has examined the effect of nicotine on alcohol. Interestingly, there has been some evidence to suggest that the effects of nicotine on alcohol may differ by gender. Acheson and colleagues (2006) found an increase in alcohol consumption among men but not women. An ecological momentary assessment (EMA) study demonstrated that when both substances were administered simultaneously, there was a joint increase in craving for both cigarettes and alcohol (Piasecki et al., 2011). Taken together, these studies highlight how individuals who co-use do qualify as a unique subgroup of heavy drinking smokers with a distinctive clinical profile and treatment needs (Dani & Harris, 2005; Littleton, Barron, Prendergast, & Nixon, 2007; Roche, Ray, Yardley, & King, 2016)

In sum, there is ample evidence highlighting the strong bidirectionality of these two substances and their associated long-term health consequences. Emerging evidence continues to support the two mechanisms of cross-reinforcement and cross-tolerance; however translational research is needed to bridge the gap between earlier pre-clinical studies and examining these mechanisms of action in human studies. As mentioned above, more research to date has examined the impact of alcohol use on cigarette smoking. While this bidirectional relationship exists, there is evidence to suggest that alcohol may more strongly influence cigarette smoking than vice versa. This may in part be due to the lack of research examining the impact of nicotine on alcohol and may highlight the robust role of alcohol increasing the complexity of treatment for smoking cessation.

Treatment Options for Heavy Drinking Smokers

One of the major difficulties in treating heavy drinking smokers is the increased likelihood they have of experiencing a smoking lapse while drinking (Kahler et al., 2008; Kahler, Spillane, & Metrik, 2010) particularly in the early stages of their smoking cessation attempt where time between initial smoking lapse and return to daily smoking has been associated with pre-treatment confidence (Brandon, Tiffany, Obremski, & Baker, 1990). Estimates suggest that up to 95% of smokers who experience a smoking lapse will progress to relapse (Garvey, Bliss, Hitchcock, Heinold, & Rosner, 1992; Kenford et al., 1994). Previous studies have shown that smokers who smoke more during their first lapse, and experience greater hedonic ratings, have a greater risk of progressing to relapse (Shiffman, Ferguson, & Gwaltney, 2006). This first lapse has been hypothesized to represent the transition from abstinence to relapse with regular smoking has (Shiffman et al., 2006; Shiffman et al., 1996). Earlier smoking cessation trials often excluded smokers with current or past AUD, resulting in underrepresentation of smokers with alcohol problems in pharmacotherapy smoking cessation trials (Leeman, Huffman, & O'Malley, 2007). Given the impact of alcohol on smoking quit attempts and the overlapping neurobiological mechanisms that maintain co-use, it is imperative to address alcohol use in smoking cessation treatment for heavy drinking smokers.

Few studies to date have examined behavioral treatments for combined cigarette and alcohol use that did not involve some form of pharmacotherapy. One pilot study examined whether including personalized feedback on alcohol response phenotype would improve brief intervention outcomes among young adult heavy drinking smokers (Fridberg, Cao, & King, 2015). At 6-month follow-up, the group with the personalized feedback reported decreasing their drinking and smoking co-use by 39% which was comparably greater than the reductions made by the group that did not receive personalized alcohol feedback (Fridberg et al., 2015). A

randomized controlled trial examining tobacco quit-lines found the inclusion of a brief alcohol intervention resulted in significantly higher smoking cessation rates for individuals with hazardous drinking (Toll et al., 2015). A recent Cochrane review found that individually delivered smoking cessation counseling was more effective than minimal contact (i.e., brief advice, self-help materials), and evidence to suggest a smaller relative benefit in treatment outcomes when participants also received pharmacotherapy, specifically nicotine replacement therapy (Lancaster & Stead, 2017). The Clinical Practice Guidelines for smoking cessation recommend that pharmacological treatments are used in combination with psychotherapy or behavioral therapy (Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, 2008). Next, we briefly review the evidence base for pharmacological treatment of smoking, drinking, and their co-use.

Varenicline: Efficacy for Reducing Cigarette and Alcohol Use

Varenicline is a high affinity, partial agonist, at the α4β2 nAChR receptor subtype and was FDA approved in 2006 for the treatment of nicotine dependence. The α4β2 nAChR receptor subtype has been strongly implicated in the addictive properties of nicotine (Picciotto et al., 1998; Tapper et al., 2004) and has become a novel molecular target for smoking cessation medications (Tutka, 2008). The rationale behind using a partial agonist is to leverage the benefits of an agonist in reducing withdrawal symptoms and an antagonist in attenuating the rewarding effects of smoking (Cahill, Stevens, Perera, & Lancaster, 2013; Jiménez-Ruiz, Berlin, & Hering, 2009; Rollema et al., 2007). In 2009 the FDA issued a black box warning, the strongest safety warning the FDA can administer due to concerns regarding suicidal thoughts and depression with varenicline. A systematic review and meta-analysis examined the neuropsychiatric adverse events associated with varenicline and found no evidence of an increased risk of suicidal ideation

or suicide (Thomas, Martin, Knipe, Higgins, & Gunnell, 2015). The authors suggested the initial black box warning was likely due to early studies consisting of observation cohorts that are more likely to be confounded by indication (Walker, 1996) and possible bias regarding industry sponsored trials reporting favorable outcomes to the study sponsor (Etter, Burri, & Stapleton, 2007). In 2016, the FDA removed the black box warning.

Clinical trials have supported varenicline's safety and efficacy as a smoking cessation aid (Jorenby et al., 2006; Oncken et al., 2006). A review of pharmacotherapies for smoking cessation found varenicline as more effective than singe forms of Nicotine Replacement Therapy (NRT) and bupropion (Cahill et al., 2013). An additional review also demonstrated that in comparison to an unaided quit attempt, varenicline increases the chances of smoking cessation two- to three-fold (Cahill, Lindson-Hawley, Thomas, Fanshawe, & Lancaster, 2016). Varenicline has also been examined for long-term efficacy and was found to be safe to administer for up to 1 year with efficacy greater than placebo in the short-term (i.e. 12 weeks) and long-term (i.e. 52 weeks) (Jorenby et al., 2006; Williams, Reeves, Billing, Pennington, & Gong, 2007). Despite these results, success rates for varenicline remain low, which may suggest that there are unexplored individual difference factors that may be influencing varenicline's efficacy.

Varenicline has also been examined as a possible treatment for reducing alcohol consumption, as the nAChR receptors in the ventral tegmental area of the brain have been proposed to mediate the reinforcing effects of alcohol (Söderpalm, Ericson, Olausson, Blomqvist, & Engel, 2000). Human laboratory studies have found varenicline to reduce craving, self-administration, and alcohol consumption in comparison to placebo (Fucito et al., 2011; McKee et al., 2009; Mitchell, Teague, Kayser, Bartlett, & Fields, 2012). The first multisite clinical trial examining varenicline for AUD in a sample of smokers and non-smokers found

varenicline to reduce percent heavy drinking days, drinks per day, drinks per drinking day, and craving for alcohol in comparison to placebo (Litten et al., 2013). There was a similar average treatment effect across smokers and non-smokers (Litten et al., 2013). These results support the potential for using varenicline in a sample of smokers to both reduce cigarette and alcohol consumption.

Naltrexone: Efficacy for Reducing Alcohol and Cigarette Use

Alcohol triggers several neurotransmitter systems and the endogenous opioids plays a key role in mediating the rewarding effects of alcohol (Herz, 1997). Evidence suggests that alcohol increases the rewarding effects through release of endogenous opioids and interactions with the dopaminergic system (Ray, Chin, & Miotto, 2010; Volpicelli, 2001). Previous studies have found that both consumption of alcohol and exposure to alcohol cues prior to drinking may increase dopamine activity in the NAcc highlighting the role of learning and reinforcement on activation of the mesolimbic dopamine pathway (Boileau et al., 2003; Kareken et al., 2004; Weiss et al., 1993). Naltrexone is an FDA approved pharmacotherapy treatment for alcohol use disorder. Naltrexone is a relatively selective opioid antagonist, with the highest affinity for the mu-opioid receptor (Littleton & Zieglgänsberger, 2003). Numerous clinical trials supported naltrexone as a safe, tolerable, and effective pharmacotherapy option for reducing drinking days, drinks per drinking day, and relapse rates (Latt, Jurd, Houseman, & Wutzke, 2002; Morris, Hopwood, Whelan, Gardiner, & Drummond, 2001; O'Malley et al., 1992; Volpicelli, Alterman, Hayashida, & O'Brien, 1992). A recent meta-analysis of the effect of naltrexone in the human laboratory setting found naltrexone to reduce craving and alcohol self-administration in comparison to placebo (Hendershot, Wardell, Samokhvalov, & Rehm, 2017). Four biobehavioral mechanisms of action have been suggested to explain the positive effects of naltrexone for

alcohol use: reduction of craving for alcohol, blunting the stimulating effects of alcohol, potentiation of sedative and unpleasant effects of alcohol, and increasing cognitive control (Ray et al., 2010).

Emerging evidence suggests that naltrexone may also be an effective pharmacotherapy option for reducing tobacco use among heavy drinking smokers. The opioidergic system has also been implicated in modulating the pharmacological effects of nicotine (Drews & Zimmer, 2010). Naltrexone has been shown to improve smoking cessation rates (Covey, Glassman, & Stetner, 1999; Fridberg, Cao, Grant, & King, 2014; A. C. King et al., 2012), while also reducing the frequency of heavy drinking days (A. King, Cao, Vanier, & Wilcox, 2009). Interestingly, one study examining data gathered as part of the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) found that smokers who received naltrexone experienced better drinking outcomes than smokers who received placebo (Fucito et al., 2012). Additionally, naltrexone has been associated with gender differences in response to naltrexone. King and colleagues (2012) found women to have greater reductions in weight gain while men had greater reductions in smoking. Previous studies have also examined naltrexone in combination with traditional pharmacotherapies of smoking cessation. Naltrexone in combination with nicotine replacement therapy has been shown to have beneficial outcomes in improving smoking cessation outcomes (Krishnan-Sarin, Meandzija, & O'Malley, 2003; O'Malley et al., 2006). Taken together, these results suggest that naltrexone may improve both alcohol and smoking outcomes for this sub-group of heavy drinking smokers.

Combination Pharmacotherapies May Improve Smoking Cessation Outcomes

Evidence for pharmacological treatments for this treatment-resistant subgroup of smokers has been limited and thus warrants further investigation. Currently, there are no pharmacological

treatments or guidelines specific to heavy drinking smokers. It has been suggested that medications aiming to block the addictive rewarding effects, increase the aversive effects, and/or reduce drug-conditioned reactivity to cues may serve as effective treatment options for heavy drinking smokers (Roche et al., 2016). As varenicline and naltrexone have both exerted effects on smoking outcomes as detailed above, these two medications in combination may serve as a promising treatment combination. Previous work from our laboratory has shown initial promising evidence for the combination of these two medications for smoking cessation outcomes (Ray et al., 2014). Ray and colleagues (2014) randomized 130 heavy drinking smokers to varenicline (VAR: 1mg twice per day), low dose naltrexone (L-NTX: 25mg once daily), varenicline plus low dose naltrexone (VAR + L-NTX), and placebo (PLAC) to examine differences in these medications on subjective response to alcohol and cigarettes craving in the human laboratory. Following nine days on study medication, participants received a priming dose of alcohol to raise their breath alcohol concentration (BrAC) to 0.06g/dl then smoked their first cigarette of the day in laboratory (Ray et al., 2014). Results revealed that post-alcohol administration, the VAR + L-NTX group had significantly reduced craving for cigarettes over and above all other medication groups (see **Figure 1a**). The VAR + L-NTX group also demonstrated reduced alcohol "high" compared to placebo or monotherapy medication groups (see Figure 1b). Results post-cigarette administration revealed that the VAR + L-NTX group had reduced cigarette craving in comparison to placebo (see **Figure 2a**). The VAR + L-NTX group also exhibited lower cigarette "high" feelings than placebo and L-NTX groups (see **Figure 2b**). Examination of self-report alcohol and cigarette use on the 9-day medication titration period revealed that the VAR + L-NTX group and L-NTX group were associated with fewer drinks per drinking day than placebo alone (see **Figure 3a**). For cigarette use, participants in the VAR + L-

NTX group had significantly fewer cigarettes per smoking day than L-NTX and placebo groups (see **Figure 3b**).

Figure 1

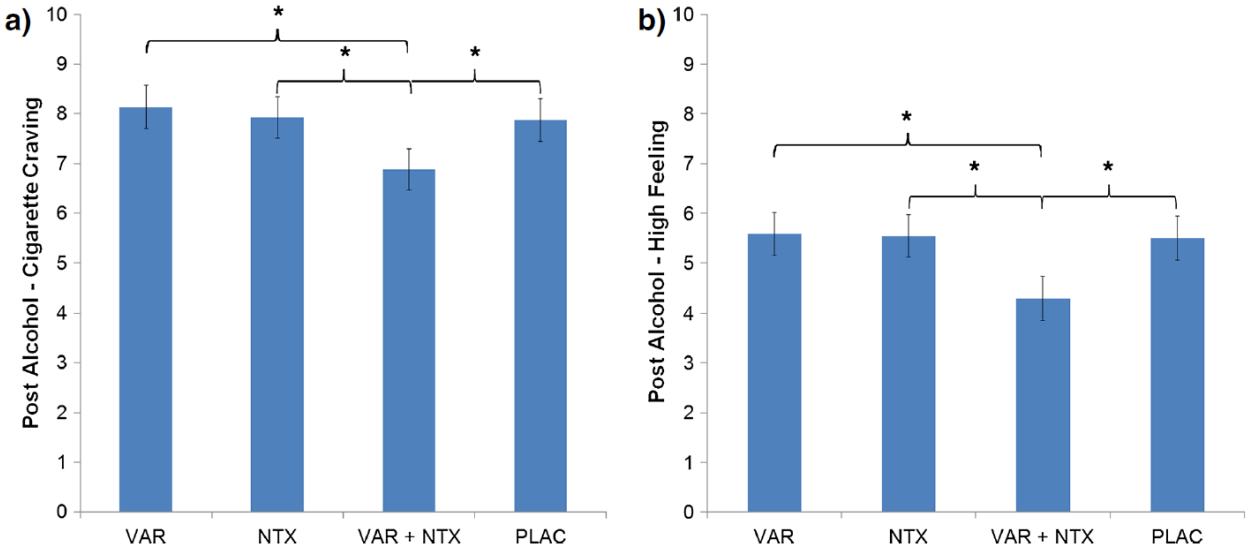

Figure 1a, 1b

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 asterisks* for $p < 0.01$.

Figure 2

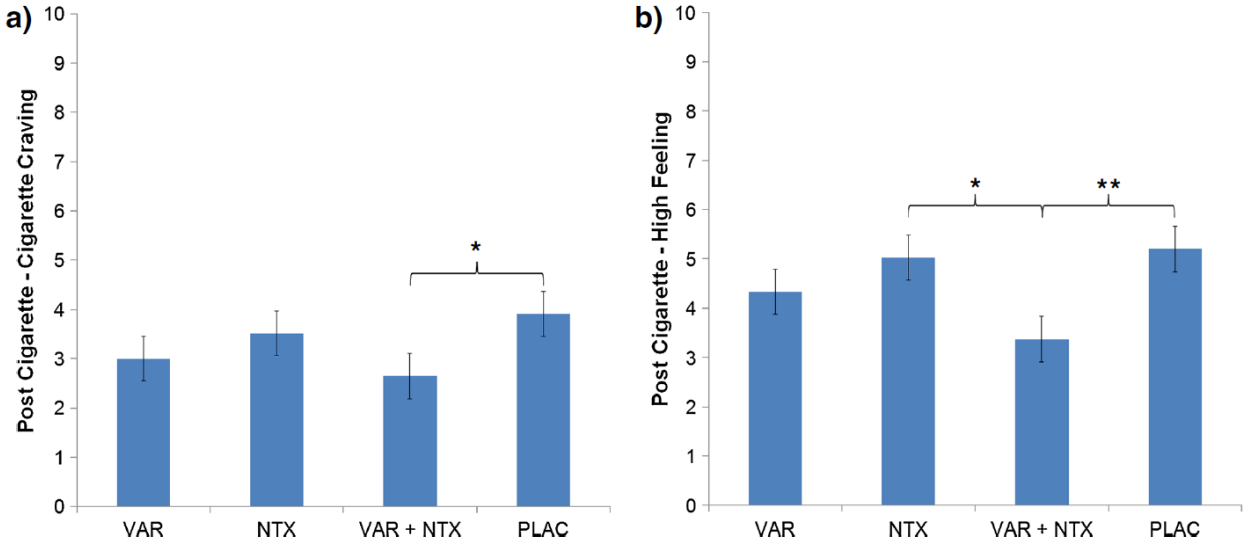

Figure 2a, 2b

Adjusted means and standard error of the mean for ratings 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 asterisks* for $p < 0.01$.

Figure 3

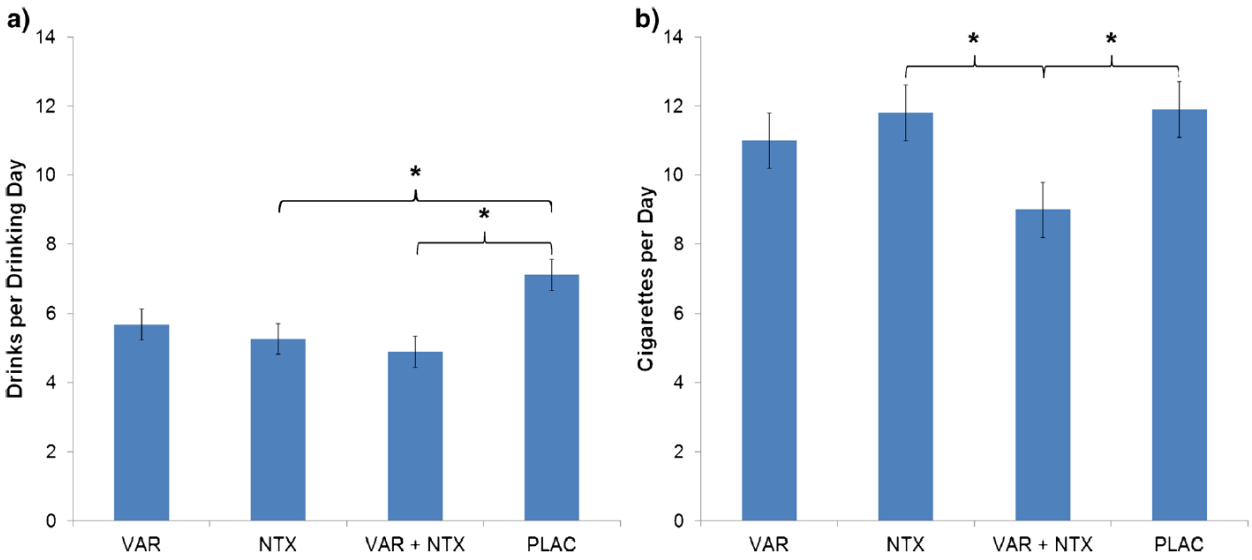

Figure 3a, 3b

Adjusted means and standard error of the mean 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 asterisks* for $p < 0.01$.

Furthermore, a subset of participants completed a neuroimaging session to examine brain responses to visual smoking related versus neutral cues (Ray et al., 2015). Results indicated significant differences in brain activation during cigarette cues for the active medication groups compared to placebo. In comparison to placebo and L-NTX groups, the VAR+NTX group displayed reduce activation of the bilateral anterior cingulate cortex (Ray et al., 2015). Interestingly, all medications reduced left NAcc activity compared to placebo suggesting that medications alone or in combination exert reductions neural signals that are associated with appetitive behavior (Ray et al., 2015). Lastly, in this study, participants smoked the cigarette following alcohol consumption with the use of a smoking topography device, allowing for examination of the nuanced manner in which individuals smoke a cigarette (Roche, Bujarski, Hartwell, Green, & Ray, 2015). Results revealed that the VAR + L-NTX group altered smoking topography resulting in a pattern of less intense puffing behavior. Specifically, active medication

groups had suppressed puff duration (length of each puff) and velocity (mean flow rate of each puff) slopes over the course of the single cigarette in comparison to placebo. The VAR + L-NTX group also had lower average inter-puff interval (time between each puff) than L-NTX and NTX groups, as well as lower average puff volume (capacity of each puff) compared to all other groups (Roche et al., 2015). Collectively, these results provide initial evidence for the potential of the combination of varenicline and naltrexone to serve a possible efficacious pharmacotherapy option for heavy drinking smokers.

The Randomized Clinical Trial (RCT)

The aforementioned findings from human laboratory studies set the stage for a randomized clinical trial conducted by the Ray Lab between 2015-2019. This randomized clinical trial was funded by the National Institute on Drug Abuse (NIDA) R01 (DA041226) (ClinicalTrials.gov identifier: NCT02698215). To date, this RCT was the first clinical trial to date to examine the combination of VAR and NTX in heavy drinking smokers for smoking cessation. This study was a double-blind, randomized clinical trial comparing varenicline alone (1 mg twice daily) plus placebo (VAR + PLAC) versus the combination of varenicline (1 mg twice daily) plus naltrexone (50 mg once daily) (VAR + NTX) for smoking cessation in a sample of heavy-drinking daily smokers who want to quit smoking. Data from this study was used for Chapter 2 and Chapter 3 of the dissertation.

Participant Recruitment and Selection: Participants were recruited from the Los Angeles community through a variety of print and online advertisements (e.g., LA Weekly, Craigslist, Facebook, Bus Advertisements). Men and women of all ethnic backgrounds were recruited into the study. Advertisements were targeted to heavy drinking smokers interested in quitting smoking and reducing their drinking. During the screening session, interested individuals called

the lab and were provided information about the study, and completed an initial telephone screen for inclusion and exclusion criteria following verbal consent. Those who met the study criteria as ascertained during the phone interview were asked to come to the laboratory to provide informed consent. After consenting, subjects were asked to provide a urine sample for cotinine verification of smoking status and complete a series of smoking and individual differences measures (described in detail below). Eligible participants then completed the screening physical exam. Those who passed the physical exam were urn randomized to one of the two medication conditions. Urn randomization was also used to balance the medication groups by gender, number of cigarettes per day, and drinks per drinking day.

Inclusion / Exclusion Criteria: For the RCT study, the inclusion criteria were: (1) Treatment-seeking for smoking cessation; (2) Between the ages of 21 and 65 and provide informed consent; (3) Smoke 5 or more cigarettes per day; (4) Currently drink heavily according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines: 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 over the past 12 months. The exclusion criteria was as follows: (1) Clinically significant alcohol withdrawal, indicated by a score ≥ 10 on the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989); (2) Lifetime history of psychotic disorders, bipolar disorders, or major depression with suicidal ideation; (3) No serious medical illness within past 6 months (significant cardiovascular disease; uncontrolled hypertension; hepatic or renal disease) that would contraindicate participation as determined by study physician; (4) Women must not be pregnant, nursing, or planning to become pregnant

while taking part in the study and must agree to a reliable method of birth control; (5) Pass the physical exam.

Study Design: Medication was titrated over a 14-day period. Participants were titrated on varenicline as follows: days 1-3, .5 mg per day; days 4-7, .5 mg twice per day, and after day 7, 1 mg twice per day for the remainder of the 12-weeks. Naltrexone was administered at 25 mg/day for days 1-5 then reached target dose (50 mg/ once daily) for the remainder of the active medication phase. Pill count was conducted at each study visit to assess for study compliance. Participants were instructed to take both study medications at the same time and were put in contact with the study physician if they reported any significant side effects. Side effects were collected in an open-ended way and then counted in categories. At each study visit, blood pressure and heart rate were assessed. Participants receive individual counseling on days 11-13 and the quit date was set for day 14 of the medication regimen. All participants were instructed to continue the study medications for 12 weeks and return to the laboratory for follow-ups 4, 8, 12, 16, and 26 weeks post quit date. Participants were compensated $350 for completion of all study visits.

Primary Results of the RCT: For the primary smoking outcome of smoking cessation, a CO level of less than or equal to 5 ppm was used to generate an estimate of 7-day point prevalence abstinence rates at 4, 8, 12, 16 weeks, and 26-weeks post treatment. For the primary drinking outcome of drinks per drinking day, the Time Line Follow Back (TLFB) was administered for both alcohol use and cigarette smoking at 4, 8, 12, 16 weeks, and 26-weeks post treatment. The primary findings from this study were that participants randomized to the VAR + PLAC condition had significantly greater smoking abstinence at week 26 than participants in the VAR + NTX condition (Ray et al., 2021). For the drinking outcome of drinks per drinking day,

there was a trend level effect for a benefit in the VAR + NTX condition during the active medication phase (Ray et al., 2021). Collectively, the primary outcomes of this trial imply that for heavy drinking smokers, varenicline alone may be sufficient to address smoking cessation and there is the potential for an added benefit of naltrexone for drinking reduction.

Chapter 1 (Etiology) – Behavioral Economics

Rationale for the Use of Behavioral Economics

One alternative approach to understanding co-use is through behavioral economics. Behavioral economics is a reinforcement based model of addiction that can be used to quantify how much money an individual is willing to spend on a valued commodity, thus measuring the relative reinforcing efficacy of the commodity (Bickel, DeGrandpre, & Higgins, 1995; Johnson & Bickel, 2006). Behavioral economics has been used across a variety of substances including alcohol (Murphy & MacKillop, 2006), cigarettes (MacKillop et al., 2008), and cannabis (Aston, Metrik, Amlung, Kahler, & MacKillop, 2016).

Chapter 1 of the dissertation examined demand for cigarettes and alcohol in a sample of heavy drinking smokers. This chapter is currently published in *Nicotine and Tobacco Research*.

Behavioral Economic Demand for Alcohol and Cigarettes in Heavy Drinking Smokers:

Evidence of Asymmetric Cross-commodity Reinforcing Value

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ABSTRACT

Introduction: Previous studies have highlighted a strong bi-directional relationship between cigarette and alcohol consumption. To advance our understanding of this relationship the present study uses a behavioral economic approach in a community sample (N=383) of non-treatment seeking heavy drinking smokers. The aims were to examine same-substance and cross-substance relationships between alcohol and cigarette use, and latent factors of demand.

Methods: A community sample of non-treatment seeking heavy drinking smokers completed an in-person assessment battery including measures of alcohol and tobacco use as well as the cigarette purchase task and the alcohol purchase task. Latent factors of demand were derived from these hypothetical purchase tasks.

Results: Results revealed a positive correlation between paired alcohol and cigarette demand indices (e.g. correlation between alcohol intensity and cigarette intensity) (*r's* =0.18 – 0.46, $p <= .003$). Over and above alcohol factors, cigarette use variables (ex. FTND and cigarettes per smoking day) significantly predicted an additional 4.5% ($p <.01$) of the variance in Persistence values but not Amplitude values for alcohol. Over and above cigarette factors, alcohol use variables predicted cigarette Persistence values ($\Delta R^2 = .013$, $p = .05$), however, did not predict Amplitude values.

Conclusions: These results advance our understanding of the overlap between cigarette and alcohol by demonstrating that involvement with one substance was associated with demand for the other substance. This asymmetric profile - from smoking to alcohol demand, but not vice versa - suggests that it is not simply tapping into a generally higher reward sensitivity and warrants further investigation.

Keywords: behavioral economics, demand, alcohol, tobacco, heavy drinking smokers

Implications: To our knowledge, no study to date has examined alcohol and cigarette demand, via hypothetical purchase tasks, in a clinical sample of heavy drinking smokers. This study demonstrates that behavioral economic indices may be sensitive to cross-substance relationships and specifically that such relationships are asymmetrically stronger for smoking variables affecting alcohol demand, not the other way around.

INTRODUCTION

Despite declining rates of cigarette use (Dwyer-Lindgren et al., 2014; Jamal et al., 2016; Ng et al., 2014), co-use between alcohol and cigarettes remains high. Recent estimates from the National Epidemiological Survey on Alcohol and Related Conditions (NESARC-III) revealed the odds of having a past 12-months Diagnostic and Statistical Manual-5 (DSM-5) nicotine use disorder (NUD) is 3.2 times higher in the presence of an alcohol use disorder (AUD), regardless of AUD severity (AOR = 3.2, 95% CI 2.93-3.49) (Chou et al., 2016). Co-use between alcohol and cigarettes has been associated with an increased risk of head and neck cancers, (Blot et al., 1988; Dal Maso et al., 2016), as well as mood disorders (Le Strat, Ramoz, & Gorwood, 2010). The negative impact of this co-use pattern extends to cessation attempts, such that daily smokers with a current or past AUD are less likely to quit smoking (Weinberger, Pilver, Hoff, Mazure, & McKee, 2013) and cigarette smoking has been linked with an increased risk of relapse to AUDs (Weinberger, Platt, Jiang, & Goodwin, 2015). Multiple underlying mechanisms of action have been proposed to explain this robust bi-directional relationship. Genetic studies have highlighted the role of the human gene cluster CHRNA5/A3/B4 in both alcohol and nicotine use (Li et al., 2010; Wang et al., 2009). Pre-clinical and behavioral pharmacology studies have also highlighted varenicline (nAChR partial agonist) reducing alcohol consumption and in improving smoking cessation outcomes (Hendrickson, Zhao-Shea, Pang, Gardner, & Tapper, 2010; Rollema & Hurst, 2018). Taken together, the epidemiological rates of co-use, its impact on treatment outcomes, and mechanisms underlying this co-use suggests that heavy drinking smokers constitute a unique subpopulation of substance users.

Towards elucidating mechanisms of co-use, heavy drinking smokers can be examined through the application of behavioral economics, which combines principles of economics and

psychology to further our understanding choice behavior (Bickel, Johnson, Koffarnus, MacKillop, & Murphy, 2014; MacKillop, 2016). The contemporary application of behavioral economics to addictive behavior is referred to as the reinforcer pathology approach, which emphasizes persistently high reinforcing value of a drug, disproportionate immediate preference for that reward despite long-term consequences, and a paucity of alternative reinforcers (Bickel et al., 2014; MacKillop, 2016). Demand curve analyses can be used to operationalize the relative reinforcing efficacy (i.e. behavior-strengthening property of a reinforcer compared to a non-reinforcer) of a substance by examining relationship between consumption of a substance and price (Bickel et al., 2014; Johnson & Bickel, 2006). Hypothetical purchase tasks, in which individuals report how much of a specific substance they would consume at increasing prices, can be used to generate a demand curve. Various indices from the demand curve reflect relative reinforcing efficacy, which has been proposed to be a heterogeneous phenomenon (Bickel, Marsch, & Carroll, 2000), can be analyzed including intensity (consumption when free), O_{max} (maximum expenditure), P_{max} (price corresponding to maximum expenditure, i.e. maximum inelastic price), Breakpoint (first price point at which consumption drops to zero), and Elasticity (overall slope of the demand curve, i.e. rate at which consumption decreases as price increases).

Various indices of demand assessed via hypothetical purchase task have been associated with real-world alcohol use. In a college sample, all five indices of demand have demonstrated significant correlations with self-report drinks per week and heavy drinking episodes per week (Murphy & MacKillop, 2006), Intensity of demand, as well as craving for alcohol, have been associated with a greater number of AUD symptoms (MacKillop et al., 2010). Indices of demand have also been examined as predictors for treatment outcomes. Following a brief alcohol intervention, greater maximum expenditure for alcohol (O_{max}) and first price suppressing

consumption to zero (Breakpoint) have been demonstrated to predict greater drinking at 6-month post-intervention follow up (MacKillop & Murphy, 2007). In the realm of tobacco use, a recent meta-analysis found all five behavioral economic indices to be strongly associated with cigarette consumption and tobacco dependence, with intensity, O_{max}, and elasticity displaying the most robust associations highlighting the robust associations between cigarette demand and cigarette use (Gonzalez-Roz, Jackson, Murphy, Rohsenow, & MacKillop, 2019). Even among cannabis use, demand for cannabis has been shown to predict cannabis use frequency and quantity (Strickland, Lile, & Stoops, 2017). Collectively, these results demonstrate how behavioral economic indices are implicated in both alcohol and tobacco dependence.

However, when taking these findings together, few studies to date have examined behavioral economic indices of alcohol in a sample of heavy drinking smokers. One previous study has found that heavy drinking smokers, relative to heavy drinking nonsmokers, report greater alcohol O_{max} and breakpoint (Amlung, MacKillop, Monti, & Miranda, 2017). An additional study with college students who reported at least one heavy drinking episode in the past month found that the same pattern of higher alcohol O_{max} and Breakpoint with those who also reported smoking at least one cigarette in the past month in comparison to non-smokers, as well as greater P_{max} (Yurasek, Murphy, Clawson, Dennhardt, & MacKillop, 2013). Amlung and colleagues (2017) proposed that it is not entirely clear whether heavy drinking smokers are more sensitive to alcohol reward specifically, or if they demonstrate a generalized hypersensitivity to reward and/or multiple drugs. Thus, further research is needed to elucidate how demand for cigarettes and alcohol may be altered and influence each other in a sample that uses both substances.

Previously, the latent structure of demand curve indices has been found to have two components, Amplitude and Persistence, with O_{max} loading on both, Intensity loading on the former and P_{max}, Elasticity, and Breakpoint loading on the latter (Aston, Farris, MacKillop, & Metrik, 2017; Bidwell, MacKillop, Murphy, Tidey, & Colby, 2012; Epstein, Stein, Paluch, MacKillop, & Bickel, 2018; Mackillop et al., 2009). Persistence reflects measures of sensitivity to increase price whereas Amplitude reflects the amount consumed and spent. In examining these two factors in relation to self-reported alcohol use and alcohol problems, Persistence has been suggested to reflect a more compulsive dimension of alcohol-seeking thus being more relevant to alcohol-dependent individuals (Mackillop et al., 2009). Amplitude has been suggested to be more salient among heavy drinkers as it is closely related to current alcohol use measures. These two-factors extend the initial five facets of demand to represent the underlying relationship among these demand indices. Using these two factors as opposed to the five demand indices may aid in reducing Type I error inflation (Aston et al., 2017).

To our knowledge, no study to date has examined alcohol and cigarette demand, via hypothetical purchase tasks, in a clinical sample of heavy drinking smokers. The aims of the present study are: 1) examine the association between latent factors of demand and demand indices for nicotine and alcohol in a sample of heavy drinking smokers, 2) examine the association between nicotine and alcohol use severity and latent factors of demand and demand indices for nicotine and alcohol respectively, and 3) test cross-substance associations between alcohol and cigarette use severity/past 30 day use and latent factors of demand and demand indices. Based on the small existing literature, we hypothesize heavy alcohol use will be associated with increased demand for cigarettes and heavier smoking will predict increased demand for alcohol.

METHODS

Participants and Procedures

Participants consisted of a community sample of non-treatment seeking daily smokers who drank heavily recruited from the greater Los Angeles area. Data for this study were collected at the initial eligibility screening visit and prior to medication assignment as part of a larger study medication study examining varenicline and naltrexone (Ray et al., 2014). The study was approved by the Institutional Review Board of the University of California Los Angeles.

Interested participants completed a phone interview to determine eligibility. Eligible participants were non-treatment seeking daily smokers (≥ 10 cigarettes per day) who were also heavy drinkers, consistent with the National Institute on Alcohol Abuse and Alcoholism guidelines of ≥14 drinks/week for men and ≥7 for women at least monthly over the prior year. If eligible following the telephone interview, participants were invited for an in-person screening visit. Participants were required to have a breath alcohol concentration (BrAC) of 0.000 g/dl and were excluded if they tested positive for any drugs, with the exception marijuana.

Measures

The following individual difference measures were collected during the initial screening visit: (a) demographics questionnaire to gather data on age, sex, race/ethnicity, education, marital status, and income; (b) Time-Line Follow-Back (TLFB; (Sobell, Sobell, Klajner, Pavan, & Basian, 1986)) to assess for frequency and quantity of alcohol and smoking use over the past 30 days; (c) Fagerström Test for Nicotine Dependence (FTND; (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991)) to assess for nicotine dependence severity; and (d) Alcohol Dependence Scale (ADS; (Horn, Skinner, Wanberg, & Foster, 1984)) to assess for alcohol dependence severity.

Behavioral Economic Indices

Behavioral economic indices were assessed with the Alcohol Purchase Task (APT) (Kiselica, Webber, & Bornovalova, 2016) and Cigarette Purchase Task (CPT) (MacKillop et al., 2012; MacKillop et al., 2008). For the APT, participants were provided with the following instructions: "Imagine that you are drinking in a typical situation when you drink. The following questions ask how many drinks you would consume if they cost various amounts of money. The available drinks are standard size domestic beer (12 oz.), wine (5 oz.), shots of hard liquor (1.5 oz.), or mixed drinks containing one shot of liquor. Assume that you did not drink alcohol before you are making these decisions and will not have an opportunity to drink elsewhere after making these stockpile drinks for a later date or bring drinks home with you". The 16 specific prices included for alcohol were: $0.00, $0.01, $0.05, $0.13, $0.25, $0.50, $1.00, $3.00, $6.00, $11.00 $35.00, $70.00, $140.00, $280.00, $560.00, $1,120.00. A similar set of instructions were given for the CPT with reference to cigarettes. The 24 specific prices included for cigarettes were: $0.00, $0.05, $0.10, $0.15, $0.20, $0.25, $0.30, $0.35, $0.40, $0.45, $0.50, $0.60, $0.70, $0.80, $0.90, $1.00, $1.20, $1.40, $1.60, $1.80, $2.00, $4.00, $8.00, $10.00. The outcomes for these purchase tasks were hypothetical, however hypothetical purchase tasks have been shown to be highly correlated with tangible outcomes (Amlung & MacKillop, 2015; Amlung, Acker, Stojek, Murphy, & MacKillop, 2012).

Data Analytic Plan

Prior to the primary analyses for the APT and CPT, invariant responding and excessive preference reversals (i.e. consuming more at higher prices) across the task were identified and removed from the analysis. Participants with missing data for intensity (consumption when free) were excluded from all analyses. A total of 461 participants completed the initial screening. For

the APT, 111 were removed at the initial data processing stage due to missing data (defined as missing all APT values; n=46), missing data for intensity (n=60), and an intensity value close to zero (i.e. .005) implying lack of understanding of the task (n=5). At the effort check stage, 28 were removed due to excessive preference reversals (n=18) and invariant responding (n=10). For the CPT, 101 were removed at the initial data processing stage due to missing data (defined as missing all CPT values; n=42) and intensity values equal to zero implying lack of understanding of the task (n=59). At the effort check stage, 28 were removed due to excessive preference reversals (n=16) and invariant responding (n=9). One additional participant was excluded due to having a majority of outlying values.

Due to purchase task data processing steps the final sample sizes for the alcohol and cigarette purchase task indices differ. Specifically, not all participants who had data present for the alcohol purchase task also had data present for the cigarette purchase task. A total of 383 participants had valid purchase task data, with 322 for the APT and 334 for the CPT. A total of 273 participants had valid data present for both the APT and CPT. Outliers at the price level and at the index level (z-score cut off 3.29) were winsorized to the exact next highest non-outlying value (Amlung et al., 2012). For the APT, the percentage of outlying responses at the item-level ranged from .6% - 1.9%. The percentage of index-level outliers ranged from .3% - 6.8%. For the CPT, the percentage of outlying responses at the item-level ranged from .6% - 3.0%. The percentage of index-level outliers ranged from .9% - 3.0%.

For alcohol demand, all indices were log transformed for normality. For cigarette demand, O_{max}, Breakpoint, and Elasticity were log transformed for normality. Four behavioral economic indices from the hypothetical purchase task (Intensity, O_{max}, P_{max}, and Breakpoint) were generated using an observed values approach.(Murphy & MacKillop, 2006) Elasticity was

derived using the exponentiated version of Hursh and Silberberg's (Hursh & Silberberg, 2008) exponential demand equation for demand curve analysis:

$$Q = Q_0 * 10^{k(e^{-\alpha Q_0 C} - 1)}$$

where Q = consumption at a given price, Q_0 = consumption at zero price, k = constant parameter reflecting the range of consumption values in $\log_{10}$ units and was set at 2 in this sample, α = derived demand parameter reflecting the rate of consumption decline associated with increasing price, and C = the price of the cigarette or alcohol.

Bivariate correlations were used to examine the relationship among behavioral economic indices within each substance (e.g. correlation among alcohol intensity and O_{max}) and between pairing indices (e.g. correlation between alcohol intensity and cigarette intensity). An exploratory factor analysis was conducted using principle component analysis (PCA) estimation method with an oblique (oblimin) rotation to allow for a multifactorial solution with correlated factors. The PCA approach is consistent with previous research examining the latent structure of demand (Aston et al., 2017; Bidwell et al., 2012; Mackillop et al., 2009), with the rationale that characterizing total variance among indices was preferable due to the high levels of variability among associations between demand indices (MacKillop et al., 2008). Factor structure was determined by an Eigenvalue >1 and by further examination of the scree plot. When interpreting the rotated factor pattern, factor loading of 0.40 on the pattern matrix was the criteria used to determine if an item significantly loaded onto a given factor (Stevens, 2012; Tabachnic & Fidell, 2000). The resulting factors were to be used as dependent variables in subsequent analyses.

A series of hierarchical multiple regressions with PROC REG were used to test our second and third aims in relation to same-substance and cross-substance associations between use severity/past 30-day use and latent factors of demand and demand indices. The primary

outcomes were the latent factors of demand derived from the PCA. Due to the lack of existing research on the traditional five behavioral economic indices for alcohol and cigarettes in a sample of heavy drinking smokers, we ran parallel models including the five indices of demand as opposed to the latent factors of demand. These results are presented in the Supplementary Materials. In the lowest block were demographic characteristics (sex, age, education, employment, race, and income). Due to the possible influence of income on choice behavior, income was included in this block of analyses. The second block included same-substance predictors (i.e. ADS and drinks per drinking day for alcohol demand indices), while the third block included cross-substance predictors (i.e. FTND and cigarettes per smoking day for alcohol demand indices). The same pattern of analyses was replicated for cigarette smoking indices, such that the second block included same-substance indicators of cigarette smoking and the third block included cross-substance indicators of alcohol use.

To control alpha inflation an omnibus approach was used in the hierarchical regression, such that if the change in R^2 was not significant, the block of coefficients was not considered further. This approach reduces alpha inflation by reducing the total number of tests. No correction for Type I error was implemented based on the rationale that Type I error needs to be considered at the level of families of hypotheses separately and not for the number of variables in the whole set of analyses reported (Dar, Serlin, & Omer, 1994). In the present analyses, the primary outcomes of the two factors of demand represent two families of hypotheses suggesting correction for Type I error may not be necessary. Results from full models including the three aforementioned blocks and reduced models, excluding non-significant blocks, are reported. Analyses were conducted in SAS University Edition version 9.4 (SAS & Version, 2003).

Power analyses for the final study sample of n=322 for the APT and n=334 for the CPT were conducted in G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009). We conducted a sensitivity analysis to determine the minimum effect size that could be reliably detected in the planned hierarchical multiple regressions with three sets of predictors (demographics, same-substance variables, cross-substance variables) in an F test for a fixed multiple regression with an R^2 increase setting the alpha level at $p<.05$ and power = .80. Across the APT and CPT, the results revealed the sample size afforded an 80% power to detect an effect size of $f^2 = .03$ which is slightly above the small effect cut-off (Cohen, 1988).

RESULTS

Sample Characteristics

Participants were, on average, 35.78 (SD = 10.61) years old and were 29% female. The racial breakdown was such that 37.5% identified as African-American, 30% Caucasian, 3% Asian, 9% Latinx, 2% Native American, and 18% multi-racial. Approximately 68% of the sample reported a pre-tax household income less than $30,000. Participants reported an average of 21.01 (SD = 7.68) drinking days within the last month and an average number of 6.76 (SD = 4.49) drinks per drinking day. For cigarette smoking, participants on average smoked cigarettes 28.91 (SD = 3.55) days in the last month and had a mean of 14.02 (SD = 7.73) cigarettes per smoking day. For alcohol use severity, participants reported an average Alcohol Dependence Scale (ADS) score of 12.93 (SD = 7.38) indicating low alcohol dependence and endorsed low to moderate nicotine dependence with a mean Fagerström Test for Nicotine Dependence (FTND) score of 4.36 (SD = 2.27).

Relationship Between Demand for Alcohol and Cigarettes APT and CPT

Demand curves representing hypothetical consumption across a range of prices are presented in **Figure 1** for alcohol and **Figure 2** for cigarettes. Correlations within demand indices of the same substance and between demand indices of cross-substances (i.e. correlation between alcohol intensity and cigarette intensity) are presented in the Supplementary Materials. For alcohol, there were significant (*p's* < .01) positive correlations between intensity and O_{max} (*r* = 0.15), O_{max} and P_{max} (*r* = 0.89), O_{max} and Breakpoint (*r* = 0.87), and P_{max} and Breakpoint (*r* = 0.91). Significant negative correlations were observed between O_{max} and Elasticity (*r* = -0.84), P_{max} and elasticity (*r* = -0.68), and Breakpoint and elasticity (*r* = -0.73). Results revealed three sets of non-significant (*p's* > .31) correlations between intensity and P_{max}, breakpoint, and elasticity. For cigarette demand indices, there were significant positive correlations within all indices with the exception of Intensity and P_{max} (*r* = -.04, *p* = .44). Correlations between pairing demand indices for alcohol and cigarettes (e.g., elasticity for alcohol and elasticity for cigarettes) revealed significant positive correlations among all pairing indices (*r's* = 0.17 – 0.45, *p* < .003).

Factor Analysis

Results from the PCA analysis and examination of the scree plot suggested two latent factors. For the APT, the two factors accounted for a total of 89.49% of the variance. The first factor representing Persistence accounted for 69.33% of the variance with an Eigenvalue of 3.47. This factor was primarily composed of O_{max}, P_{max}, breakpoint, and elasticity. The second factor representing Amplitude accounted for 20.02% of the variance with an Eigenvalue of 1.01. This factor was primarily composed of Intensity. The two factors exhibited a small correlation (*r* = .06). Remaining factors accounted for a small proportion of the variance with small Eigenvalues (all < .36). For the CPT, the two factors accounted for a total of 82.92% of the variance. The first factor representing Persistence accounted for 61.83% of the variance with an Eigenvalue of 3.09.

This factor was primarily composed of O_{max}, P_{max}, breakpoint, and elasticity. The second factor representing Amplitude accounted for 21.09% of the variance with an Eigenvalue of 1.05. This factor was primarily composed of intensity and P_{max}. The two factors exhibited a small correlation (r = .18). Remaining factors accounted for a small proportion of the variance with small Eigenvalues (all $\leq$ .43). Pattern matrix reflecting the partial correlations between each variable and each rotated factor are presented in the Supplementary Materials. These resulting factors align with previous research (Aston et al., 2017; Bidwell et al., 2012; Mackillop et al., 2009).

Demand for Alcohol Results from the hierarchical regression analyses for alcohol demand are presented in **Table 1**. When examining Persistence, full models revealed the first block of demographics was not significant as it accounted for 4% of the variance (p = .31) and thus was not considered further for Persistence models. Alcohol use variables accounted for 4.0% of the variance (p < .01) such that greater drinks per drinking day (p = .01) predicted greater Persistence values. ADS scores were non-significant (p = .08). Over and above these alcohol factors, the addition of cigarette use variables significantly predicted an additional 4.5% (R^2 of the block = .09). Specifically, FTND scores predicted significantly greater Persistence values (p < .01), however cigarettes per smoking day was not a significant predictor (p = .73). When examining Amplitude, the first block of demographics accounted for 15.2% of the variance (p < .01). The second block adding alcohol use variables accounted for an additional 18.2% of the variance (p < .01) such that greater ADS scores and greater drinks per drinking day predicted greater intensity of demand for alcohol (*p's* < .01). However, the addition of cigarette use variables in the third block did not significantly predict alcohol intensity over and above alcohol use variables (ΔR^2 = .003, p = .55). A summary of the results with the traditional five

indices of demand as opposed to the two factors are presented in Supplementary Materials. The results align directly with the results presented above with the 2-factor solution.

Demand for Cigarettes

Results from the hierarchical regression analyses for cigarette demand are presented in **Table 2**. When examining Persistence, the first block of demographics accounted for 7.3% of the variance ($p = .01$). The second block adding cigarette use variables accounted for an additional 7.0% (R^2 of the block = .14) of the variance ($p < .01$) such that greater FTND scores and greater cigarettes per smoking day predicted greater Persistence values (*p's* < .02). However, the addition of alcohol use variables in the third block did not significantly predict Persistence values over and above cigarette use variables ($\Delta R^2 = .010$, $p = .16$). When examining Amplitude, full models revealed the first block of demographics was not significant as it accounted for 3.9% of the variance ($p = .31$) and thus was not considered further for Amplitude models. Cigarette use variables accounted for 3.24% of the variance ($p < .01$) such that greater FTND scores and greater cigarettes per smoking day predicted greater Persistence values (*p's* < .01). The addition of alcohol use variables in the third block significantly predict Amplitude over and above cigarette use variables ($\Delta R^2 = .01$, $p = .05$), however when examining the coefficients neither ADS scores nor drinks per drinking day were significant (*p's* > .13). A summary of the results with the traditional five indices of demand as opposed to the two factors are presented in Supplementary Materials. The results generally align directly with the results presented above with the 2-factor solution.

DISCUSSION

In a large sample of heavy drinking smokers, this study examined the association between latent factors of demand for nicotine and alcohol, in terms of same-substance associations cross-substance associations between use severity/past 30 day use for each substance in relation to demand for the other substance (i.e. how alcohol dependence and use predicts demand for cigarettes). In examining same-substance relationships reflected in the second block of the hierarchical regression models for alcohol, a relatively consistent pattern emerged such that greater alcohol use severity, as indexed by ADS and past 30-day use, was associated with greater derived Persistence and Amplitude values. For demand for cigarettes, there was a similar pattern of consistency in cigarette use variables, represented by FTND and past 30-day cigarette use, as these variables were associated with both Persistence and Amplitude.

These findings were consistent with the literature and support the notion that use and dependence of a substance is related to demand for a substance that can be captured through hypothetical purchase tasks (Gonzalez-Roz et al., 2019; MacKillop et al., 2010). Results from our final aim of testing cross-substance associations revealed an interesting pattern whereby cigarette dependence and use predicted Persistence values for alcohol, however not Amplitude values for alcohol. For Persistence, these effects were seen in the expected direction whereby greater FTND predicted greater Persistence values. The same pattern was not seen in predicting cigarette demand such that alcohol dependence and use did not significantly predict Persistence values over and above alcohol use factors. However, alcohol use and dependence significantly predicted Amplitude values. Notably, this alcohol variables in the final block reached statistical significance with change in R^2, but when examining the coefficients of this block, neither drinks per drinking day nor ADS scores were significant. Further, the additional amount of variance this

cross-substance use block was able to predict in Amplitude was rather small (1.3%) in comparison to the significant cross-substance use block predicting Persistence values (4.5%).

Results of our principle component analysis aligned with previous literature supporting that Persistence reflects four main dimensions of the demand curve, maximum expenditure (O_{max}), price corresponding to maximum expenditure (P_{max}), first price suppressing consumption to zero (Breakpoint), and the overall slope of the demand curve (elasticity). This factor Persistence represents interrelated measures of sensitivity to escalating price that has been hypothesized to reflect how far, in terms of price, an individual is willing to spend on alcohol (Mackillop et al., 2009). The second factor Amplitude consisted of only one demand indices, Intensity, thus reflecting how much in consumption an individual is willing to consume (Mackillop et al., 2009). These findings suggest that the Persistence factor is operative in these findings for alcohol, suggesting that greater tobacco involvement is associated with insensitivity to the escalating response cost for alcohol. This pattern did not transition to cigarette outcomes, where results indicate the alcohol involvement is associated with greater overall consumption when free as represented by the Amplitude factor.

These results align in part with previous work examining alcohol demand in a sample of heavy drinking smokers. We found greater nicotine dependence to relatively consistently predict greater willingness to spend on alcohol reflected in the Persistence factor which is consistent with Amlung and colleagues (2017) findings of smokers experiencing greater alcohol O_{max} and Breakpoint than non-smokers. Additionally, our results support Yurasek and colleagues (2013) finding that P_{max} for alcohol was also elevated among smokers. When examining additional comorbidities, a recent study found greater alcohol demand among those who co-use alcohol and cannabis (Morris et al., 2018). Furthermore, an early study of commodity specificity revealed

that tobacco demand is fundamentally independent of food demand suggesting that purchase tasks are not simply capturing a generic reward sensitivity (Chase, Mackillop, & Hogarth, 2013). In line with what has previously been suggested (Amlung et al., 2017), there is the possibility of a general hypersensitivity to all rewards that individuals who co-use both alcohol and cigarettes may experience. If there were a generalized hypersensitivity to reward, we would expect to see a consistent pattern across cigarettes and alcohol such that alcohol use would predict cigarette demand and vice versa. In our sample, we found nicotine dependence and use to be relatively consistent in predicting greater insensitivity to the escalating response cost for alcohol via Persistence factor while alcohol dependence and use only predicted Amplitude reflecting intensity of demand for cigarettes.

These results imply from a behavioral economics framework, there may be a stronger effect of nicotine dependence on demand for alcohol than the other way around (i.e., asymmetric cross-commodity reinforcing value). There are various possibilities by which tobacco involvement would predict greater reinforcing value of alcohol. One possibility is a methodological issue such that is plausible that this sample had a more stable smoking pattern (10+ cig/day) with more variability in alcohol use, which in turn may explain these effects. In samples that use cigarettes more sporadically, alcohol may have a stronger effect driving demand for cigarettes. Another possibility is asymmetric pharmacological interactions with alcohol potentiating nicotine's effects but the opposite not being true to the same extent. From a behavioral economics standpoint, this is turn could mean there are asymmetical behavioral interactions, such that smoking is more of a complement than alcohol with smoking making drinking better to a larger extent than drinking makes smoking better. A final possibility is that smoking involvement is a proxy for other items, such as comorbid psychiatric issues (ex.

depression, anxiety) or other risk factors, such as adverse childhood events. From this perspective, alcohol becomes more valuable because smokers tend to be more disadvantaged and otherwise vulnerable.

Results indicated significant correlations within demand indices for cigarettes among all demand indices, with the exception of Intensity and P_{max}. When examining demand for alcohol, nearly all demand indices were highly correlated apart from intensity which did not correlate with P_{max}, Breakpoint, and Elasticity. While each of these demand indices are functionally related all having been derived from the same demand curve, the construct of relative reinforcing efficacy value is proposed to be heterogenous in nature (Bickel et al., 2000). Thus, the consistent patterns of correlations may serve as a reflection of the demand curve, and deviations in correlations within a substance may reflect a unique aspect of our co-use population where by demand indices for one substance, namely cigarettes, are more strongly inter-related than demand indices for alcohol. The higher correlations may also have been a result of the differences in pricing structure.

The present study should be interpreted in light of its strengths including a large sample size and use of all five behavioral economic indices to examine the effects alcohol could have on all aspects of the demand curve for cigarettes and vice versa. Limitations include the use of ADS and FTND as self-report measures of use severity, as opposed to a formal AUD or TUD diagnoses. In addition, the APT used an early price structure that was modelled on a progressive-ratio operant schedule, with a doubling of response requirements that leads to the inclusion of non-market prices. This approach includes large intervals between prices that can inflate variance and may be responsible, for example, in the within-task differences in correlations for the APT and CPT, which used a narrower range of market-compatible prices.

In summary, our results show that latent factors of demand derived from behavioral economic indices may be sensitive to cross-substance relationships and specifically that such relationships are asymmetrically stronger for smoking variables affecting alcohol demand, not the other way around. Whether this is a function of differential pharmacological interactions between alcohol and nicotine or whether it is because smoking severity is a proxy for other factors that lead to higher alcohol reinforcing value cannot be inferred in the current study, but warrants subsequent examination. More broadly, understanding cross-commodity demand relationships has the potential to illuminate both overlapping and non-overlapping aspects of substance misuse.

Table 1. Hierarchical Regression Analysis Predicting Latent Factors of Alcohol Demand

		Persistence			Amplitude	
	□□R^2	*b*	Std. Err.	□□R^2	*b*	Std. Err.
Block 1	---			.152		
Sex		---	---		.325*	.116
Age		---	---		-.032*	.005
Education		---	---		-.023	.016
Employ. = Full-Time		---	---		.140	.155
Employ. = Part-Time		---	---		.027	.152
Race = African Am.		---	---		-.098	.136
Race = Asian		---	---		.151	.368
Race = Latino/a		---	---		.143	.199
Race = Native Am.		---	---		-.195	.486
Race = Multi-Racial		---	---		-.020	.154
Income		---	---		-.020	.033
Block 2	.040			.182		
ADS		.014	.008		.039*	.007
DPDD		.032*	.013		.059*	.011
Block 3	.045			---		
FTND		.099*	.028		---	---
CPSD		-.003	.009		---	---

Abbreviations: Employ. = Employment

Note: R^2 change, unstandardized regression coefficients, and standard errors presented for each block. Reference group for employment status is unemployed, and Caucasian for race. Results presented are from reduced models excluding blocks that were not significant ('--' indicates non-significant block where block coefficients were not considered further). * indicates significance at $p \leq 0.05$.

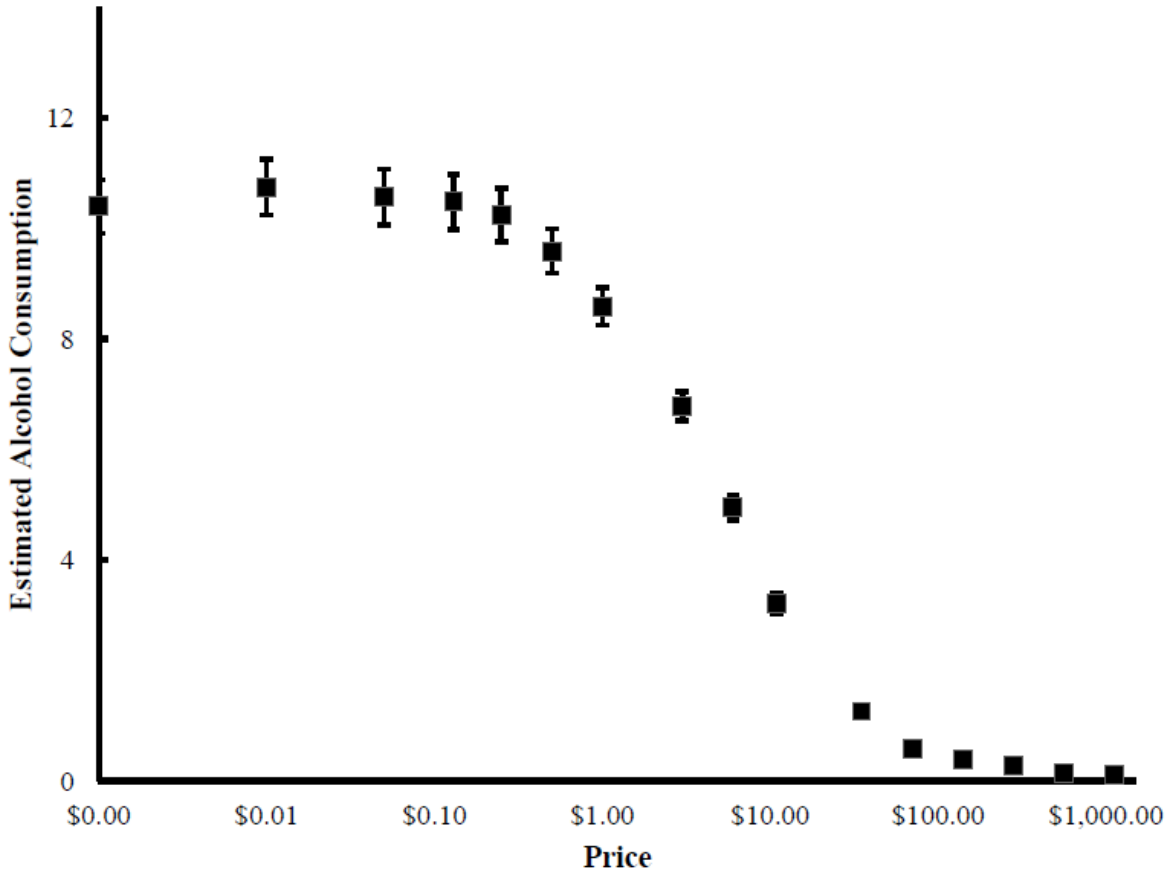
Table 2. Hierarchical Regression Analysis Predicting Latent Factors of Cigarette Demand

		Persistence			Amplitude	
	□□R^2	*b*	Std. Err.	□□R^2	*b*	Std. Err.
Block 1	.073			---		
Sex		.253*	.120		---	---
Age		.005	.006		---	---
Education		-.023	.020		---	---
Employ. = Full-Time		.029	.160		---	---
Employ. = Part-Time		.260	.156		---	---
Race = African Am.		-.344*	.138		---	---
Race = Asian		-.135	.313		---	---
Race = Latino/a		-.440*	.205		---	---
Race = Native Am.		.086	.450		---	---
Race = Multi-Racial		-.095	.160		---	---
Income		.080*	.034		---	---
Block 2	.070			.328		
FTND		.074*	.033		.060*	.024
CPSD		.020*	.008		.065*	.007
Block 3	---	---	---	.013		
ADS		---	---		.010	.006
DPDD		---	---		.017	.011

Abbreviations: Employ. = Employment

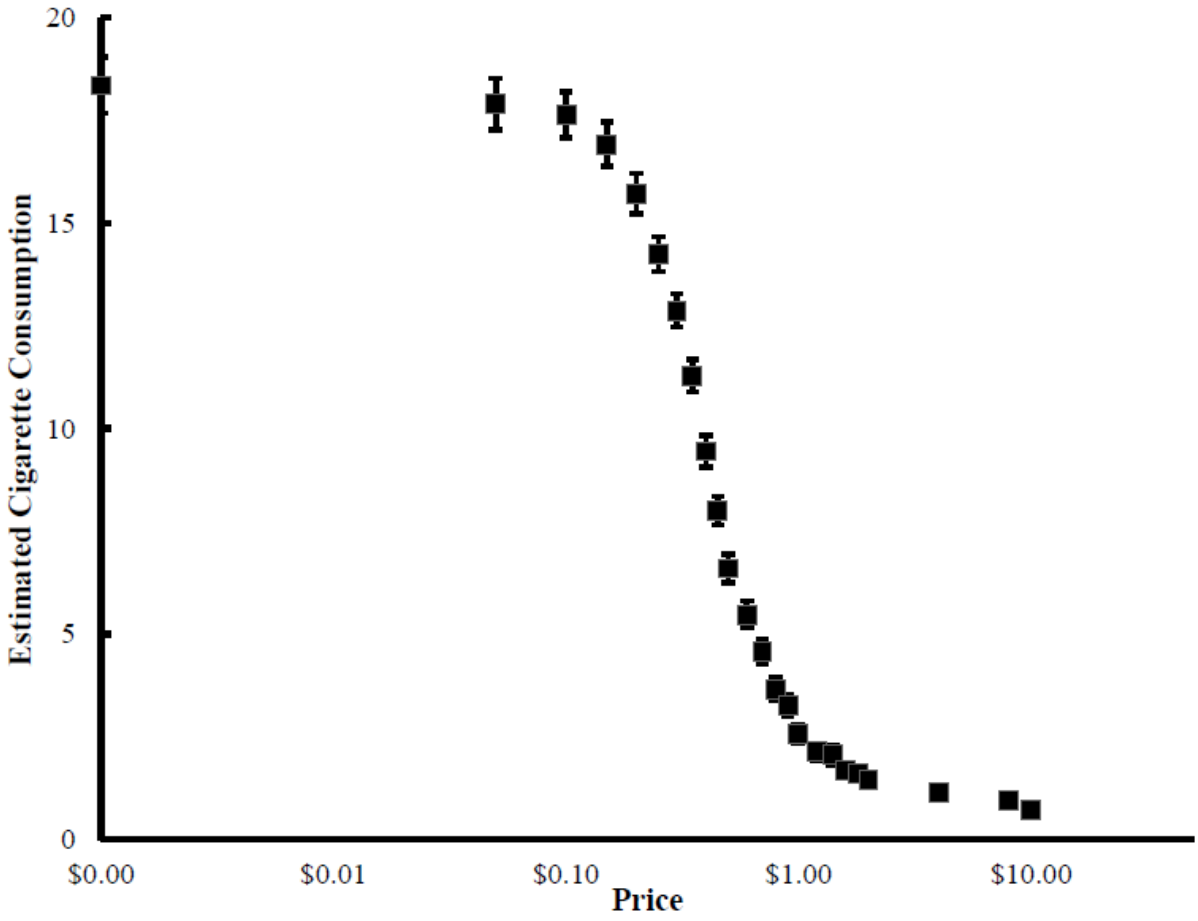
Note: R^2 change, unstandardized regression coefficients, and standard errors presented for each block. Results presented are from reduced models excluding blocks that were not significant ('--' indicates non-significant block where block coefficients were not considered further). * indicates significance at $p \leq 0.05$.

Figure 1. Demand curve for number of drinks purchased on the Alcohol Purchase Task (APT).



Log coordinates for Price on the horizontal axis are used for proportionality. Intensity is depicted as value of .001 instead of zero due to log axis. Only participants with complete and valid data are included.

Figure 2. Demand curve for number of cigarettes purchased on the Cigarette Purchase Task (CPT).



Log coordinates for Price on the horizontal axis are used for proportionality. Intensity is depicted as value of .001 instead of zero due to log axis. Only participants with complete and valid data are included.

Supplementary Materials

Table 1. Correlations Within Demand Indices and Between Alcohol and Cigarette Demand Indices

	1.	**2.**	**3.**	**4.**	**5.**	**6.**	**7.**	**8.**	**9.**	**10.**
1. APT – Intensity	1.00									
2. APT – O_{max}	.15**	1.00								
3. APT – P_{max}	-.01	.89**	1.00							
4. APT – Breakpoint	.05	.87**	.91**	1.00						
5. APT – Elasticity	-.06	-.84**	-.68**	-.72*	1.00					
6. CPT – Intensity	**.20****					1.00				
7. CPT – O_{max}		**.45****				.42**	1.00			
8. CPT – P_{max}			**.36****			-.04	.62**	1.00		
9. CPT – Breakpoint				**.46****		.21**	.68**	.59**	1.00	
10. CPT – Elasticity					**.18****	-.38**	-.85**	-.59**	-.58**	1.00

Note: Upper left triangle displays correlation coefficients within alcohol demand indices. Lower right triangle displays correlations coefficients within cigarette demand indices. Displayed in bold are correlation coefficients between pairing demand indices. All APT demand indices were log transformed for normality, and CPT – O_{max}, Breakpoint, and Elasticity were log transformed. * $p \leq .05$, ** $p \leq .01$

Table 2. Pattern Matrices for Principle Component Analysis of the Indices of Demand

	APT		CPT	
	Persistence	Amplitude	Persistence	Amplitude
Intensity	.001	.999	.066	.952
O_{max}	.964	.091	.854	.274
P_{max}	.945	-.086	.907	-.352
Breakpoint	.944	-.020	.827	.001
Elasticity	-.864	-.020	-.813	-.267

Note: A criterion of .40 was used to determine whether an index significantly loaded on a factor

Table 3. Hierarchical Regression Analysis Predicting Alcohol Demand Indices

	R^2									
	Intensity		O_{max}		P_{max}		Breakpoint		Elasticity	
	R^2	□□R^2	R^2	□□ R^2	R^2	□□ R^2	R^2	□□ R^2	R^2	□□R^2
Block 1	.15	.15	--	--	--	--	--	--	--	--
Block 2	.34	.18	.06	.06	.03	.03	.03	.03	.03	.03
Block 3	--	--	.12	.05	.08	.06	.07	.04	.05	.02

	Coefficients									
	Intensity		O_{max}		P_{max}		Breakpoint		Elasticity	
	b	SE	*b*	SE	*b*	SE	*b*	SE	*b*	SE
Block 1										
Sex	**.09**	**.03**	--	--	--	--	--	--	--	--
Age	**<-.01**	**<.01**	--	--	--	--	--	--	--	--
Education	<-.01	<.01	--	--	--	--	--	--	--	--
Emp. = Full-Time	.04	.04	--	--	--	--	--	--	--	--
Emp. = Part-Time	<.01	.04	--	--	--	--	--	--	--	--
Race = African Am.	-.03	.04	--	--	--	--	--	--	--	--
Race = Asian	.04	.10	--	--	--	--	--	--	--	--
Race = Latino/a	.04	.06	--	--	--	--	--	--	--	--
Race = Native Am.	-.05	.14	--	--	--	--	--	--	--	--
Race = Multi-Racial	<.01	.04	--	--	--	--	--	--	--	--
Income	<-.01	<.01	--	--	--	--	--	--	--	--
Block 2										
ADS	**.01**	**<.01**	.01	<.01	<.01	<.01	<.01	<.01	**<-.01**	**<.01**
DPDD	**.02**	**<.01**	**.03**	**<.01**	**.02**	**<.01**	**.02**	**<.01**	<-.01	<.01
Block 3										
FTND	--	--	**.07**	**.02**	**.08**	**.02**	**.05**	**.02**	**-.04**	**.02**
CPSD	--	--	<-.01	<.01	<-.01	<.01	<.01	<.01	<.01	<.01

Abbreviations: Emp. = Employment *Note:* Results presented are from reduced models excluding blocks that were not significant ('--' indicates non-significant block where block coefficients were not considered further). R^2 and R^2 change for each block are presented in the upper half of the table. Unstandardized regression coefficients and standard errors are presented in the lower half of the table. For the coefficients section, bold values indicate significance at $p<.05$.

Table 4. Hierarchical Regression Analysis Predicting Cigarette Demand Indices

	R^2									
	Intensity		O_{max}		P_{max}		Breakpoint		Elasticity	
	R^2	□□R^2	R^2	□□ R^2	R^2	□□ R^2	R^2	□□ R^2	R^2	□□R^2
Block 1	--	--	--	--	.07	.07	--	--	.08	.08
Block 2	.31	.31	.16	.16	--	--	.02	.02	.23	.15
Block 3	.33	.02	--	--	--	--	--	--	--	--

	Coefficients									
	Intensity		O_{max}		P_{max}		Breakpoint		Elasticity	
	b	SE	*b*	SE	*B*	SE	*b*	SE	*b*	SE
<u>Block 1</u>										
Sex	--	--	--	--	.05	.03	--	--	**-.11**	**.05**
Age	--	--	--	--	<.01	<.01	--	--	**<-.01**	**<.01**
Education	--	--	--	--	<-.01	<.01	--	--	<.01	<.01
Emp. = Full-Time	--	--	--	--	-.03	.04	--	--	-.04	.06
Emp. = Part-Time	--	--	--	--	.03	.04	--	--	-.08	.06
Race = African Am.	--	--	--	--	**-.07**	**.04**	--	--	**.15**	**.06**
Race = Asian	--	--	--	--	-.14	.09	--	--	-.02	.13
Race = Latino/a	--	--	--	--	**-.11**	**.06**	--	--	**.21**	**.08**
Race = Native Am.	--	--	--	--	-.03	.12	--	--	-.11	.18
Race = Multi-Racial	--	--	--	--	-.02	.04	--	--	.06	.06
Income	--	--	--	--	**.02**	**<.01**	--	--	**-.03**	**.01**
<u>Block 2</u>										
FTND	**.68**	**.27**	**.02**	**.01**	--	--	.02	<.01	**-.03**	**<.01**
CPSD	**.70**	**.08**	**.02**	**<.01**	--	--	<.01	<.01	**-.02**	**<.01**
<u>Block 3</u>										
ADS	**.15**	**.07**	--	--	--	--	--	--	--	--
DPDD	.15	.13	--	--	--	--	--	--	--	--

Abbreviations: Emp. = Employment *Note:* Results presented are from reduced models excluding blocks that were not significant ('—' indicates non-significant block where block coefficients were not considered further). R^2 and R^2 change for each block are presented in the upper half of the table. Unstandardized regression coefficients and standard errors are presented in the lower half of the table. Breakpoint block 2 was trending (p=.06). For the coefficients section, bold values indicate significance at p<.05.

Chapter 2 (Treatment) – Sex Hormones

Rationale for the Role of Sex Hormones

Various sex differences exist in relation to cigarette use. Prior evidence has suggested that female smokers are at increased risks for negative health consequences when compared to males (USDHHS, 2014), with women experiencing greater nicotine withdrawal symptoms, craving, and negative affect (Leventhal et al., 2007; Pang & Leventhal, 2013), poorer smoking cessation outcomes (Smith, Bessette, Weinberger, Sheffer, & McKee, 2016; Philip H Smith et al., 2015), and increased risk of mortality (Kenfield, Stampfer, Rosner, & Colditz, 2008). These smoking differences may be related to changes in hormone levels because of menstrual cycle phase. Two hormones of interest that have been shown to vary across the menstrual cycle are progesterone (P4) and estradiol (E2) (Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006). The menstrual cycle can be divided into two phases: the follicular (or proliferative) phase and the luteal (or secretory) phase (Treloar, Boynton, Behn, & Brown, 1967). The follicular phase begins the first day of menses and extends until ovulation. At the beginning of the follicular phase, P4 and E2 levels are low. P4 levels reach their peak during the luteal phase. E2 begins to increase during the follicular phase, reaching a peak at the end of this phase which is signaled by ovulation occurring approximately day 14 of a typical 28 – 30- day menstrual cycle. During the luteal phase, E2 decreases reaching an intermediate secondary peak. By the late luteal (i.e., pre-menstrual) phase, both P4 and E2 levels decrease (Weinberger, Smith, et al., 2015).

Changes in sex hormones, specifically P4 and E2, regulate numerous neurotransmitter systems, thus influencing a variety of behaviors, including those related to problematic substance use. Gender differences have been noted in the neuropharmacological actions of nicotine (Pauly, 2008), such that P4 and E2 have been associated with the rewarding effects of nicotine (Torres,

Natividad, Tejeda, Van Weelden, & O'Dell, 2009), with E2 regulating nicotine-induced release of dopamine (Dluzen & Anderson, 1997). A recent meta-analysis by Weinberger and colleagues (2015) suggested that the luteal phase of the menstrual cycle, a time in which P4 and E2 levels are elevated, is associated with greater nicotine withdrawal and moderately higher craving than the follicular phase, a time of low P4 levels. Severity of pre-menstrual symptoms, often occurring towards the end of the luteal phase when E2 and P4 levels are elevated, is associated with smoking behavior, nicotine withdrawal, and relapse (Allen et al., 2014; Perkins et al., 2000; Sakai & Ohashi, 2013). These results suggest that sex hormone levels, as a function of menstrual cycle phase, may affect smoking related behaviors and ability to quit smoking.

Sex differences have also been examined in response to opioid receptor antagonists such as naltrexone. Naltrexone has been shown to produce greater nicotine withdrawal and ACTH and cortisol levels in women than men (Epstein & King, 2004; Roche, Childs, Epstein, & King, 2010). Menstrual cycle phase and sex hormone levels have been shown to affect responses to naltrexone (Roche & King, 2015). A previous study enrolled 70 subjects (n = 24 males) in a double-blind, placebo-controlled human laboratory study in which men and women completed two sessions where they received either 50 mg oral naltrexone or placebo in a randomized, counterbalanced order. Women were randomized to complete both sessions in either the early follicular (n = 23) or luteal (n = 23) phase of their menstrual cycle. Due to the change in sex hormone levels across the menstrual cycle, the early follicular and luteal phases of the menstrual cycle allowed for a comparison of high and low E2 and P4 levels. Hormone measurements of E2, P4, follicle stimulating hormone (FSH), and luteinizing hormone (LH) were used to confirm menstrual cycle phase.

Figure 4

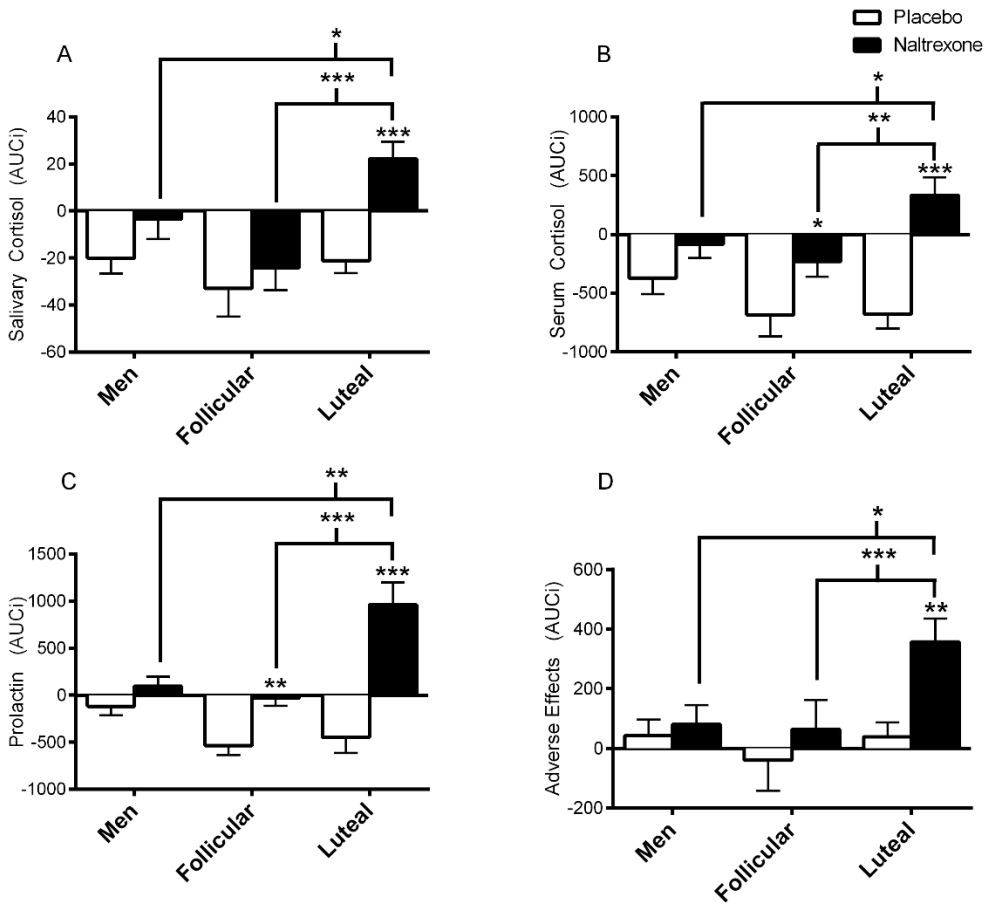


Figure 4a, 4b, 4c, 4d
Area under the curve with respect to the increase from baseline levels (AUCi) of response to naltrexone. Naltrexone significantly elevated salivary cortisol (A), serum cortisol (B), and prolactin (C), and the severity of adverse effects (D) from baseline to a greater extent in luteal phase women than men and follicular women. *Post hoc*: Asterisks above brackets indicate between groups differences of naltrexone response, non-bracketed asterisks above a bar graph indicate within group differences of naltrexone vs. placebo responses; *p < 0.05, **p < 0.01,***p < 0.001. Hormone levels are reported as mean AUCi ± SEM

In luteal women, but not early follicular women or men, naltrexone increased salivary cortisol from baseline compared with placebo (see **Figure 4A**). Naltrexone significantly increased serum cortisol (see **Figure 4B**) and prolactin (see **Figure 4C**) in both early follicular and luteal women, but not men. Of note, luteal women's serum cortisol (see **Figure 4B**) and prolactin (see **Figure 4C**) responses to naltrexone were significantly greater than those of both men and early follicular women. In luteal women, but not in men and early follicular women,

naltrexone increased the severity of adverse effects from baseline (see **Figure 4D**). These results suggest that women in the luteal phase of the menstrual cycle, most likely due to high P4 and E2 levels, are more sensitive to the effects of naltrexone compared to men and early follicular women with low P4 and E2 levels. The increased negative health consequences and worse smoking cessation outcomes provide clear evidence for the necessity of finding smoking cessation medications that are effective among women.

Chapter 2 of the dissertation examined the effects of sex hormones on smoking and drinking outcomes among premenopausal women during a randomized controlled trial for smoking cessation and drinking reduction. This chapter is currently published in *Alcohol and Alcoholism.*

The effects of menstrual cycle hormones on responses to Varenicline and Naltrexone among female heavy drinking smokers

ReJoyce Green, Daniel J.O. Roche, and Lara A. Ray

Abstract

Aims: Women often experience poorer smoking cessation outcomes in comparison to men. Menstrual cycle phase and sex hormones may influence smoking behavior and alter response to opioid antagonist medications. Less is known about the effects of sex hormones in response to pharmacotherapy for female heavy drinking smokers.

Methods: The present study is a secondary analysis of premenopausal female heavy drinking smokers who completed a 12-week randomized clinical trial comparing varenicline plus placebo versus varenicline plus naltrexone for smoking cessation and drinking reduction. Participants (n=26; total observations=66) provided saliva samples for assays of progesterone (P4) and estradiol (E2) post-randomization at weeks 4, 8, and 12. We examined the effects of P4/E2 ratio and medication on smoking and drinking outcomes.

Results: For drinking outcomes, there was a significant interaction for percent days abstinent (b = .017, p = .05), suggesting that greater P4/E2 ratio is associated with greater percent days abstinent for women assigned to the varenicline plus naltrexone condition. There were no interaction effects for the remaining drinking outcomes (p's $\geq$ .12). Results found no significant interaction effect of P4/E2 ratio and medication on smoking abstinence (p = .19).

Conclusion: Our results imply that when women show a greater P4/E2 ratio, typically observed during the luteal phase of the menstrual cycle, they experience an added benefit of naltrexone, versus placebo, for drinking outcomes as shown by greater percent days abstinent. Additional studies in larger samples are warranted as sex hormones offer important information above and beyond comparing women versus men.

Short Summary

When the ratio of progesterone (P4) to estradiol (E2) is high, as we would expect in the luteal phase of the menstrual cycle, women may experience an added benefit of naltrexone compared to when P4/E2 ratios are low, as we would expect in the follicular phase.

Keywords: progesterone (P4), estradiol (E2), varenicline, naltrexone, smoking cessation, heavy drinking smokers

Introduction

Cigarette smoking remains a leading preventable cause of morbidity and mortality. Sex differences in cigarette smoking and smoking cessation rates have been noted. The 2019 National Health Interview Survey (NHIS) found 14% of U.S. adults reported current cigarette smoking; of that, 15.3% were men and 12.7% were women (Cornelius et al., 2020). While men are more likely to smoke than women (Cornelius et al., 2020), women may be at greater risk for worse health consequences, have greater difficulty quitting, and often have less success in smoking cessation trials (Perkins, 2001, Schnoll et al., 2007, Smith et al., 2015). It is therefore essential that sex be examined in smoking cessation treatment.

While pharmacological treatments are available to aid in smoking cessation and drinking reduction, their efficacy is moderate. Varenicline is a first-line treatment for smoking cessation (Jorenby et al., 2006) that has shown benefit on drinking outcomes as well (O'Malley et al., 2018). Several studies have found that the effects of varenicline on smoking outcomes may be sex dependent. A meta-analysis by McKee and colleagues (2016) found that in comparison to men, varenicline was more effective among female smokers for short and immediate smoking cessation outcomes but was equally efficacious for longer term outcomes. These findings are promising, however in contrast to the aforementioned findings of women experiencing worse outcomes in smoking cessation trials. Naltrexone has a robust literature for drinking outcomes (Kranzler and Soyka, 2018) and has also been used in a host of smoking cessation trials in heavy drinking smokers with mixed results (David et al., 2014, Kahler et al., 2017, King et al., 2006, King et al., 2012).

Studies of sex effects have also considered the role of menstrual cycle hormones on smoking and drinking behaviors. At the onset of menses and throughout the follicular phase of the

menstrual cycle, progesterone (P4) remains low. After ovulation, P4 rises to its peak level by mid-luteal phase and gradually declines before the next menses. Conversely, estradiol (E2) is lowest during menses, rises throughout the follicular phase, peaks at ovulation, and then reaches a secondary peak during the luteal phase before again declining. In comparison to the luteal phase, women randomized to quit smoking in the follicular phase exhibited worse cessation outcomes as shown by fewer days to relapse from continuous abstinence and prolonged abstinence (Allen et al., 2008). When examining hormone values directly, P4 has been shown to be protective in reducing smoking by decreasing the rewarding aspects of smoking, while E2 may increase smoking through increasing smoking reward (Lynch and Sofuoglu, 2010, Wetherill et al., 2016). An observational study in non-treatment seeking smokers revealed that higher within-subject levels of P4 were associated with reduced cigarettes per day, however there was no effect of estradiol on cigarettes per day (Baker et al., 2021). Furthermore, exogenous progesterone has also been shown to promote smoking cessation among women (Allen et al., 2021, Tosun et al., 2019).

Specific to alcohol use, P4 and E2 have also been shown to have a distinct association with alcohol use. Alcohol consumption, both in a naturalistic environment and in a controlled experimental condition, has been associated with reductions in P4 (Peltier et al., 2021). Greater endogenous E2 was associated with an increased likelihood of drinking and binge drinking on weekend days, and these effects were the strongest in the context of low P4 (Martel et al., 2017). The effect of hormone levels on alcohol consumption may also be dependent on mood: women were more likely to consume alcohol on days when their progesterone levels were low *and* they were experiencing greater negative mood than their typical mood state (Holzhauer et al., 2020). Conversely, when women were experiencing an increase in progesterone, they were more likely

to consume alcohol on days when they reported a positive mood (Holzhauer et al., 2020). Relative to smoking cessation, fewer studies have examined the impact of P4 or E2 on alcohol reduction or abstinence outcomes. Collectively, these studies suggest the potential for P4 to serve as a protective factor, and E2 a risk factor, for both smoking behavior and alcohol use.

In addition to examining P4 and E2 separately, past studies have examined the ratio of P4 to E2 in relation to cigarette use (Saladin et al., 2015, Schiller et al., 2012). Schiller and colleagues (2012) examined how ratios of P4/E2 and E2/P4 may alter smoking topography in a sample of female cigarette smokers. They found the ratio of P4/E2 was more strongly correlated with smoking behavior than the ratio of E2/P4 (Schiller et al., 2012). Lastly, there is evidence to suggest that pharmacotherapy may alter crucial hormone levels that could impact smoking behaviors. A prior examination of brief pharmacotherapy for smoking cessation found an increase in progesterone levels following treatment with varenicline and nicotine replacement therapy; of note, this effect was predominantly driven by those randomized to the nicotine replacement therapy group (Saladin et al., 2015). Interestingly, there is also evidence that the acute effects of naltrexone may be sex-dependent with regard to menstrual cycle phase. Roche and King (2015) found that in response to an acute dose of naltrexone, women in the luteal phase exhibited greater cortisol and prolactin responses, and reported greater severity of adverse effects, in comparison to women in the follicular phase and men.

Taken together, the literature suggests that both varenicline and naltrexone have sex-dependent effects that may be best captured mechanistically through assessing menstrual cycle hormones. Ray and colleagues (2021) conducted a randomized controlled trial for smoking cessation and drinking reduction. Participants were assigned to receive either (a) varenicline plus placebo or (b) varenicline plus naltrexone for 12 weeks, with follow-up appointments conducted

at week-12 and week-26. The results from this randomized clinical trial by Ray and colleagues (2021) found participants randomized to the varenicline plus placebo condition reported greater smoking cessation at week-26. For alcohol use outcomes, there was some benefit of the combined varenicline plus naltrexone for reducing drinks per drinking day however it did not meet statistical significance (Ray et al., 2021). This study highlights the potential benefits of combined pharmacotherapy for predominantly alcohol use outcomes among heavy drinking smokers.

The present study is an exploratory secondary analysis of Ray and colleagues (2021), supported by an NIH supplement to investigate sex-differences. At weeks 4, 8, and 12 post-randomization and during the active medication phase, participants provided saliva samples for assays of P4 and E2. The present study examines the effects of the ratio of P4/E2 during the active medication phase as predictors of smoking and drinking behaviors.

Methods

Participants and Study Design

This study was approved by the University of California, Los Angeles Institutional Review Board (IRB) (ClinicalTrials.gov identifier: NCT02698215). A detailed description of the study procedures can be found elsewhere (Ray et al., 2021). In short, 34 women were included in the present secondary analyses. All women were premenopausal, regularly cycling women. One woman reported using hormonal contraceptives and was still included in the present analyses. Women were required to smoke $\geq$ 5 cigarettes per day, have a breath carbon monoxide (CO) level of $\geq$ 4ppm, and meet National Institute on Alcohol Abuse and Alcoholism (NIAAA; Abuse and Alcoholism, 1995) criteria for heavy drinking for women: > 7 drinks per week or $\geq$ 4 drinks

per occasion at least once per month over the past 12 months. All participants received a 30–45-minute counseling session specific to heavy drinking smokers (Kahler et al., 2008) prior to their smoking quit date. Topics covered in this counseling session were triggers for smoking relapse, coping strategies for smoking cessation, and the impact of alcohol during a smoking cessation attempt. Participants were not instructed to remain abstinent from alcohol, rather they were informed it was ultimately their choice how much they would like to change their drinking. Participants were randomized to one of two medication conditions: 2 mg/day varenicline + 50 mg/day naltrexone, or 2 mg/day varenicline + matching placebo pills. Details on the medication titration period can be found elsewhere (Ray et al., 2021). Following randomization, participants returned to the laboratory at the following weeks: 4, 8, 12, 16, and 26. For the purpose of this study, results are limited to the active medication phase, consisting of weeks 4, 8, and 12. Of the initial 34 women, a total of 26 women were included in the final analyses as they met the inclusion criteria and had hormone data present for at least one timepoint during the active medication phase. The data underlying this article are not publicly available.

Measures

Participants completed the following individual difference measures at their initial screening visit: a) demographics questionnaire; b) Timeline Follow-Back (TLFB; Sobell and Sobell, 1992) to assess smoking and drinking in the 30 days prior to the initial screening visit; c) Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991), a self-report questionnaire to assess for nicotine dependence. The following measures were collected at each follow-up visit: TLFB for smoking and drinking outcomes.

Data Analysis Plan

Details on hormone assay procedures can be found in the **Supplementary Materials**. One participant had no E2 detected for follow-up week 12. A value of 0.01 was imputed for this participant as this value was below the lower limit sensitivity for E2. Raw hormone values were entered into models as single variable ratio of P4/E2. Ratio of P4/E2 is expected to be the highest during the luteal phase and lower during the follicular phase (Schiller et al., 2012). Two outliers were detected (Z-score of |>| 2) for the ratio of P4/E2 and were re-coded into the next highest non-outlying value. Our final sample size for our analyses was $N = 26$ with data present for at least one timepoint across the 3 time points during the active medication phase, resulting in 66 total observations due to occasional missing data throughout the study.

All analyses were conducted in SAS University Edition version 9.4 (SAS Institute, Cary, NC). Primary smoking outcome was smoking abstinence (binary) defined as carbon monoxide (CO) $\leq$ 5ppm and was assessed the day of each study visit at weeks 4, 8, and 12. Primary drinking outcomes were drinks per drinking day, percent heavy drinking days, percent days abstinent, and drinking days. For each study visit (week-4, week-8, and week-12), drinking outcomes reflected the 28-days prior to the study visit. For example, drinks per drinking day at week-8 represents the number of drinks per drinking day from study visit at week-4 to study visit at week-8. Analysis examined the effects of *Medication*, a two-level between-subjects factor (0 = Varenicline + Placebo, 1 = Varenicline + Naltrexone), *P4/E2 ratio*, *Week*, a three-level within-subjects factor (Week = Follow-Up 4, Follow-Up 8, Follow-Up 12; coded 1 – 3), and *medication* × *P4/E2 ratio* interaction. Due to the large values of P4/E2 relative to other variables in the model, P4/E2 was rescaled by dividing by 10. Covariates in the model included baseline values of the outcome, aside from smoking abstinence which did not include a covariate. PROC GLIMMIX was used for our binary outcome of smoking abstinence. PROC MIXED was used

for the remaining continuous drinking outcomes. An unstructured covariance matrix was specified for all PROC MIXED models.

Results

Sample Characteristics

Participants were on average 34.88 years old (SD = 8.10), and 46.15% identified as Black or African-American. At the initial screening visit, participants on average smoked 13.21 (SD = 9.33) cigarettes per smoking day, expired CO level of 10.69 (SD = 7.04), and average FTND score of 4.5 (SD = 2.16) indicating moderate nicotine dependence. For drinking outcomes at the initial screening visit, participants consumed an average of 5.04 (SD = 3.66) drinks per drinking day; 51% (35%) of those days were heavy drinking days. Participants also reported 35% (27%) days abstinent.

The raw hormone values of were similar across timepoints for P4 at Follow-Up 4 (mean = 163.69, SD = 117.29) and Follow-Up 8 (mean = 157.39, SD = 65.97). Values were slightly larger for Follow-up 12 with a noticeably larger standard deviation (mean = 447.93, SD = 1370.49). For E2, values were similar across all timepoints (Follow-Up 4 = 1.84 + .50, Follow-Up 8 = 2.25 + 1.05; Follow-up 12 = 2.11 + 1.41). Outlier screening was conducted at the level of P4/E2 ratio, not at the individual hormone level, and outliers with a Z-score > |2| were winsorized to the next highest non-outlying. A total of 2 outliers were winsorized to the next highest non-outlying value. Across time, similar ratios for raw P4/E2 were observed post-outlier screening between Follow-Up 4 (Mean = 87.03, SD = 53.19, skew = 1.38, kurtosis = 1.67) and Follow-Up 8 (Mean = 72.96, SD = 25.64, skew = 0.75, kurtosis = 0.67), with slightly higher values observed at Follow-up 12 (mean = 92.66, SD = 65.77, skew = 1.22, kurtosis = 0.42). To

assess for within-person variability of P4/E2 across study visits, coefficient of variation (CV) was calculated for each participant who had hormone data present for at least two timepoint during the active medication phase (n=23). The average CV was 37%, with a range of 4% - 85%. This suggests that across the study visits, there was some degree of within-person variability in ratio of P4/E2.

Smoking Outcome

Results of primary smoking and drinking outcomes are summarized in **Table 1**. Results for smoking abstinence revealed a significant medication effect (AOR = .09, 95% CI = .01 – .82) such that those in the varenicline plus placebo condition exhibited greater odds of smoking abstinence. Ratio of medication × P4/E2 was non-significant (AOR for VAR+PLAC = .88, 95% CI = .73 – 1.06; AOR for VAR+NTX = 1.09, 95% CI = .84 – 1.40). The effect of P4/E2 on smoking abstinence throughout the clinical trial did not differ based on medication condition. Week was also significant with greater smoking abstinence reported as time progressed in the active medication phase of the trial (AOR = 2.65, 95% CI = 1.04 – 6.74). For a one-unit change in week (i.e., transition from week-8 to week-12), the odds of achieving smoking abstinence increase by 2.65.

Drinking Outcomes

For percent days abstinent, there was a significant medication × P4/E2 interaction (b = .017, p = .05) and is displayed in **Figure 1**. Follow-up analyses of the effect of P4/E2 within each medication condition found a non-significant P4/E2 effect in those assigned to varenicline plus placebo (*n.* = 17; b = .004, p = .23); however, there was a significant effect of P4/E2 in those randomized to varenicline plus naltrexone (*n.* = 9; b = .023, p = .008). While the effect is small,

it does suggest that for participants assigned to the varenicline plus naltrexone condition, greater P4/E2 ratio is associated with greater percent days abstinent in the 28-days leading up to the study visits. For drinks per drinking day, percent heavy drinking days, and drinking days there was a non-significant medication × P4/E2 interaction (p = .50, .36, and .12 respectively). The lower order effects were also non-significant (p's $\geq$ .38).

Discussion

The present study was an exploratory secondary data analysis to examine the effects of menstrual cycle hormones among premenopausal women on smoking and drinking outcomes during a clinical trial testing varenicline and naltrexone for smoking cessation and drinking reduction. The parent study for this secondary analysis found a benefit of combined varenicline and naltrexone for drinking outcomes, however not for smoking outcomes (Ray et al., 2021). Given previous work suggesting women in the luteal phase may be more sensitive to the effects of naltrexone (Roche and King, 2015), we were particularly interested in examining whether there was an interaction between medication and sex hormones. For smoking abstinence, we found no interaction effect between medication and ratio of P4/E2 or lower-order simple effect of P4/E2. There was a significant effect of medication in favor of those in the varenicline plus placebo condition experiencing greater smoking abstinence. This aligns with the results of the larger clinical trial (Ray et al., 2021).

For the drinking outcome percent days abstinent, there was a significant interaction between medication and the ratio of P4/E2. In comparison to varenicline plus placebo, greater P4/E2 ratio was associated with greater percent days abstinent for those in the varenicline plus naltrexone condition. Since we expect to see higher P4/E2 ratio during the luteal phase, our results imply that during the luteal phase, participants in the combined varenicline plus naltrexone exhibited

improvements in their drinking behavior as indexed by greater percent days abstinent in the 28-days leading up to the study visit. It is also possible that women who had relatively higher P4 and/or lower E2 during their luteal phase are more likely to be responsive to naltrexone. These results align with the findings of Roche and King (2015) in which women in the luteal phase were more sensitive to the acute hormonal effects and subjective effects of naltrexone, notably with increases in cortisol and severity of adverse effects in the luteal phase. Our results suggest that during a time when the ratio of P4/E2 is high, as we would expect in the luteal phase, women may experience an added benefit of naltrexone compared to when P4/E2 ratios are low, as we would expect in the follicular phase. It may be that the luteal phase is a time when women are more responsive to *both* the positive (i.e., clinical benefits) and negative (i.e., side effects) effects of naltrexone. However, this finding should be viewed with caution, as there were no significant interactive or lower-order simple effects for the remaining drinking outcomes. The larger study from where these data was culled showed that the largest reduction in drinks per drinking day occurred from baseline to follow-up week 4, with notably smaller changes from week 4 through week 12 (Ray et al., 2021). Greater changes in drinking outcomes may be needed to detect any influence of P4/E2 ratio.

Previous studies have shown an effect of P4 and E2 on smoking outcomes, independent of each other (Baker et al., 2021, Tosun et al., 2019) and as a ratio of P4/E2 (Schiller et al., 2012). However, our results did not show an effect of lower or higher P4/E2 ratios on smoking abstinence and cigarette per day during the trial. It is possible that our sample did not have large enough variation in menstrual cycle phase across the three study visits. Due to each follow-up visit occurring approximately 4-weeks apart, we potentially captured women around the same phase of the menstrual cycle, and thereby similar P4/E2 ratios, at each assessment. This was to

some degree reflected in the average values of P4, E2, and the P4/E2 ratio of our sample. However, the CV estimates for our sample indicated moderate within-person variability across the active medication phase, which was also supported by the larger standard deviations when examining raw P4/E2 values, suggesting some degree of variation in P4/E2 between repeated measures during the active medication phase of this study. Future studies are needed to examine these effects in a larger sample with equal proportions of women in the luteal and follicular phase throughout the trial. Further, gathering assessments every 2 weeks to observe within-person changes in response to the combination of varenicline plus naltrexone on smoking and drinking outcomes would be important to further understand the preliminary findings reported herein.

The present study must be interpreted in light of strengths and weaknesses. Strengths include hormonal assays of both P4 and E2 at each follow-up appointment, comprising six hormonal assays per participant across the 12 weeks. Limitations include a small sample size and the assessment period of 4 weeks, which potentially limited within-person assessment across distinct phases of the menstrual cycle. While studies have found a relationship between sex hormones and smoking behavior (Baker et al., 2021), when summarized across a 4-week period, some of those nuanced effects may be less detectable. Another limitation includes the lack of objective measurements of alcohol consumption, such as EtG or CDT. The addition of these objective alcohol consumption measurements may have provided additional validation to self-report alcohol consumption.

In conclusion, this study provides preliminary evidence on the potential role of the effect of biomarkers of sex differences, namely P4/E2 ratio, among female heavy drinking smokers undergoing treatment. While a majority of analyses were null, there was an intriguing medication

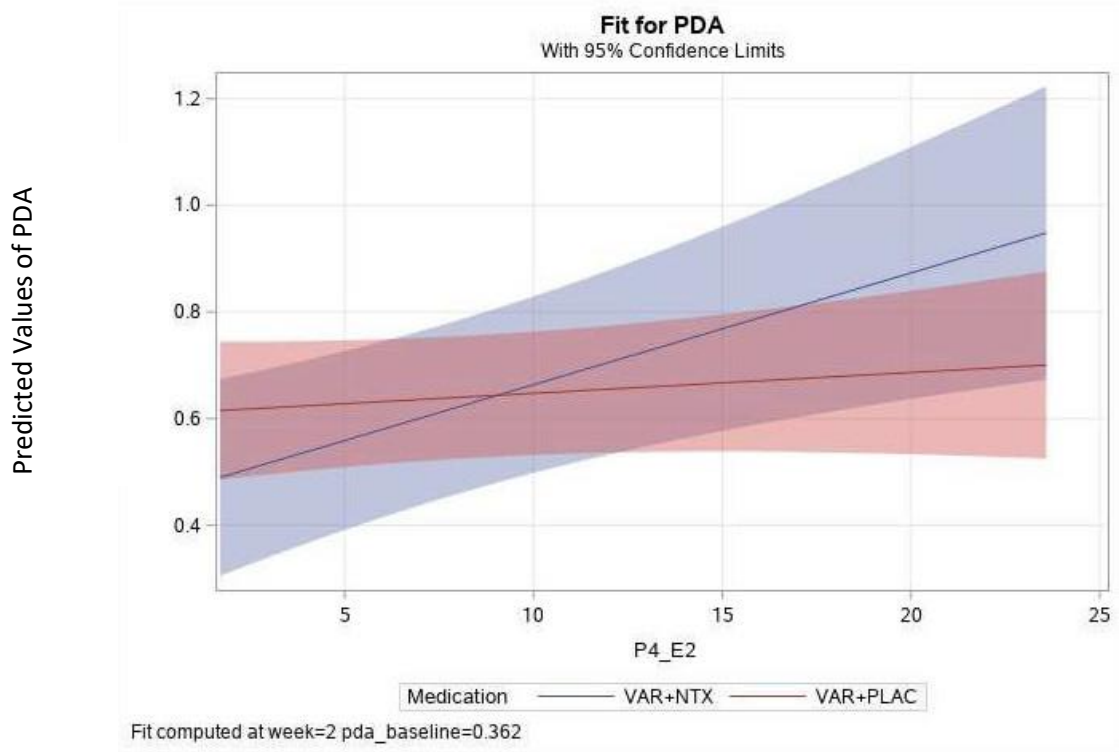
by hormone level interaction such that varenicline plus naltrexone increased percent days abstinent among women with greater P4/E2 ratio compared to the varenicline plus placebo condition. Additional studies of these effects in larger samples are warranted and sex hormones offer important information above and beyond comparing groups on the bases of sex.

Table 1. Smoking and Drinking Outcomes

	Smoking Outcome			Drinking Outcomes										
	Quit			DPDD			PHDD			PDA			DD		
	Log Odds	SE	*p*	b	SE	*p*	b	SE	*p*	b	SE	*p*	b	SE	*p*
Intercept	.594	1.200	.626	2.067	.793	.016	.241	.139	.092	.373	.108	.002	.647	3.888	.869
Med															
VAR+NTX	-4.120	1.782	.027*	.418	.974	.670	-.044	.174	.803	-.154	.123	.218	2.177	3.515	.539
VAR+PLAC	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
P4/E2	-.126	.091	.175	.017	.044	.701	-.006	.008	.450	.004	.004	.390	-.113	.127	.377
4-week study visit	.974	.461	.042*	-.357	.188	.065†	-.053	.035	.144	.001	.019	.952	.070	.524	.895
Med × P4/E2															
VAR+NTX	.207	.155	.190	-.058	.085	.497	.014	.015	.363	.017	.009	.053*	-.379	.241	.124
VAR+PLAC	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Covariate: Baseline measure of outcome	--	--	--	.304	.113	.010*	.423	.173	.020*	.644	.185	.001*	.528	.177	.005*

Note: b = unstandardized beta estimates, SE = standard error, DPDD = drinks per drinking day, PHDD = percent heavy drinking days, PDA = percent days abstinent, DD = drink days. Covariates in all models include corresponding baseline measure of outcome.
*Indicates significance at $p \leq .05$, † Indicates trending at $p = .06$

Figure 1. Effect of medication and P4/E2 ratio on Percent Days Abstinent (PDA) from alcohol.



Note: Analyses revealed a significant medication × P4/E2 interaction (b = .017, *p* = .05) such that greater P4/E2 ratio is associated with greater percent days abstinent for participants assigned to the varenicline plus naltrexone condition.

Supplemental Materials for

The effects of menstrual cycle hormones on responses to Varenicline and Naltrexone among female heavy drinking smokers

Description of Hormone Assay Procedures

Premenopausal women provided saliva samples at randomization and each follow-up visit. Saliva samples were assayed at Salmetrics' SalivaLab (Carlsbad, CA) without modifications to the manufacturer's protocol. All samples were thawed at room temperature, vortexed, then centrifuged for 15 minutes at approximately 3,000 RPM immediately before performing the assay. Saliva samples were tested using the high sensitivity enzyme immunoassay for progesterone (P4) (Cat. No. 1-1502) and estradiol (E2) (Cat No. 1-3702). P4 sample test volume was 50 μl saliva per determination, had a lower limit sensitivity of 5 pg/ml, average intra-assay coefficient of variation of 6.20%, and an average inter-assay coefficient of variation 7.55%. E2 had a sample test volume was 100 μl saliva per determination, lower limit sensitivity of 0.1 pg/ml, average intra-assay coefficient of variation of 7.13%, and an average inter-assay coefficient of variation 7.45%.

Chapter 3 (Treatment) – Relationship Between Drinking and Smoking

Rationale for the Relationship Between Drinking and Smoking

Few studies to date have examined potential mediators of varenicline alone. These studies have found reductions in craving (tonic and cue-provoked) and reward from smoking (Brandon et al., 2011) as well as cigarettes per day, nicotine dependence, and satisfaction from cigarettes as mediating varenicline outcomes (Hughes et al., 2011). A previous trial comparing varenicline and sustained-release bupropion found superior effects of varenicline on attenuating craving and reward from cigarettes and proposed further study to examine how these subjective differences between two medications may mediate differential effects on smoking abstinence (West, Baker, Cappelleri, & Bushmakin, 2008). During a smoking cessation attempt, alcohol use is a strong trigger for a smoking lapse (Kahler et al., 2009; Kahler, Spillane, & Metrik, 2010). Clinical practice guidelines recommend that those engaging in a smoking cessation attempt avoid or reduce their alcohol use (Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, 2008). Given the robust bidirectional relationship between smoking and drinking, it is imperative to further our understanding of how the use of one substance influences the other, especially in the context of treatment.

Chapter 3 of the dissertation examined whether drinking outcomes mediated the relationship between medication and cigarettes per smoking day during the active medication phase (week 4, 8, and 12) and follow-up phase (week 16 and 26). This chapter is currently published in *Experimental and Clinical Psychopharmacology*.

The Relationship Between Drinking and Smoking in a Clinical Trial for Smoking Cessation and Drinking Reduction

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Abstract

Heavy drinking smokers experience poorer smoking cessation outcomes. Less is known about the relationship between drinking and smoking among those who are trying to reduce or abstain from both substances. The present study used data from 115 heavy drinking smokers who completed a 12-week clinical trial comparing varenicline alone (1 mg/bid) versus varenicline (1 mg/bid) plus naltrexone (50 mg/day) for smoking cessation and drinking reduction. We tested whether drinking outcomes mediated the relationship between medication and cigarettes per smoking day (CPSD) during the active medication phase (week 4, 8, and 12) and follow-up phase (week 16 and 26). CPSD and drinking variables predicted respective use at subsequent timepoints (*p's* < .0001). Results revealed a non-significant mediation effect of our primary mediator drinks per drinking day (DPDD) at Week 12 (95% CI = [-1.03, .58]) and Week 26 (95% CI = [-.09, .51]), and our secondary mediators of percent heavy drinking days (PHDD) and percent days abstinent (PDA) (Week 12: 95% CI = [-.14, .35]; Week 26: 95% CI = [-.15, .41]). Cross-lagged effects (e.g. Week 4 drinking predicting Week 8 smoking) were non-significant between DPDD and CPSD (*p's* $\geq$ .07), and PHDD and PDA and CPSD that met our a-priori cut off (*p's* $\geq$ .02). There was a significant relationship between drinking and smoking concurrently indicated by fixed error covariances (CPSD and DPDD: $p < .01$; CPSD and PDA $p = .01$). Our findings highlight an association between drinking and smoking behaviors respectively across the span of 6 months.

Keywords: smoking cessation; drinking reduction; varenicline; naltrexone

Public Significance Statement: This study elucidates the relationship between drinking and smoking in the context of a clinical trial for smoking cessation and drinking reduction.

Throughout active medication phase, and follow-up, greater drinking and smoking is consistently associated with greater use of the respective substances

The Relationship Between Drinking and Smoking in a Clinical Trial for Smoking Cessation and Drinking Reduction

It is now widely recognized that cigarette smoking and drinking are behaviorally and clinically intertwined. Epidemiological data from the 2019 National Survey on Drug Use and Health (NSDUH) found that 21.7% of adults reported using cigarettes over the last year (USDHHS, 2019). The same survey found 10.7% reported daily cigarette use and 6.3% reported heavy alcohol use over the past month (USDHHS, 2019). Individuals with a mild or moderate alcohol use disorder (AUD) have exhibited a smoking prevalence 2 times higher than those without an AUD (Weinberger, Funk, & Goodwin, 2016). The trend continues with those with a severe AUD having a smoking prevalence 3 times higher than those without an AUD (Weinberger et al., 2016). Conversely, nicotine use has also been shown to impact alcohol use. Individuals with any nicotine use disorder are 2.5 times more likely to meet criteria for a 12-month AUD diagnosis, and 3.2 times more likely to meet criteria for a lifetime AUD diagnosis (Grant et al., 2015). The effect of nicotine on alcohol use is so robust that even low levels of nicotine have been shown to increase quantity of alcohol consumption. In comparison to non-smokers, non-daily smokers may experience an increased risk for hazardous drinking and for receiving a DSM-IV alcohol diagnosis (Harrison, Desai, & McKee, 2008). Previous studies have made salient how co-use of both substances may increase their acute rewarding effects (Cross, Lotfipour, & Leslie, 2017), and promote cross-tolerance of both substances (Funk, Marinelli, & Lê, 2006), further perpetuating co-use. The negative health consequences from cigarette use (USDHHS, 2010, 2014) and alcohol use (WHO, 2019), including increased risk for various cancers and cardiovascular diseases, underscores the need to concomitantly reduce the use of both substances.

Alcohol use hinders smoking cessation attempts. Over the last two decades, the number of adult cigarette smokers who have engaged in a smoking cessation attempt has increased (USDHHS, 2020). The average smoker attempts to quit smoking multiple times with estimates ranging from 6 to upwards of 30 or more attempts before one is successful in sustaining abstinence from cigarettes for at least 1 year (Chaiton et al., 2016). Previous studies found that moderate and heavy alcohol use increases the risk of smoking lapses during a smoking cessation attempt (Kahler et al., 2009; Kahler, Spillane, & Metrik, 2010). A recent study by Lynch and colleagues (2019) found that in comparison to nondrinkers, at 1-month post smoking cessation treatment, moderate drinkers experienced greater odds of continued smoking, however, at 7-months post-treatment, the odds of continued smoking were not different to that of nondrinkers. For heavy drinkers, in comparison to non-drinkers, the increased odds of continued smoking remained for 1-month and 7-months post-treatment (Lynch et al., 2019). These studies underscore the importance of addressing alcohol co-use, particularly at higher levels, during an initial smoking quit attempt and thereafter. A previous clinical trial integrated a brief alcohol intervention in the context of smoking cessation treatment and found greater smoking abstinence among those who received integrated treatment compared to those who only received standard smoking cessation treatment (Kahler et al., 2008). Transitioning results such as these into clinical practice, it is recommended that those trying to quit smoking limit or abstain from alcohol as much as possible (Clinical Practice Guideline Treating Tobacco Use and Dependence 2008 Update Panel, 2008). Taken together, these findings highlight the need for interventions that can simultaneously address smoking cessation and drinking reduction to target the amplified, negative effects of conjoint use in treatment.

One of the main limitations of the field has been that clinical trials focus either on smoking or on drinking as a primary outcome, but rarely target both behaviors simultaneously. To address this limitation, our group has recently completed a 12-week clinical trial combining varenicline and naltrexone for smoking cessation and drinking reduction in a sample of heavy drinking daily smokers (Ray et al., 2021). Varenicline, a selective nicotinic acetylcholine partial agonist, is an FDA approved medication for smoking cessation (Jorenby et al., 2006; Oncken et al., 2006). While naltrexone, a non-selective opioid receptor antagonist, is an FDA approved for the treatment of alcohol use disorder (O'Malley et al., 1992; Volpicelli, Alterman, Hayashida, & O'Brien, 1992). This recently completed clinical trial provides a unique opportunity to examine behavior change across the two substances as both measures of alcohol and cigarette consumption were assessed concurrently throughout the clinical trial. This study randomized heavy drinking smokers to receive varenicline plus placebo or varenicline plus naltrexone. Results indicated that smoking abstinence at 26 week follow-up was significantly higher in the varenicline plus placebo group, compared to the varenicline plus naltrexone group (Ray et al., 2021). For the primary drinking outcome of drinks per drinking day, there was a main effect of medication in favor of the combined medication group at the 12 week end of medication phase; however, this effect was not sustained at the 26 week follow-up (Ray et al., 2021). These results shed light on the impact of combination pharmacotherapy in the context of smoking cessation and drinking reduction.

The present study leverages data from the aforementioned clinical trial to interrogate the relationship between smoking and drinking across the treatment (12 weeks) and follow-up periods (26 weeks). Using a cross-lagged panel model, we examine the directional influence that drinking and smoking variables have on each other over time. We were primarily interested in

testing whether drinking outcomes mediate the relationship between pharmacotherapy and smoking outcomes. Through using cigarettes per smoking day as our smoking outcome, we were able to test how reductions in drinking are associated with reductions in smoking beyond a binary quit or no quit. Our primary drinking variable of interest was drinks per drinking day which aligns with the previously mentioned trial (Ray et al., 2021) such that drinks per drinking day was the primary drinking outcome of that study. Our secondary drinking mediators of interest are percent heavy drinking days and percent days abstinent. These were also two secondary drinking outcomes in the primary trial (Ray et al., 2021). Based on the literature we hypothesize that compared to participants in the varenicline plus placebo condition, those in the varenicline plus naltrexone condition will experience greater reductions in drinking, thus leading to greater reductions in smoking. While the primary outcomes of the study found varenicline alone was associated with greater smoking abstinence, we hypothesized that the combined medication condition may be sensitive to a wider range of smoking behaviors, via cigarettes per smoking day. We also hypothesized that drinking and smoking will be related across the duration of the trial, and that reductions in drinking would lead to reductions in smoking. This study provides a unique contribution by extending beyond the main effect of medication on smoking and drinking outcomes and by interrogating mechanisms of action of the combination of varenicline plus naltrexone on drinking and smoking reduction.

Method

Participants

Participants were recruited via print, mass transit, radio, and social media advertisements as part of a larger clinical trial for smoking cessation and drinking reduction (ClinicalTrials.gov identifier: NCT02698215). The clinical trial was approved by the Institutional Review Board

(IRB) of the University of California, Los Angeles (UCLA). A consort diagram for trial enrollment has been recently published (Ray et al., 2021). Interested participants called the laboratory and completed a phone screening prior to being invited for an in-person screening visit. Inclusion criteria were: a) treatment-seeking for smoking cessation and a desire to reduce or quit drinking; b) between ages 21 – 65; c) smoke > 5 cigarettes per day for the past year and carbon monoxide reading $\geq$ 4 ppm; and d) meet National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines for heavy drinking (men: > 14 drinks per week, $\geq$ 5 drinks per occasion at least once per month over the past 12 months; women: > 7 drinks per week, $\geq$ 4 drinks per occasion at least once per month over the past 12 months). Exclusion criteria included the following: a) clinically significant alcohol withdrawal as indicated by a score $\geq$ 10 on the Clinical Institute Withdrawal assessment for Alcohol (CIWA-Ar); b) lifetime DSM-V diagnosis of bipolar disorder, psychotic disorder, major depressive disorder with suicidal ideation, or current substance use disorder (aside from alcohol and nicotine); and c) women could not be pregnant or nursing and had to be practicing effective contraception.

Procedures

Participants were required to produce a breath alcohol concentration (BrAC) of 0.00 g/dl at all study visits and to test negative for all substances excluding cannabis. Participants deemed eligible after the in-person screening visit completed a physical exam to establish medical eligibility and were then randomized to one of two medications: (a) 2mg of varenicline tartrate plus matching placebo pills or (b) 2mg of varenicline tartrate plus 50mg of naltrexone. All participants took the first dose of medication under observation during the randomization visit. A detailed description of the study procedures, including medication titration procedures and monitoring of side effects, is provided in Ray et al. (2021). During the randomization visit,

participants engaged in a 30–45-minute counseling session specifically for heavy drinking smokers (Kahler et al., 2008), set a smoking quit date, and discussed a drinking goal of abstinence or reduction. Post-randomization, participants returned to the laboratory for in-person assessment visits at Weeks 4, 8, 12, 16, and 26.

Measures

A series of individual differences measures were collected at the in-person screening visit, including: a) demographics questionnaire; b) Structured Clinical Interview for DSM-5 (SCID5; First, Spitzer, Gibbon, & Williams, 1995); c) Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991); d) Clinical Institute Withdrawal for Alcohol (CIWA-Ar; Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989); e) Timeline Follow-back to assess for past alcohol consumption and cigarette use (TLFB; Sobell & Sobell, 1992); and f) Smoking History Questionnaire to assess for past smoking behavior. During each post-randomization visit, research assessments were completed including the TLFB, along with carbon monoxide (CO) recordings. For the present study, the primary outcome measure was cigarettes per smoking day derived from the TLFB. The primary mediator of interested was drinks per drinking day also derived from the TLFB. The primary mediator was selected given that it represents the a priori registered drinking outcome for the trial. The secondary mediators of interest were two of the secondary registered drinking outcomes, namely percent heavy drinking days and percent days abstinent also derived from the TLFB. Both drinking and smoking outcomes derived from the TLFB were measured concurrently. We report how we determined our sample size, all data exclusions (if any), all manipulations, and all measures in the study. This study was not preregistered and the data and study materials are not available online.

Data Analysis

All analyses were conducted in SAS University Edition version 9.4 (SAS Institute, Cary, NC). A cross-lagged panel model with PROC CALIS was used to test the proposed mediation models of drinking outcomes mediating the effects of medication on cigarettes per smoking day. We conducted a total of 2 cross-lagged panel models across 5 time points during the active medication phase (Week 4, 8, 12) and follow-up phase (Week 16 and Week 26). The first model tested drinks per drinking day as the primary mediator. The second model tested percent heavy drinking days and percent days abstinent as secondary mediators. A conceptual diagram of the cross-lagged panel models is presented in Figure 1A and Figure 1B for drinks per drinking day, and Figure 2A and Figure 2B for percent heavy drinking days and percent days abstinent. Our predictor across all models was medication condition (0 = varenicline + placebo; 1 = varenicline + naltrexone) and our outcome was cigarettes per smoking day. For each visit, cigarettes per smoking day was averaged across the 28 days leading up (i.e., preceding) the visit. In other words, cigarettes per smoking day at Week 12 consisted of cigarettes per smoking day averaged across 28 days prior to week 12 of participant enrollment in the trial. The same approach was used to define drinks per drinking day, percent heavy drinking days, and percent days abstinent.

For the functional relationships between observed variables in the cross-lagged panel models, the path from medication to drinking variables and cigarettes per smoking day during the active medication phase was a free parameter. All drinking and smoking variables had fixed first-order autoregressions (i.e. one fixed path for drinks per drinking day, one fixed path for cigarettes per smoking day) from Week 4 through Week 16 due to equal spacing of 4-weeks between each measurement. We controlled for baseline drinking and smoking by allowing them to freely predict the respective variable at Week 4 (i.e., baseline drinking predicts drinking at

Week 4 and baseline smoking predicts smoking at Week 4). Due to the unequal timepoints between Week 16 and Week 26, we allowed for a free autoregression between these last timepoints. First-order cross-lagged effects were included as free parameters (i.e. drinks per drinking day at Week 4 predicting cigarettes per smoking day at Week 8 and vice versa). Lastly, initial models indicated large standardized residual covariances associated with the drinks per drinking day at Week 4. Due to the smoking quit date occurring at the start of the active medication phase, it is possible that greater changes in smoking, and possibly drinking, occurred during the first 4 weeks of the trial. Therefore, we allowed for a second-order autoregression as a free path between Week 4 and Week 12 to allow for any changes during Week 4 to influence Week 12. To account for the relationship between smoking and drinking variable within a time period, error covariances between drinking variables and cigarettes per smoking day at each timepoint were fixed to be equal across timepoints. By specifying error covariances, we specifically aimed to account for the correlated errors due to the strong evidence highlighting the relationship between drinking and smoking behaviors concurrently. For the first model, this included one set of fixed error covariances between drinks per drinking day and cigarettes per smoking day. For the second model, three sets of error covariances were specified: one for percent heavy drinking days and cigarettes per smoking day, a second for percent days abstinent and cigarettes per smoking day, and a third for percent heavy drinking days and percent days abstinent. We did not anticipate the relationship between these variables to differ over time, therefore fixed the error covariances across time.

Due to multiple paths in the cross-lagged panel models, we constrained our indirect paths of interest to those in which drinking variables were present first, followed by subsequent drinking variables or smoking variables, and ending with cigarettes per smoking day at Week 12

and Week 26. These indirect paths are displayed in bold in Figure 1A and 2A for Week 12 and Figure 1B and 2Bfor Week 26. When testing drinks per drinking day as a mediator, there were a total of 3 indirect paths that were aggregated in our test of indirect effects at Week 12 (Figure 1A) and a total of 11 paths were aggregated at Week 26 (Figure 1B). The same approach of selecting indirect effects to aggregate was applied to the second model testing percent heavy drinking days and percent days abstinent as mediators. A total of 6 paths were aggregated when cigarettes per smoking day at Week 12 was the outcome (Figure 2A), and a total of 22 paths for Week 26 (Figure 2B). Of note, these mediators were tested simultaneously in the model such that the indirect paths for percent heavy drinking days and percent days abstinent were aggregated.

In order to properly account for the fact that our outcome (i.e., cigarettes per smoking day) was positively skewed by virtue of participants who abstained from smoking at various points throughout the trial, maximum likelihood estimation was used with the Satorra-Bentler scaled chi-square test statistics and the associated sandwich-type standard error estimates (Satorra & Bentler, 1994). For the individual path estimates, we set our a-priori cut-off at $p <$ .0125 to correct for the 4 sets of cross-lagged paths. In addition, percentile bootstrap confidence intervals were used to conduct inference on the aggregated indirect effect. An advantage of bootstrapping in our sample is that this method makes no assumption regarding the shape of the sample distribution of the indirect effect (Hayes, 2018). An initial model was estimated followed by a total of 2,000 bootstrapped estimates of the aggregated indirect effect with 95% confidence intervals. If the confidence interval did not contain zero, then the test of our indirect effect was considered statistically significant. At baseline our sample consisted of 165 heavy drinking smokers who were randomized to one of the two medication conditions. However, due to the maximum likelihood estimation method with the Satorra-Bentler correction described above,

only those with complete data were used in our cross-lagged panel models. While there was some attrition throughout the trial, the sample size based on the availability of complete data across medication groups remained relatively consistent throughout the trial, ending with 115 total participants at Week 26. Thus, our final sample size for the results described herein was 115. To examine any changes when using the full sample, we also conducted the same models with full maximum likelihood estimation (FIML), with no Satorra-Bentler correction, to make use of all available data. SAS does not allow for simultaneous use of the Satorra-Bentler correction and FIML, therefore the Satorra-Bentler correction was not used when employing FIML. The fit indices and path estimates for these models are presented in Supplementary Materials.

Results

Sample Characteristics

Our sample for the present analyses consisted of 115 (42 female) heavy drinking daily smokers who were randomized to one of the two medication conditions. Participants were on average 42.34 (SD = 11.74) years old, with 48.70% identified as African-American, 31.30% White, and 20% reporting another race or mixed race. Most participants reported working full-time (30.43%) or part-time (26.09%). Income breakdown was such that 57.39% reported a pre-tax household income of less than $30,000, 16.52% reported an income of at least $30,000 but less than $45,000, and 26.09% reported an income greater than $45,000. At baseline, participants reported an average of 29.35 (SD = 1.96) smoking days and 14.21 (SD = 8.39) cigarettes per smoking day in the 30 days. The average FTND score in the sample was 4.47 (SD = 2.18) indicating moderate nicotine dependence. For alcohol measures, participants reported an average of 19.63 (SD = 8.06) drinking days and 6.14 (SD = 3.67) drinks per drinking day in the 30 days

leading up to the baseline assessment. Past 12-month prevalence of AUD was as follows: 28.7% no AUD, 28.7% mild AUD, 27.83% moderate AUD, and 14.78% severe AUD. Presented in **Table 1** is a summary of our sample size, smoking outcomes, and drinking outcomes at baseline and throughout the trial, including the active medication phase (12 weeks) and follow-up phase (26 weeks), broken down by medication condition. While there was some attrition throughout the trial, the sample size based on the availability of complete data across medication groups remained relatively consistent throughout the trial, ending with 115 total participants at Week 26. Across the full trial, cigarettes per smoking day ranged from 2.77 – 4.46 for those in the varenicline + placebo, and 2.77 – 4.77 for those in the varenicline + naltrexone. The range for drinks per drinking day in the varenicline + placebo condition was 3.25 - 3.92 and in the varenicline + naltrexone condition was 2.85 – 3.14.

Cross-Lagged Panel Models

Primary Mediator: Drinks per Drinking Day (DPDD)

Fit indices indicated that this model had adequate fit: χ^2 (df=52) = 164.38, $p < .0001$; SRMR = .11; AGFI = .71; RMSEA [95% CI]: .08 [05, 11]. A summary of the paths in this cross-lagged panel model results for our primary mediator of drinks per drinking day is presented in **Table 2**. Reported herein are unstandardized coefficients. Results for the medication paths indicated there was no significant effect of medication on drinks per drinking day (*p's* $\geq$ .27) or cigarettes per smoking day (*p's* $\geq$ .19). The autoregressions indicated a significant positive effect of drinks per drinking day (*p's* < .001) and cigarettes per smoking day (*p's* < .001) on respective subsequent timepoints throughout the trial. The second-order autoregression of Week 4 regressed on Week 12 was also significant for drinks per drinking day ($b = .39$, $p = .05$), however not for cigarettes per smoking day ($b = .10$, $p = .08$). Baseline drinks per drinking day was a significant

predictor of drinks per drinking day at Week 4 (b = .23, p = .005), and baseline cigarettes per smoking day was a significant predictor of cigarettes per smoking day at Week 4 (b = .35, p = .006).

The cross-lagged associations between drinks per drinking day and cigarettes per smoking day were non-significant across each time point (p's $\geq$ .07). The fixed error covariances between drinks per drinking day and cigarettes per smoking day were estimated to be 1.44 and were significant across time (p < .01). The total effect of medication on cigarettes per smoking day at Week 12 was non-significant (b = .43, p = .66). At Week 26, the total effect of medication was also non-significant (b = .36, p = .65). Percentile bootstrap confidence intervals for the indirect effect of medication group on cigarettes per smoking day at Week 12 through the aggregated drinks per drinking day paths found no significant effect of the mediator (95% CI = [-1.03., .58]). The same pattern of results was observed at Week 26 (95% CI = [-.09, .51]).

Secondary Mediators: Percent Heavy Drinking Days (PHDD) and Percent Days Abstinent (PDA)

Fit indices indicated that this model had adequate fit: χ^2 (df=125) = 254.66, p < .0001; SRMR = .11; AGFI = .73; RMSEA [95% CI]: .07 [.05, .08]. A summary of paths in this cross-lagged panel model for percent heavy drinking days and percent day abstinent are presented in **Table 3**. There were no significant effects of medication on percent heavy drinking days (p's $\geq$ .40), percent days abstinent (p's $\geq$ .29), or cigarettes per smoking day (p's $\geq$ .19). Autoregressions revealed a significant positive effect of percent heavy drinking days (p's < .001), percent days abstinent (p's < .001), and cigarettes per smoking day (p's < .001) on their respective subsequent timepoints. Baseline percent heavy drinking days (b = .25, p < .01), percent days abstinent (b = .49, p < .0001), and cigarettes per smoking day (b = .35, p = .01)

predicted their respective subsequent variables at Week 4. Second-order autoregressions of Week 4 regressed on Week 12 were significant for percent heavy drinking days (b = .33, p = .001), however not significant for percent days abstinent (b = .02, p = .73) or cigarettes per smoking day (b = .11, p = .08).

The cross-lagged associations between percent heavy drinking days and percent days abstinent and cigarettes per smoking day were non-significant according to our a-priori cut-off (p's $\geq$ .02). The fixed error covariances between percent heavy drinking days and cigarettes per smoking day were estimated to be .09 and non-significant (p = .08). However, there were significant fixed error covariances between percent days abstinent and cigarettes per smoking day estimated to be -.08 (p = .01), and percent heavy drinking days and percent days abstinent estimated to be < -.01 ($p \leq$ .01). Results of percentile bootstrap confidence intervals of the indirect effect showed no significant effect of an indirect pathway of percent heavy drinking days and percent days abstinent at Week 12 (95% CI = [-.14, .35]) or Week 26 (95% CI = [-.15, .41]).

Results from models using all available data with FIML revealed a similar pattern of results across our primary and secondary mediators (see Supplemental Materials). When examining drinks per drinking day as the primary mediator, there was the addition of the second-order autoregressive path from Week 4 to Week 12 being significant (drinks per drinking day: b = .38; p < .0001; cigarettes per smoking day: b = .11; p = .01). In addition, for drinks per drinking day, the path from baseline to Week 4 no longer met our threshold for significance (b = .11; p = .03). Percentile bootstrapped confidence intervals for the indirect effects of our primary mediator drinks per drinking day remained non-significant at Week 12 (95% CI = [-.83, .60]) and Week 26 (95% CI = [-.06, .58]). Percentile bootstrapped confidence intervals for the indirect

effect of percent heavy drinking days and percent days abstinent also remained non-significant at Week 12 (95% CI = [-.11, .39]) and Week 26 (95% CI = [-.11, .44]).

Discussion

In a sample of treatment-seeking heavy drinking daily smokers enrolled in a smoking cessation and drinking reduction clinical trial, we examined the directional influence drinking and smoking variables have on each other over time. We hypothesized that smoking outcomes are influenced by pharmacotherapy through a sequence in which pharmacotherapy influences drinking behaviors, which then influences smoking behavior at a subsequent timepoint. We did not find a significant medication effect across our primary or secondary drinking outcomes. We did find consistent significant autoregression over time across all drinking variables, and cigarettes per smoking day. While each of our drinking and smoking variables were measured concurrently, the study design allowed us to examine the presence of cross-lagged associations. We did not find significant cross-lagged associations between our primary or secondary drinking variables and cigarettes per smoking day that met our a-priori alpha cutoff. There was no significant indirect effect of pharmacotherapy on cigarettes per smoking day through our primary or secondary drinking variables. These results indicate that while there was some degree of stability in our constructs over time, as indicated by the autoregressions, drinking variables did not explain the effect of pharmacotherapy on cigarettes per smoking day. Notably, these findings may be distinct from the primary trial in that only 115 individuals provided complete data and were therefore included in these mechanistic models.

This study is one of the first to examine concurrent and lagged smoking and drinking in the context of a combined smoking cessation and drinking reduction treatment. Other studies have shown that drinking episodes are associated with smoking lapses (Kahler et al., 2009;

Kahler et al., 2010), which provided initial support for our hypothesis that changes in drinking behavior could occur prior to changes in smoking behavior. Contrary to our hypothesis, the effect of drinking on smoking was not a pathway through which medication exerted its effect on smoking outcomes, nor was there a direct effect of medication condition on cigarettes per smoking day during the active medication phase. It may be that this phenomenon is observed in a smaller time scale than our study design allowed for us to test. Methods such as ecological momentary assessment (EMA) may be able to further understand the role of drinking in this context. Previous studies utilizing EMA have highlighted how alcohol can predict smoking after covarying for contextual factors such as time of day, location, and presence of other smokers (Piasecki, McCarthy, Fiore, & Baker, 2008), and how co-use is associated with greater urge to use both alcohol and cigarettes (Piasecki et al., 2011). Our results aligned broadly with these findings, as we found a significant fixed error covariances between drinking variables and cigarettes per smoking day at each time point. These results highlight the relationship between drinking and smoking within a single time period. The application of EMA methods to pharmacotherapy treatment studies may shed new lights on how these medications may disrupt alcohol, and subsequent smoking behaviors.

Given the context of our study with a focus on smoking cessation, and drinking reduction *or* cessation, it is possible that participants in our sample did not have a strong desire to substantially reduce their drinking given that the range of drinking throughout the trial was arguably limited. And that the addition of naltrexone on varenicline was not sufficient to promote the clinical level of drinking reduction that was required to observe a direct effect during the active medication phase, or an indirect effect on cigarettes per smoking day through drinking variables. Future studies may benefit from examining varying levels of drinking

reduction or cessation, as well as larger sample sizes, to further understand the sensitivity in the combination of varenicline plus naltrexone. A previous study by Anton and colleagues (2018) found naltrexone was more efficacious in reducing percent heavy drinking days among those who were smokers versus non-smokers. However, naltrexone did not exert a direct effect on smoking behavior itself (Anton et al., 2018). It is possible that naltrexone may still exhibit an added benefit for heavy drinking smokers, albeit in comparison to non-smoking heavy drinkers.

While approved for smoking cessation, varenicline has been shown to reduce alcohol consumption in heavy drinking smokers (McKee et al., 2009; Mitchell, Teague, Kayser, Bartlett, & Fields, 2012). However, there have been studies to suggest that varenicline does not reduce alcohol consumption (de Bejczy et al., 2015; Plebani et al., 2013). Pre-clinical research has shown the combination of varenicline and naltrexone to be more effective than low doses of either medication alone in reducing alcohol use in mice (Froehlich et al., 2016). Human laboratory research has also shown a benefit of combined varenicline and naltrexone reducing drinks per day and cigarettes per smoking day (Ray et al., 2014). A study comparing varenicline versus varenicline plus naltrexone on ability to resist smoking after completing an alcohol challenge did not find a benefit of the combined medication on delayed smoking (Roberts, Shi, Tetrault, & McKee, 2018). Our results add to the somewhat mixed literature on potential benefits of combined varenicline and naltrexone on smoking outcomes in the presence of alcohol. Mixed literature notwithstanding, our results do underscore the degree to which drinking and smoking behaviors fluctuate together over time as indexed by respective stability in drinking and smoking variables over time and error covariance between drinking and smoking variables.

The clinical implications of this study, based on our significant fixed error covariances, are that throughout the entire cessation attempt, the drinking patterns continue to predict smoking

patterns across the medication and follow-up periods. In other words, as individuals attempt to reduce their drinking, their smoking behavior at one time point continues to influence smoking at the next time point. In the context of treatment, there is evidence to support why it is feasible to address more than one substance at a time (Kalman, Kim, DiGirolamo, Smelson, & Ziedonis, 2010). An examination of barriers to smoking cessation among alcohol dependent patients made salient a concern that quitting smoking may increase urges to drink or use other substances to an overwhelming degree, or make it more difficult to stay sober during substance abuse treatment (Asher et al., 2003). These concerns are contradicted by studies showing that smoking cessation does not have a negative effect on substance use outcomes, rather it can often have a positive outcome (McKelvey, Thrul, & Ramo, 2017; Prochaska, Delucchi, & Hall, 2004). Specific to alcohol, smoking cessation does not offset abstinence from alcohol and may go as far as increasing the likelihood of maintaining alcohol abstinence (Gulliver, Kamholz, & Helstrom, 2006). A recent study supported these results showing that smoking cessation does not increase binge drinking among patients with serious mental illness (Hammett et al., 2019). In addition, individuals who are motivated to reduce their drinking during the smoking cessation attempt may be more vulnerable to the iatrogenic effects of alcohol on smoking. In other words, the clinical recommendation that individuals reduce their drinking during a quit attempt is well supported by these data as these two behaviors are still strongly related throughout a cessation attempt. Furthermore, independent of one another, we found use of each substance is predictive of future use respectively across 6-months. This calls attention to the potential benefit of reductions in either substance at any phase of a cessation attempt to exert a meaningful impact on successive use. However, even individuals who are actively addressing their drinking and receiving

pharmacotherapy for alcohol use are continuously affected by the bidirectional relationship between smoking and drinking.

The present study must be interpreted in light of strengths and limitations. Strengths include study design affording multiple assessments of drinking and smoking behaviors across a span of 6 months and within subjects. Additionally, the use of percentile bootstrap confidence intervals to assess the indirect effect in our mediation models as this approach has been shown to produce inferences that are more likely to be accurate than the normal theory approach (i.e. Sobel test) (Hayes, 2018). A noteworthy limitation is that while we did not have excess attrition throughout, reductions in our sample size across the trial may have reduced our power to detect more nuanced relationships, including mediated effects, among medication, drinking, and smoking outcomes.

In closing, the present study found drinking behaviors did not significantly mediate the effect of pharmacotherapy on smoking behaviors across the span of 6 months in a sample of heavy drinking smokers engaged in a treatment tailored to promote smoking cessation and drinking reduction. While the main results of the trial showed compelling quit rates and superiority of varenicline plus placebo, compared to varenicline plus naltrexone, the study adds to the importance of targeting smoking and drinking concomitantly. The main findings for the drinking outcome showed a modest superiority of varenicline plus naltrexone on reductions in drinks per drinking day, compared to varenicline plus placebo. Since the main trial (Ray et al., 2021) showed a complex picture with drinking and smoking results lacking alignment, it is perhaps unsurprising that drinking did not mediate medication effects on smoking. Nevertheless, smoking and drinking behaviors remained intertwined across the trial, primarily at the cross-sectional level of analysis. Among participants engaged in smoking cessation and drinking

reduction, our results generally confirmed the previous findings that smoking and drinking are intertwined and remain so throughout treatment. As such the concurrent use of alcohol and cigarettes remains a critical clinical target with the potential to result in dramatic improvements to health outcomes with successful smoking cessation and drinking reduction.

Table 1. Sample size, drinking, and smoking outcomes at baseline and throughout the clinical trial.

	Baseline	Week 4		Week 8		Week 12		Week 16		Week 26	
Medication Condition	---	VAR + PLC	VAR+ NTX	VAR + PLC	VAR+ NTX	VAR+ PLC	VAR+ NTX	VAR+ PLC	VAR+ NTX	VAR+ PLC	VAR+ NTX
N	165	74	68	72	60	65	57	65	55	63	52
Smoking Variables											
CPSD	14.16 (8.07)	4.46 (5.60)	3.40 (5.52)	3.30 (5.37)	2.77 (4.64)	2.77 (5.42)	2.92 (5.99)	2.78 (5.51)	3.45 (6.29)	2.97 (5.85)	4.77 (7.39)
Cigarette Abstinence (n)	---	40	35	41	31	44	32	35	27	37	20
Continued Smoking (n)	---	34	33	31	29	21	25	30	28	26	32
Drinking Variables											
DPDD	6.47 (4.22)	3.92 (3.00)	3.14 (2.46)	3.68 (2.87)	2.98 (2.43)	3.40 (3.00)	2.91 (2.72)	3.70 (3.03)	2.85 (2.67)	3.25 (3.31)	3.13 (3.48)
PHDD (%)	63 (33)	37 (35)	32 (36)	36 (37)	29 (37)	33 (37)	29 (37)	38 (37)	32 (39)	29 (36)	31 (41)
PDA (%)	33 (27)	66 (30)	70 (32)	69 (28)	72 (31)	70 (29)	72 (30)	68 (32)	68 (35)	68 (34)	70 (36)
Drink Days	20.18 (8.00)	9.47 (8.42)	7.88 (8.60)	8.64 (7.93)	7.63 (8.45)	8.31 (8.22)	7.81 (8.47)	9.08 (9.05)	8.84 (9.73)	7.86 (8.58)	7.38 (9.25)

Note: CPSD = Cigarettes per Smoking Day; DPDD = Drinks per Drinking Day; PHDD = Percent Heavy Drinking Day; PDA = Percent Days Abstinent. Means and standard deviation displayed in parentheses for each medication group unless otherwise noted. VAR + PLC = Varenicline + Placebo medication condition; VAR+NTX = Varenicline + Naltrexone medication condition. Abstinent from cigarettes defined as Carbon Monoxide (CO) reading < 5 ppm.

Table 2. Summary of Path Estimates for Drinks per Drinking Day (DPDD)

	Medication Effects				Autoregressions				Cross-Lagged Effects		
Path	*b*	SE	*p*	Path	*b*	SE	*p*	Path	*b*	SE	*p*
Med → DPDD4	-.51	.46	.27	DPDD0 → DPDD4	.23	.08	**<.01**	DPDD4 → CPSD8	-.13	.11	.23
Med → DPDD8	-.22	.36	.53	DPDD4 → DPDD8	.61[a]	.08	**<.0001**	DPDD8 → CPSD12	-.13	.07	.07
Med → DPDD12	.13	.38	.73	DPDD4 → DPDD12	.39	.20	.05	DPDD12 → CPSD16	-.02	.07	.74
Med → CPSD4	-.81	.97	.40	DPDD8 → DPDD12	.61[a]	.08	**<.0001**	DPDD16 → CPSD26	-.01	.10	.93
Med → CPSD8	.42	.48	.38	DPDD12 → DPDD16	.61[a]	.08	**<.0001**	CPSD4 → DPDD8	.04	.03	.29
Med → CPSD12	.62	.47	.19	DPDD16 → DPDD26	.72	.14	**<.0001**	CPSD8 → DPDD12	-.03	.03	.38
				CPSD0 → CPSD4	.35	.12	**<.01**	CPSD12 → DPDD16	.02	.02	.46
				CPSD4 → CPSD8	.87[b]	.05	**<.0001**	CPSD16 → DPDD26	.03	.04	.50
				CPSD4 → CPSD12	.10	.06	.08				
				CPSD8 → CPSD12	.87[b]	.05	**<.0001**				
				CPSD12 → CPSD16	.87[b]	.05	**<.0001**				
				CPSD16 → CPSD26	.96	.05	**<.0001**				

Note: *b* = unstandardized coefficient estimates; SE = standard error; DPDD = drinks per drinking day; CPSD = cigarettes per smoking day. '0' indicates baseline. Significant effects defined at a-priori threshold of $p < .0125$ in bold.

[a] indicates a fixed parameter for the autoregressions of DPDD.

[b] indicates a fixed parameter for the autoregressions of CPSD.

Table 3. Summary of Path Estimates for Percent Heavy Drinking Days (PHDD) and Percent Days Abstinent (PDA)

	Medication Effects				Autoregressions				Cross-Lagged Effects		
Path	*b*	SE	*p*	Path	*b*	SE	*p*	Path	*b*	SE	*p*
Med → PHDD4	-.02	.06	.72	PHDD0 → PHDD4	.25	.09	**<.01**	PHDD4 → CPSD8	.13	.82	.88
Med → PHDD8	-.05	.06	.40	PHDD4 → PHDD8	.55[a]	.06	**<.0001**	PHDD8 → CPSD12	-1.31	.55	.02
Med → PHDD12	.02	.05	.75	PHDD4 → PHDD12	.33	.10	**.001**	PHDD12 → CPSD16	.21	.61	.73
Med → PDA4	.04	.05	.44	PHDD8 → PHDD12	.55[a]	.06	**<.0001**	PHDD16 → CPSD26	-.51	.96	.60
Med → PDA8	-.01	.02	.61	PHDD12 → PHDD16	.55[a]	.06	**<.0001**	PDA4 → CPSD8	.01	.81	.99
Med → PDA12	-.03	.03	.29	PHDD16 → PHDD26	.59	.10	**<.0001**	PDA8 → CPSD12	-.52	.46	.26
Med → CPSD4	-.81	.97	.40	PDA0 → PDA4	.49	.09	**<.0001**	PDA12 → CPSD16	.29	.80	.72
Med → CPSD8	.49	.46	.29	PDA4 → PDA8	.88[b]	.03	**<.0001**	PDA16 → CPSD26	-.18	1.00	.85
Med → CPSD12	.62	.47	.19	PDA4 → PDA12	.02	.06	.73	CPSD4 → PHDD8	.01	<.01	.20
				PDA8 → PDA12	.88[b]	.03	**<.0001**	CPSD8 → PHDD12	<.01	<.01	.23
				PDA12 → PDA16	.88[b]	.03	**<.0001**	CPSD12 → PHDD16	<.01	<.01	.40
				PDA16 → PDA26	.88	.06	**<.0001**	CPSD16 → PHDD26	<.01	<.01	.39
				CPSD0 → CPSD4	.35	.13	**.01**	CPSD4 → PDA8	<-.01	<.01	.03
				CPSD4 → CPSD8	.85[c]	.05	**<.0001**	CPSD8 → PDA12	<.01	<.01	.89
				CPSD4 → CPSD12	.11	.06	.08	CPSD12 → PDA16	<-.01	<.01	.09
				CPSD8 → CPSD12	.85[c]	.05	**<.0001**	CPSD16 → PDA26	<.01	<.01	.88
				CPSD12 → CPSD16	.85[c]	.05	**<.0001**				
				CPSD16 → CPSD26	.96	.05	**<.0001**				

Note: *b* = unstandardized coefficient estimates; SE = standard error; PHDD = percent heavy drinking days; PDA = percent days abstinent; CPSD = cigarettes per smoking day. '0' indicates baseline. Significant effects defined at a-priori threshold of $p < .0125$ in bold.

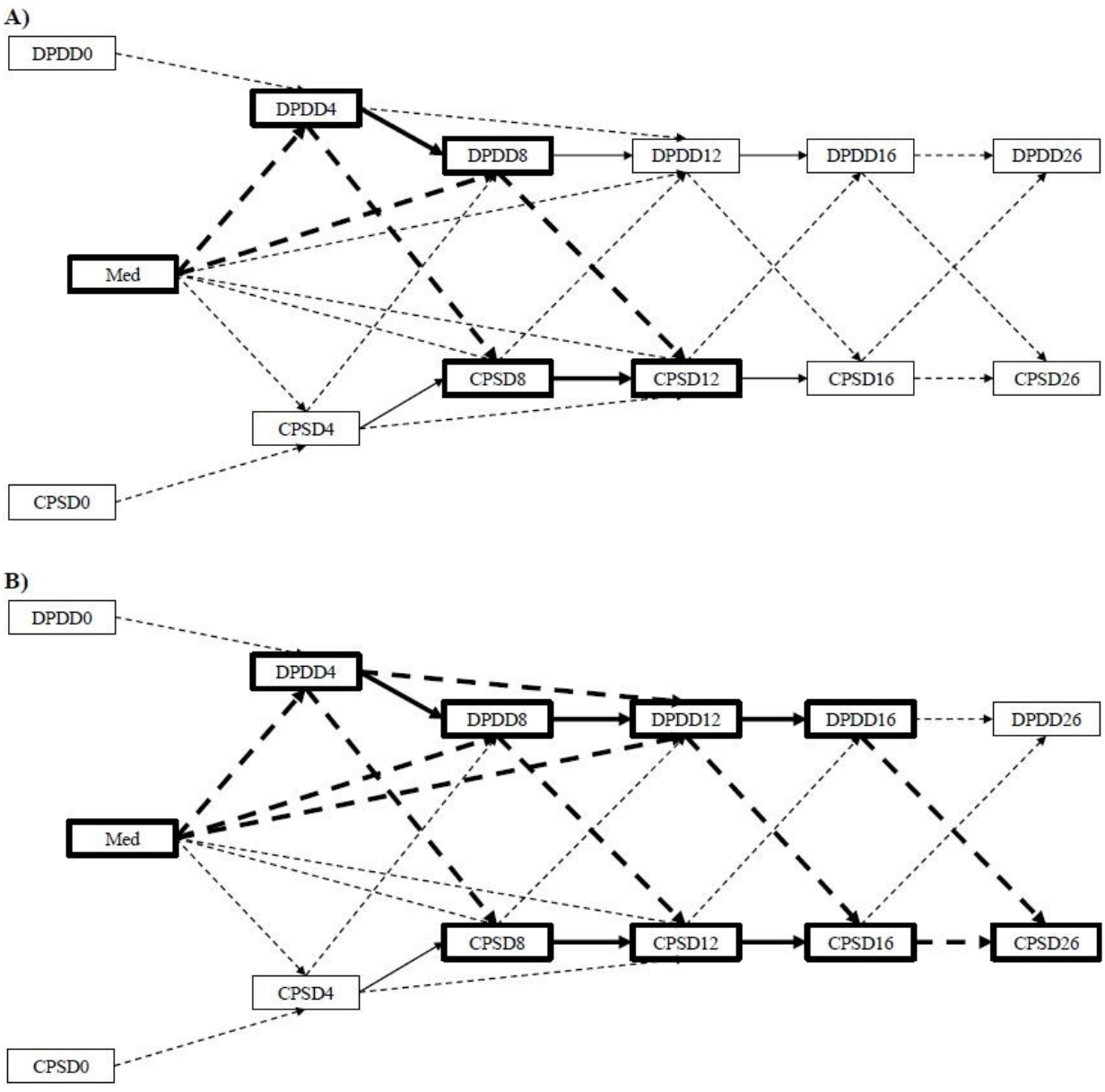
[a] indicates a fixed parameter for the autoregressions of PHDD.

[b] indicates a fixed parameter for the autoregressions of PDA.

[c] indicates a fixed parameter for the autoregressions of CPSD.

Figure 1.

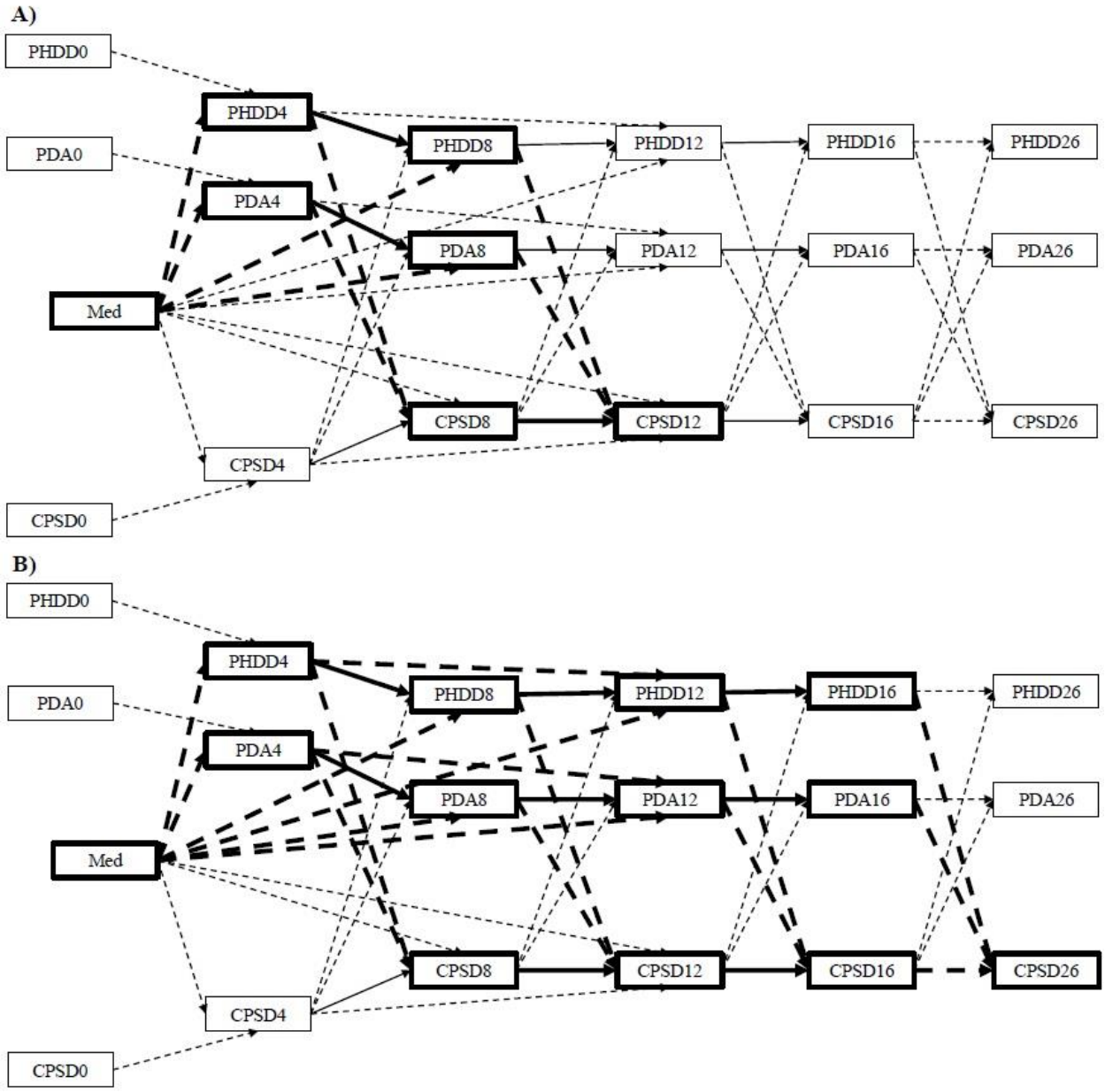
Conceptual Diagram for Drinks per Drinking Day (DPDD)



Note: A conceptual diagram for cross-lagged panel models to examine whether Drinks per Drinking Day (DPDD) mediates the effect of medication on Cigarettes per Smoking Day (CPSD). In bold are paths for indirect effects tested at week 12 (a) and week 26 (b). Fixed error covariances specified between DPDD and CPSD at each time point. Free error variances were specified for each variable.

Figure 2

Conceptual Diagram for Percent Heavy Drinking Days (PHDD) and Percent Days Abstinent (PDA)



Note: A conceptual diagram for cross-lagged panel models to examine whether Percent Heavy Drinking Days (PHDD) and Percent Days Abstinent (PDA) mediates the effect of medication on Cigarettes per Smoking Day (CPSD). In bold are paths for indirect effects tested at week 12 (a) and week 26 (b). Three sets of fixed error covariances were specified between PHDD and CPSD, PDA and CPSD, and PHDD and PDA at each time point. Free error variances were specified for each variable.

Discussion

The dissertation project examined both etiology and treatment of the unique subgroup of heavy drinking smokers. Etiology of heavy drinking smokers was examined from a behavioral economics framework (see Chapter 1) as one way in which to demonstrate the bidirectional nature of co-use, as well as nuanced complexities in the ways these substances exert cross-substance effects (e.g., how alcohol use predicts demand for cigarettes and vice versa). The results made salient how behavioral economic indices may be sensitive to cross-substance relationships. They also further explained the bidirectional relationship between cigarettes and alcohol, showing that such relationships are asymmetrically stronger for smoking variables affecting alcohol demand, not the other way around.

Treatment was examined through Chapter 2 (sex hormones) and Chapter 3 (relationship between drinking and smoking), utilizing data drawn from the RCT described above. The translation of basic science and experimental pharmacology findings to clinical samples is imperative to elucidate our understanding the role of relevant biological variables such as sex hormones, and to further understand the mechanisms of action underlying pharmacological treatment response on clinical outcomes. Recent findings implicating menstrual cycle phase with smoking behavior and clinical responses to naltrexone have emerged from experimental pharmacology studies. However, these results have not been consistently extended to clinical trials. While our results did not show an effect of the ratio of P4/E2 on smoking outcomes, we did observe an effect of P4/E2 ratio on the drinking outcome of percent days abstinent. These findings are important as they underscore how sex hormones offer important information above and beyond comparing groups on the bases of sex. For Chapter 3, while our results did not reveal drinking outcomes to mediate the relationship between medication condition and smoking

outcomes, we did see a consistent pattern throughout active medication phase, and follow-up, where greater drinking and smoking is consistently associated with greater use of the respective substances. These findings call attention to how the relationship between drinking and smoking can be maintained throughout a 6-month clinical trial and furthers the need for the development of treatment options that can target *both* alcohol and cigarette use in heavy drinking smokers.

Together, these studies use a translation framework that combines pharmacology, experimental psychology, and biomarkers of sex differences in order to address the clinical implications of the co-use of alcohol and cigarettes. These studies advance a precision medicine approach whereby the complimentary between smoking and drinking can be clinically targeted. These studies position the candidate to have a unique and impactful program of research drawing from experimental psychopharmacology, sex differences, advanced data analytic methods, and a patient-centered clinical framework.

Appendix

Appendix A: Chapter 1 – Alcohol Purchase Task (APT)

Appendix B: Chapter 1 – Cigarette Purchase Task (CPT)

Appendix A: Chapter 1 - Alcohol Purchase Task (APT)

APT

Please respond to these questions honestly, as if you were actually in this situation.

Imagine that you are drinking in a TYPICAL SITUATION when you drink. The following questions ask how many drinks you would consume if they cost various amounts of money. The available drinks are standard size domestic beer (12 oz.), wine (5 oz.), shots of hard liquor (1.5 oz.), or mixed drinks containing one shot of liquor. Assume that you did not drink alcohol before you are making these decisions, and will not have an opportunity to drink elsewhere after making these stockpile drinks for a later date or bring drinks home with you.

How many drinks would you consume if they were FREE? _____

How many drinks would you consume if they were 1¢ each? _____

How many drinks would you consume if they were 5¢ each? _____

How many drinks would you consume if they were 13¢ each? _____

How many drinks would you consume if they were 25¢ each? _____

How many drinks would you consume if they were 50¢ each? _____

How many drinks would you consume if they were $1 each? _____

How many drinks would you consume if they were $3 each? _____

How many drinks would you consume if they were $6 each? _____

How many drinks would you consume if they were $11 each? _____

How many drinks would you consume if they were $35 each? _____

How many drinks would you consume if they were $70 each? _____

How many drinks would you consume if they were $140 each? _____

How many drinks would you consume if they were $280 each? _____

How many drinks would you consume if they were $560 each? _____

How many drinks would you consume if they were $1120 each? _____

Appendix B: Chapter 1 - Cigarette Purchase Task (CPT)

CPT

Imagine a TYPICAL DAY during which you smoke. **How many cigarettes would you smoke at the following prices?** The available cigarettes are your favorite brand. Assume that you have the same income/savings that you have now, and NO ACCESS to any cigarettes or nicotine products other than those offered at these prices. In addition, assume that you could would consume cigarettes that you request on that day; that is, you cannot save or stockpile cigarettes for a later date.

1. How many cigarettes would you smoke if they were	FREE?	[$0 per pack]	_____
2. How many cigarettes would you smoke if they were	5¢ each?	[$1 per pack]	_____
3. How many cigarettes would you smoke if they were	10¢ each?	[$2 per pack]	_____
4. How many cigarettes would you smoke if they were	15¢ each?	[$3 per pack]	_____
5. How many cigarettes would you smoke if they were	20¢ each?	[$4 per pack]	_____
6. How many cigarettes would you smoke if they were	25¢ each?	[$5 per pack]	_____
7. How many cigarettes would you smoke if they were	30¢ each?	[$6 per pack]	_____
8. How many cigarettes would you smoke if they were	35¢ each?	[$7 per pack]	_____
9. How many cigarettes would you smoke if they were	40¢ each?	[$8 per pack]	_____
10. How many cigarettes would you smoke if they were	45¢ each?	[$9 per pack]	_____
11. How many cigarettes would you smoke if they were	50¢ each?	[$10 per pack]	_____
12. How many cigarettes would you smoke if they were	60¢ each?	[$12 per pack]	_____
13. How many cigarettes would you smoke if they were	70¢ each?	[$14 per pack]	_____
14. How many cigarettes would you smoke if they were	80¢ each?	[$16 per pack]	_____
15. How many cigarettes would you smoke if they were	90¢ each?	[$18 per pack]	_____
16. How many cigarettes would you smoke if they were	$1.00 each?	[$20 per pack]	_____
17. How many cigarettes would you smoke if they were	$1.20 each?	[$24 per pack]	_____
18. How many cigarettes would you smoke if they were	$1.40 each?	[$28 per pack]	_____
19. How many cigarettes would you smoke if they were	$1.60 each?	[$32 per pack]	_____

20. How many cigarettes would you smoke if they were	$1.80 each?	[$36 per pack]	_____
21. How many cigarettes would you smoke if they were	$2.00 each?	[$40 per pack]	_____
22. How many cigarettes would you smoke if they were	$4.00 each?	[$80 per pack]	_____
23. How many cigarettes would you smoke if they were	$6.00 each?	[$120 per pack]	_____
24. How many cigarettes would you smoke if they were	$8.00 each?	[$160 per pack]	_____
25. How many cigarettes would you smoke if they were	$10.00 each?	[$200 per pack]	_____

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