THE IMPACT OF SNUS AND ETHANOL ON CIGARETTE CRAVING AND CONSUMPTION

by

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Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy

at

Dalhousie University
Halifax, Nova Scotia
December 2018

DEDICATION PAGE

I dedicate this dissertation to my partner Danielle. I was going to dedicate this to our son Kit, but it was you who put with all the uncertainty and delay of gratification alongside of me while writing this dissertation. None of this would have happened without your unending support and belief in me.

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ABSTRACT

This dissertation examines the extent to which Swedish snus, a moist oral tobacco product, impacts the effect of alcohol consumption on cigarette smoking and craving. Alcohol-induced cigarette craving has been noted through anecdotal self-report by smokers who drink and also robustly demonstrated in lab-based studies, yet the mechanism by which this occurs is unknown and contested in the literature. Experimental confounds need to be controlled as thoroughly as possible to study the alcohol-tobacco co-use phenomenon. Swedish snus allows experimenters to administer a tobacco product to North American participants without activating the expectancies associated with other smoking devices or tobacco products. As well, snus is pasteurized instead of burnt, meaning that any effects snus has on alcohol-induced cigarette craving and consumption can be attributed to those tobacco factors, including nicotine, found within tobacco, and not the additional compounds present within cigarette smoke.

Three lab-based studies were conducted utilizing double-blind procedures. In the first two of them, only dependent smokers who drank alcohol were recruited. In the third, both dependent and non-dependent smokers who also drank were recruited. The studies examined the effect snus had on cigarette administration and craving when preceded by alcohol administration (Studies 1 and 3) or followed by it (Study 2). In Study 1, snus reduced the number of cigarette puffs and how hard dependent smokers worked for additional puffs when snus was administered before a one-hour progressive ratio (PR) task (Barrett, 2010); this was true regardless of alcohol consumption. Neither alcohol nor snus influenced cigarette craving before the PR task. In Study 2, snus administration preceded alcohol administration, followed by the PR task. Snus increased the latency to start smoking, whereas alcohol increased efforts to earn puffs. Study 3 was designed similarly to Study 1, with a more extended tobacco abstinence period and a smaller dose of snus, but with both dependent and non-dependent smokers. In Study 3 snus reduced dependent smokers' puffs and how hard they worked to earn additional puffs similar to Study 1, but snus did not affect non-dependent smokers' cigarette craving or smoking behavior. Alcohol increased cigarette craving and latency to start smoking only with non-dependent smokers.

The results of these studies show that snus reduces cigarette consumption regardless of alcohol or placebo beverage consumption in tobacco-dependent smokers. The findings also suggest that chemicals found in non-pyrolyzed tobacco, including nicotine, can satiate tobacco consumption in dependent smokers. This relationship appears to be different for non-dependent smokers who may be motivated to consume tobacco for different pharmacological or psychological reasons including different cigarette specific expectations, or non-pharmacological sensory-motor properties of smoking.

LIST OF ABBREVIATIONS USED

alcohol dehydrogenase (ADH)

aldehyde dehydrogenase (ALDH2)

blood alcohol concentration (BAC)

Brief Biphasic Alcohol Effects Scale (B-BAES)

carbon monoxide (CO)

cyclic adenosine monophosphate (cAMP)

daily dependent smokers (DDS)

Ecological Momentary Assessment (EMA)

Fagerström Test for Cigarette Dependence (FTCD)

Fagerström Test for Nicotine Dependence (FTND)

γ- aminobutyric acid (GABA)

γ- aminobutyric acid A ($GABA_A$)

hypothalamic-pituitary-adrenal (HPA)

nicotinic cholinergic receptor (nAChR)

nucleus accumbens (NAc)

N-methyl-D-aspartate (NMDA)

non-daily non-dependent smokers (NNS)

Short version of the Michigan Alcoholism Screening Test (SMAST)

monoamine oxidase (MAO)

nicotine replacement therapy (NRT)

parts per million (ppm)

progressive ratio (PR)

Questionnaire of Smoking Urges-Brief (QSU-B)

randomized control trials (RCTs)

serotonin - 5-hydroxytryptamine-3 (5-HT3)

single nucleotide polymorphisms (SNP)

Subjective Rating Scale (SRS)

tobacco-specific nitrosamines (TSNAs)

ventral tegmental area (VTA)

ACKNOWLEDGEMENTS

I would like to acknowledge first and foremost Dr. Sean Barrett for taking me on as graduate student and trusting me to conduct research with the two most deadly drugs in our society, alcohol and tobacco.

I want to thank my committee members Drs. Sherry Stewart, Kim Good, as well as my former committee member Dr. Natalie Rosen for the many suggestions and comments in both the analysis and writing of this research.

I would also like to express gratitude to all the research assistants on these projects including Ari Franklin, Karen Hecimovic, Joel Sardina, Parisa Asadnejad, Tehmina(Annie) Haider, and Ekaterina Reymarova for assisting with running participants and making this research possible, as well to Dr. Hera Schlagintweit for her support both in and out of the lab.

Finally, I would like to thank Grammarly, Mendeley, and Dr. Sean Roach for helping me organize my thoughts and grammar.

CHAPTER 1: INTRODUCTION

ALCOHOL-TOBACCO CO-USE PHENOMENON

Excluding caffeine, alcohol and tobacco are the most frequently used psychoactive substances in Canada (Canadian Centre on Substance Abuse [CCSA], 2005; Health Canada, 2013a). The Canadian Addiction Survey, conducted by the CCSA in 2004, found that 79.3% of all Canadians 15 years of age and older reported alcohol use in the past year; 14% of Canadians were former drinkers and present abstainers, while only 7% were lifetime alcohol abstainers (CCSA, 2005). Health Canada's more recent Canadian Tobacco Use Monitoring Survey found that 16% of Canadians were current tobacco smokers (12% daily and 4% non-daily smokers), with an additional 28% of Canadians reporting lifetime smoking (Health Canada, 2013a).

Because alcohol and tobacco have different psychopharmacological properties and different methods of consumption, they are often studied separately. However, there are many reasons to study these substances in combination. For example, these substances are commonly co-administered (Falk, Yi, & Hiller-Sturmhöfel, 2006). Although there are no formal Canadian statistics examining what percentages of drinkers smoke or smokers drink, American statistics indicate that 78.3% of smokers also consume alcohol and 33.2% of drinkers also smoke (Falk et al., 2006). When smokers drink, they typically consume tobacco (Einstein, Hughes, & Hindmarch, 1975; Falk et al., 2006; Harrison, Hinson, & McKee, 2009; Jackson, Colby, & Sher, 2010; Piasecki et al., 2011; Witkiewitz et al., 2012). In fact, alcohol use is a common reason for relapse to smoking among those attempting to discontinue smoking (Cooney, Cooney, Pilkey,

Kranzler, & Oncken, 2003; Falk et al., 2006; Leeman et al., 2008; McKee, Krishnan-Sarin, Shi, Mase, & O'Malley, 2006). There is experimental evidence that alcohol increases tobacco use (e.g., Burton & Tiffany, 1997; Glautier, Clements, White, Taylor, & Stolerman, 1996; McKee, Harrison, & Shi, 2010; McKee et al., 2006; Mello, Mendelson, & Palmieri, 1987; Mello, Mendelson, Sellers, & Kuehnle, 1980; Mintz et al., 1985). However, not all experimental studies have found this alcohol effect (e.g., Peloquin et al., 2013; Perkins et al., 2005; Rose et al., 2004). Similarly, there are studies demonstrating that tobacco consumption can either increase or decrease (Acheson, Mahler, Chi, & de Wit, 2006; Barrett, Tichauer, Leyton, & Pihl, 2006; Dermody & Hendershot, 2017) subsequent alcohol use. The fact that we do not yet have a clear understanding of this phenomenon is problematic, especially given the lethality of both alcohol and tobacco. As of 2002, 16.64% of all deaths in Canada were attributable to tobacco use, and 4.07% were related to alcohol use (Patra, Taylor, Rehm, Baliunas, & Popova, 2007). A 30-year cohort study of Scottish men demonstrated that male smokers who also drank 15+ units of alcohol a week were 3.5 times more likely to have died by 65 than never smokers who drank 0-14 units of alcohol weekly (Hart, Davey Smith, Gruer, & Watt, 2010). Without a clear understanding of the functional characteristics of the alcohol-tobacco co-use phenomenon, clinical interventions to reduce alcohol-induced tobacco use have no guiding principles to follow beyond suggesting that tobacco users also abstain from alcohol when quitting tobacco (Kalman, Kahler, Garvey, & Monti, 2006).

Since alcohol and tobacco consumption influence each other, the alcohol-tobacco relationship is best understood as a unique construct. Studying either alcohol or tobacco

in isolation cannot contribute to our understanding of the co-use phenomenon (Sobell, Sobell, Kozlowski, & Toneatto, 1990).

ALCOHOL INCREASING TOBACCO USE HYPOTHESES

The most agreed upon, although contested, aspect of the alcohol-tobacco co-use phenomenon is that alcohol increases subsequent tobacco use. What is presently debated in the literature is how alcohol increases tobacco use. The underlying mechanism to explain this relationship remains controversial. Multiple studies have demonstrated this phenomenon experimentally in the lab (Burton & Tiffany, 1997; Glautier, Clements, White, Taylor, & Stolerman, 1996; McKee, Harrison, & Shi, 2010; McKee et al., 2006; Mello, Mendelson, & Palmieri, 1987; Mello, Mendelson, Sellers, & Kuehnle, 1980; Mintz et al., 1985) and retrospectively (Dierker et al., 2006; Nichter, 2006). More recently, ecological momentary assessment (EMA) methods, protocols where smokers report their behaviour and cigarette craving throughout the day, have also been used to examine alcohol and tobacco co-use in people's daily lives (Batel, Pessione, Maître, & Rueff, 1995; Falk et al., 2006; Jackson et al., 2010; Jackson, Sher, & Cooper, 2002; Piasecki et al., 2011; Piasecki, Wood, Shiffman, Sher, & Heath, 2012; Sher, Gotham, Erickson, & Wood, 1996; Shiffman et al., 2014). However, Dermody and Hendershot's (2017) critical review of the alcohol-tobacco/nicotine experimental co-administration research highlighted that not every study has reliably found alcohol to increase tobacco use. The authors attribute this variability to the different methodologies utilized across experiments addressing different nuanced effects of alcohol on future tobacco and nicotine use. The limitations of the existing studies will be discussed later in this dissertation.

With methods and results varying between studies, there is no definitive explanation of why alcohol increases tobacco use. One hypothesis is that alcohol increases tobacco craving or urge to smoke, which increases tobacco consumption. Numerous co-administration studies have found alcohol-induced increases in tobacco craving (e.g., Burton & Tiffany, 1997; Epstein, Sher, Young, & King, 2007; Field, Mogg, & Bradley, 2005; King & Epstein, 2005; King, McNamara, Angstadt, & Phan, 2010; King, Epstein, Conrad, McNamara, & Cao, 2008; King, McNamara, Conrad, & Cao, 2009; Oliver et al., 2013; Sayette, Martin, Wertz, Perrott, & Peters, 2005). The alcohol-induced increase in tobacco craving before tobacco consumption may reflect an increase in "liking" of and enjoyment of cigarette puffs while drinking (e.g., Rose et al., 2004). The alcohol-induced increase in tobacco consumption could also reflect either that tobacco reduces the sedative effects of alcohol, or that alcohol reduces tobacco satiation (Oliver et al., 2013). Another theory is that alcohol increases the consumer's expectancy of tobacco's sought-after pharmacological effects (Field et al., 2005; Kirchner & Sayette, 2007). However, when subjects consume a placebo alcohol beverage, the expectation of a pharmacological effect of alcohol also causes a subjective increase in craving and subsequent tobacco consumption to occur (Erblich et al., 2009; Kahler et al., 2012; McKee et al., 2010; Niaura et al., 1988).

Other alcohol-tobacco co-use theories include the theory that alcohol leads to "myopia"– that is, it selectively interferes with decision-making – causing people to smoke more when they drink because of a decline in the conscious ability to limit their smoking behavior (Steele & Josephs, 1990). As well, a substantial body of research supports that alcohol increases reactivity to cues associated with smoking opportunities.

These smoking cues act as conditioned cues due to frequent pairing of alcohol with smoking. These cues become reinforcing on their own later and are known as secondary reinforcers. Serving alcohol to a smoker often signals a present smoking opportunity. Since alcohol forecasts a smoking opportunity, alcohol can become a conditioned secondary reinforcer to the chemicals consumed during cigarette consumption (Drobes, 2002; Duka & Townshend, 2004; Field et al., 2005; McGrath, Peloquin, Ferdinand, & Barrett, 2015; Peloquin, McGrath, Telbis, & Barrett, 2014; Sayette et al., 2005; Shiffman et al., 2013). However, EMA studies demonstrate that although alcohol does increase cigarette craving, real-world craving including consumption or proximity to alcohol does not adequately predict tobacco use (Piasecki et al., 2011; Shiffman et al., 2014, 2015).

SUMMARY OF ALCOHOL-TOBACCO CO-USE HYPOTHESES

Throughout many studies of the alcohol-tobacco use relationship, the predominant finding is that alcohol increases tobacco use in most lab-based situations. Although this does not predict all alcohol-related smoking behavior, alcohol appears to increase cigarette craving in all but a few studies. These studies have utilized many different methodologies. Moreover, there are numerous hypotheses as to *why* alcohol increases cigarette craving each of which suggests specific intervention strategies. For example, if alcohol does increase tobacco cue salience, then quitting smokers should understand that watching others smoke while they are drinking will make quitting more difficult. On the other hand, if alcohol pharmacologically reduces the satiating effects of the chemicals within tobacco smoke that smokers are dependent upon (primarily nicotine), then supplementing smokers who are trying to quit with these critical tobacco chemical factors

(e.g., using nicotine replacements) when drinking may decrease their desire to smoke more while drinking.

Experimentation with human participants has yet to fully elucidate the alcohol-tobacco co-use phenomenon in lab-based studies. Understanding the neurobiological mechanisms of alcohol and tobacco may delineate how alcohol-induced cigarette craving and consumption occurs. The following section will review the neurobiological literature of both alcohol and tobacco pharmacological mechanisms. The purpose of this review is to help determine what unique pharmacological interactions, not detectable by lab-based alcohol-tobacco co-use or observational studies with research participants, influence tobacco craving and consumption.

NEUROBIOLOGICAL CONSIDERATIONS

Numerous neurobiological theories have been put forward to explain the alcohol-tobacco use phenomenon (Booker & Collins, 1997; Cardoso et al., 1999; Chatterjee et al., 2010; Correa et al., 2011; Davis & De Fiebre, 2006; Ericson, Löf, Stomberg, & Söderpalm, 2009; Funk, Marinelli, Le, & Lê, 2006; Kalman, 1998; Kalman, Morissette, & George, 2012; King et al., 2010; Kouri et al., 2004; Larsson, Edström, Svensson, Söderpalm, & Engel, 2005; Leeman et al., 2007; Li, Volkow, Baler, & Egli, 2007; Marszalec, Aistrup, & Narahashi, 1999; Mascia et al., 2001; McKee & Weinberger, 2013; Narahashi et al., 2001; Oliver et al., 2013; Rose et al., 2004; Sobell, Sobell, & Agrawal, 2002; Söderpalm, Ericson, Olausson, Blomqvist, & Engel, 2000; Vengeliene, Bilbao, Molander, & Spanagel, 2008; Zacny, 1989). Theories that focus on the shared neurological systems upon which both alcohol and tobacco act are essential to understanding the alcohol-tobacco co-use phenomenon. There is evidence that alcohol

can activate (Davis & De Fiebre, 2006; Narahashi et al., 2001) and cause long-term changes to nicotinic cholinergic receptors (nAChRs) (Davis & De Fiebre, 2006), which are the principal receptors that nicotine is known to activate. Nicotine, considered the primary alkaloid responsible for tobacco use (Balfour, 2009; Benowitz, 2010; Markou, 2008; Stolerman & Jarvis, 1995), is a nicotinic cholinergic receptor (nAChR) agonist that opens ligand-gated ion channels customarily activated by acetylcholine throughout the body. Different expressions of the α and β subunits of these receptors affect their reactivity when exposed to nicotine (Mineur & Picciotto, 2008). Receptor subtypes are determined by an individual's genes (Schlaepfer, Hoft, & Ehringer, 2008; Swan et al., 2006), which suggests a genetic contribution to why certain individuals have more difficulty reducing their smoking behavior than others. Specifically, the $\alpha_4\beta_2$ and α_7 subtypes of nAChRs found in the brain are thought to play an essential role in the development of nicotine dependence, with the $\alpha_4\beta_2$ subtype having a higher affinity for nicotine than the α_7 subtype. Ethanol – ethyl alcohol – is the primary psychoactive chemical found in all alcoholic beverages, and is known to bind to a wide range of neuronal receptor targets. These receptors include N-methyl-D-aspartate (NMDA), γ-aminobutyric acid A ($GABA_A$), glycine, 5-hydroxytryptamine(serotonin)-3 (5-HT3), L-type Ca^{2+} channels, and G protein-activated inwardly rectifying K^+ channels, as well as nAChRs (Vengeliene et al., 2008). One study by Marszalec, Aistrup, and Narahashi (1999) found that alcohol interferes with nicotine's desensitization of the $\alpha_4\beta_2$ subtypes of nAChRs. Usually, after a nicotine molecule activates an nAChR, it becomes temporarily inactivated via desensitization, the process by which cells regulate and adapt to higher levels of nicotine in nicotine-dependent individuals. Alcohol reduces the extent to which

nicotine desensitizes neurons with $\alpha_4\beta_2$ nAChR subunits, making it easier for such cells to fire and causing alterations in the nicotine-induced signaling process. Altering how cells with nAChRs function may be a factor in motivating alcohol and nicotine co-use (Narahashi et al., 2001). Ethanol influences the nicotinic receptor systems through more than one receptor subtype, also inhibiting the α_7 subtype of nAChR, which plays a role in context learning (Rollema et al., 2007) and modulates the neurotoxic effect of alcohol withdrawal (Mulholland et al., 2003).

Another prominent neurobiological theory of the alcohol-tobacco co-use phenomenon is that both alcohol and tobacco share underlying reinforcement systems (Schlaepfer et al., 2008). nAChRs exist throughout the brain, and nicotine administration causes a release of dopamine in the mesolimbic area, the corpus striatum, and the frontal cortex – regions of the brain that are involved in drug-induced reward and addictive behaviors (Balfour, Wright, Benwell, & Birrell, 2000). As well, nicotine potentiates glutamate release, which in turn causes dopaminergic cells in the ventral tegmental area (VTA) to fire and release dopamine (Markou, 2008). This increased glutamatergic release causes a reduction in GABA-mediated inhibitory tone while also causing an increase in the responsiveness of dopaminergic neurons in the region. In turn, the amount of dopamine released from their terminal buttons in the nucleus accumbens (NAc) within the striatum increases. The greater level of dopamine in ventral striatal regions reduces the threshold for reward stimulation and appears to increase responsiveness to rewards in general (Chaudhri et al., 2006). This lowered threshold for reward stimulation and increased responsiveness (Clark, Lindgren, Brooks, Watson, & Little, 2001) is believed to play a role in nicotine dependence formation.

Ethanol's most salient pharmacological mechanisms related to reward and reinforcement are best understood from the perspective of ethanol as a $GABA_A$ receptor agonist (Kumar et al., 2009). Activation of $GABA_A$ receptor-containing neurons within the NAc can influence both the dopaminergic system and the endogenous opioid system (Spanagel, 2009). $GABA_A$ receptors are chloride ion channels which, when activated, hyperpolarize neurons, leading to neuronal inhibition (Kumar et al., 2009). The stimulant effects of ethanol when blood alcohol concentration (BAC) levels rise are believed to be due to the inhibition of the GABAergic feedback system located in the NAc. Disinhibition of interneurons projecting to dopaminergic neurons in the VTA increases the release of dopamine in the NAc (Boileau et al., 2003; Ramchandani et al., 2011; Schreckenberger et al., 2004). Ethanol administration has also been shown to stimulate the release of endorphins. Endorphins, which are endogenous opioid receptor agonists, are released into the NAc through an independent mechanism when consuming alcohol. Alcohol once more increases dopamine levels while simultaneously increasing endogenous opioid levels in the NAc. Researchers believe that opioids are released because opioid receptor antagonists are known to inhibit the reinforcing effects of ethanol by indirectly reducing the levels of dopamine in the NAc (Rösner et al., 2010). At present, how alcohol releases opioids is not fully understood (for a review of proposed systems involved in dopamine release in the NAc, see Spanagel, 2009).

The mechanism that causes alcohol to release opioids is separate from the mechanism that causes the sedative effects of alcohol. Sedative effects of alcohol are believed due to the general inhibition of NMDA receptors on cortical $GABA_A$ neurons reducing glucose metabolism throughout the cerebral cortex, as well as downstream

effects where alcohol activates adenosine A2a receptors which stimulates cyclic adenosine monophosphate (cAMP)-dependent kinase protein kinases attached to $GABA_A$ neurons which leads to the subjective "intoxicating" effects of alcohol. However, the ethanol concentration required to produce intoxication is higher than that needed for the initial stimulating effects experienced by drinkers (Hendler, Ramchandani, Gilman, & Hommer, 2013). Therefore, the dominant subjective sedating effect of alcohol, which may decrease dopamine release, is different from the initial neurological inhibition that occurs with lower doses of alcohol consumption.

Both nicotine and alcohol cause an increase in striatal dopamine, as well activate the limbic system, although through different processes. Activation of the limbic system appears to be essential in the development of substance addictions (Koob & Le Moal, 2008; Wise & Koob, 2014). Striatal activation is also believed to underlie the cross-priming phenomenon seen with alcohol and nicotine in lab-based studies, which functions similarly to how amphetamine primes gambling behavior (Zack & Poulos, 2004). Consuming a small dose of alcohol stimulates the limbic system, increasing the motivation to consume other substances that also activate the limbic system, including nicotine.

These neurobiological studies show how pharmacological and neurobiological processes may contribute to the phenomenon of alcohol increasing smoking behavior. It is clear that alcohol and nicotine share some common neuronal targets (Davis & de Fiebre, 2006; Lê, Corrigall, Harding, Juzytsch, & Li, 2000). Alcohol can either sensitize or inhibit the effects of nicotine through direct or indirect neuronal activation or inhibition of the limbic reinforcement pathways. As well, nicotine is known to indirectly

activate the same GABAergic neurons that alcohol activates, causing a release of dopamine in the same limbic reinforcement systems. Alcohol-tobacco co-use is both a pharmacological and psychological phenomenon, with unique patterns of neuronal activity observed when both alcohol and tobacco are co-administered, which they often are in smokers who drink (Falk et al., 2006).

Potential impact of a shared reinforcement system

Both psychological and neurobiological theories underscore the importance of the shared reinforcement system underlying the alcohol-tobacco relationship. Psychological theories explain the behavior (i.e., alcohol use increases subsequent tobacco use) and neurobiological studies demonstrate that alcohol and nicotine influence each other's pharmacology within the nervous system. Evidence also supports that consuming either substance increases the likelihood of the other being co-administered because both substances target a shared reinforcement system. This may explain why it is difficult for smokers to abstain from using tobacco when they are quitting smoking if they continue to consume alcohol, including smokers who supplement their nicotine intake by medical means.

In the most extensive meta-analysis of smoking cessation products to date (Cahill, Stevens, Perera, & Lancaster, 2013), nicotine replacement therapy (NRT) – using pharmaceutical methods to deliver bioavailable nicotine – was found to increase the odds that an individual would quit smoking by 1.84 times relative to a placebo product. Even with the assistance of an NRT, however, only 5% of Canadian smokers who attempt to quit smoking each year are successful with an NRT, compared to the 2.7% of smokers who attempt to quit and are successful per year who do not use an NRT (Health Canada,

2013a). These rates are similar to those seen in the UK and United States (Centers for Disease Control and Prevention, 2011; West & Brown, 2011).

NRT smoking cessation randomized control trials (RCTs) rarely include participant data regarding alcohol use; when they do, trials typically screen out participants with an alcohol use disorder. A study by Leeman, Huffman, and O'Malley (2007) examined the use of alcohol-related exclusion criteria in smoking cessation pharmacotherapy trials. Out of 149 clinical trials included in their review, only two of 125 trials involving NRTs reported explicitly looking for participants with a history of alcohol dependence and who were in remission. They also found that 38% of the 125 NRT trials had explicit criteria screening out participants with signs of alcohol abuse or dependence. This statistic is troubling since alcohol-dependent individuals are three times more likely to be dependent on tobacco than those without alcohol dependence (45% versus 13% in the United States; Grant, Hasin, Chou, Stinson, & Dawson, 2004; Heffner, Mingione, Blom, & Anthenelli, 2011). As well, alcohol-dependent individuals in clinical populations show even higher rates of tobacco dependence (Heffner et al., 2011; Hurt et al., 1995; Kahler et al., 2010), ranging from 47% to 92% (Batel et al., 1995; Hitschfeld et al., 2015; Kalman, 1998; Kalman et al., 2012; Sobell et al., 2002). Additionally, people who drink or used to be dependent on alcohol have low rates of quitting smoking (Hays et al., 1999; Kahler et al., 2010; Kalman, Kahler, Garvey, & Monti, 2006).

One smoking cessation pharmacotherapy that targets nAChRs also appears to influence alcohol consumption. Varenicline, a selective nAChR partial agonist, works by blocking the antagonistic action of nicotine on nAChRs on dopaminergic cells while also

acting as a weak agonist at these same receptor sites. Blocking nicotine and activating the receptor causes a lower level of dopamine to be released from these dopaminergic neurons with nAChRs in the NAc than from nicotine exposure, reducing subjective nicotine withdrawal. In clinical trials, the drug increases the odds ratio of quitting to 2.88 times higher than with a placebo product (Cahill, Stead, & Lancaster, 2007; Cahill et al., 2013). In animal studies, varenicline reduces alcohol (Chatterjee et al., 2010) and nicotine consumption (Wouda et al., 2011), counteracts the dopamine-enhancing effects of alcohol, and antagonizes the dopamine stimulatory effect of nicotine after five days of pre-treatment (Ericson et al., 2009). Varenicline also reduces alcohol consumption in humans (Childs, Roche, King, & de Wit, 2012; McKee et al., 2009); it believed to do so by competitively binding to $\alpha_4\beta_2$ receptors compared to alcohol's lower binding affinity to this nAChR receptor subtype (Benowitz, 2009; Rollema et al., 2007). Varenicline's competitive binding properties reduce the reinforcing properties of both alcohol and nicotine when used separately or concurrently.

INITIATION OF NICOTINE DEPENDENCE THROUGH ALCOHOL AND TOBACCO USE

The extant body of research demonstrates that the alcohol-tobacco relationship exists and may be maintained through shared reinforcement pathways and the release of dopamine in the NAc. However, this does not address how individuals initially become dependent on nicotine. NRTs have low abuse potential (West et al., 2000) and nicotine has been shown to have initially weak reinforcing properties in animals (Deneau & Inoki, 1967; Dougherty, Miller, Todd, & Kostenbauder, 1981). Studies also show that non-dependent smokers are unlikely to smoke to reduce nicotine withdrawal, the depressive symptoms and affect dysregulation seen when acute tobacco abstinence occurs (Watkins,

Koob, & Markou, 2000). Instead, non-dependent smokers seem to smoke for positively reinforcing purposes (Shiffman, Dunbar, Scholl, & Tindle, 2012). Other reinforcing chemicals found in tobacco, such as acetaldehyde, harman, norharman, nornicotine, cotinine, 2,3'-dipyridyl, anatabine, and anabasine, might contribute to the initiation of smoking behavior prior to the development of dependence on nicotine (Hoffman & Evans, 2013). It is possible that these chemicals, or others found in cigarette smoke, may cause denicotinized cigarettes to be reinforcing and effectively reduce craving for nicotine-containing cigarettes, along with their stimulus properties, associative learning, and other sensory-motor factors which come from consuming denicotinized cigarettes (Barrett, 2010; Barrett & Darredeau, 2012; Brauer et al., 2001; Rose, Salley, Behm, Bates, & Westman, 2010; Tidey, Rohsenow, Kaplan, Swift, & Ahnallen, 2013).

Acetaldehyde, the primary metabolite of ethanol, is produced through oxidation by alcohol dehydrogenase (Talhout, Opperhuizen, & van Amsterdam, 2007). This chemical is also abundant in tobacco smoke (0.6 – 2.1 mg/cigarette) due to the pyrolysis of polysaccharides (Paschke, Scherer, & Heller, 2002; Seeman, Dixon, & Haussmann, 2002), and produces a similar subjective experience to ethanol consumption (Correa et al., 2011). Acetaldehyde is also known to increase ethanol consumption (Quintanilla & Tampier, 2002) and leads to conditioned place-preference in alcohol-preferring rats (Rodd-Henricks et al., 2002). It also increases the reinforcing properties of ethanol (Mascia et al., 2001) and reinforces nicotine self-administration in juvenile rats (Belluzzi, Wang, & Leslie, 2005). Acetaldehyde also appears to modulate nicotine's effect on the hypothalamic-pituitary-adrenal axis (HPA), the neurocircuitry involved in the stress response (Cao et al., 2007).

However, not all smokers consume tobacco solely for the nicotine content (i.e., Rusted, Mackee, Williams, & Willner, 1998), and the effect of non-nicotine factors on this population is unknown. In fact, very light smokers who display few if any signs of dependence on tobacco represent a heterogeneous class of smokers that appear to be differently affected by both alcohol and tobacco. Some of these smokers may one day become dependent on nicotine, or may have previously been dependent on nicotine but have since reduced their cigarette use (Campbell, Bozec, McGrath, & Barrett, 2011). Others may remain throughout their lives an occasional non-daily long-term smoker and are typically known as "chippers" (Shiffman, 1989). These latter individuals' smoking behavior is more contingent on their present level of stress (Buchmann et al., 2010), which may explain part of their motivation to consume tobacco.

Acetaldehyde in the brain may result from the metabolism of ethanol in neurons found in the brain (Hipolito, Sanchez, Polache, & Granero, 2007); alternatively, it may be transported across the blood-brain barrier and into the brain (Correa et al., 2011; Jones, 1995) after being produced by ethanol metabolism in the liver or inhaled via tobacco smoke. Acetaldehyde is then able to react with catecholamines and indoleamines in the brain to form new reinforcing substances (Deitrich & Erwin, 1980; Setshedi, Wands, & Monte, 2016), including monoamine oxidase (MAO) inhibitors such as harman and norharman. Harman is known to increase alcohol administration in rats (Adell & Myers, 1994; Rommelspacher, Büchau, & Weiss, 1987) and to inhibit MAO-A levels in humans, contributing to the reduced level of free MAO in the brain (Herraiz & Chaparro, 2005). Serum norharman levels are also known to influence infrequent and low nicotine-dependent smokers' (chippers) cigarette craving specifically, an effect not seen with

dependent smokers (Eijnden, Spijkerman, & Fekkes, 2003). Norharman's effect on chippers' cigarette craving strongly suggests that they consume cigarettes for non-nicotine tobacco factors.

Furthermore, there are other known differences in how chippers behave in response to alcohol and tobacco. Tobacco consumption in chippers is often observed during alcohol co-administration (Dierker et al., 2006; Epstein et al., 2007; King et al., 2010; McKee et al., 2010; Nichter, 2006; Shiffman et al., 2014; Shiffman & Paty, 2006) and increases in the presence of other smokers (Hogarth, Mogg, Bradley, Duka, & Dickinson, 2003; Shiffman et al., 2014). Chippers also have an increased tobacco craving response to smoking cues compared with dependent smokers in experimental studies (Lazev, Herzog, & Brandon, 1999; Vollstädt-Klein et al., 2011). For most smokers, including chippers, their first-ever cigarette is consumed while they are drinking alcohol (O'Loughlin, Karp, Koulis, Paradis, & Difranza, 2009). As well, chippers' alcohol use increases when they are smoking (Barrett et al., 2006), which potentiates their cue-induced tobacco craving (Peloquin et al., 2014). Alcohol consumption while smoking further increases chippers' need to smoke for tobacco's negatively reinforcing properties (Kirchner & Sayette, 2007). Chippers have a different relationship with alcohol than do dependent smokers, but the two groups of smokers likely share a common trait where non-nicotinic tobacco factors influence smoking initiation.

METHODOLOGICAL LIMITATIONS OF CURRENT ALCOHOL-TOBACCO CO-USE RESEARCH

The aforementioned neurobiological studies demonstrate that the alcohol-tobacco co-use phenomenon involves multiple factors that reinforce the co-administration of both

substances. Specifically, both alcohol and nicotine activate nAChRs, and both alcohol and nicotine share a common reinforcement system. Moreover, alcohol and its primary metabolite acetaldehyde, also found in tobacco smoke, appear to influence smokers to consume nicotine. Finally, acetaldehyde and other non-nicotinic chemicals in tobacco facilitate early exposure to nicotine by causing tobacco smoke to be initially reinforcing, leading many to eventual dependence on nicotine. Also pertinent to understanding the alcohol-tobacco use relationship, several social and experimental caveats still need to be addressed before a broader understanding of how alcohol motivates tobacco use can occur. Understanding social and psychological factors that influence smoking is required before interventions can be designed to reduce alcohol-induced smoking behavior.

The first caveat is that animal models are the basis of most neurobiological research into the mechanisms of alcohol and nicotine co-use. Animal models of alcohol and nicotine pathways cannot account for psychological and social factors that are known to influence tobacco use in humans. Social factors include the price of and access to tobacco (Vijayaraghavan, Messer, White, & Pierce, 2013). Psychological factors include the expectancy of craving relief (Dar, Rosen-Korakin, Shapira, Gottlieb, & Frenk, 2010; Kenneth Perkins, Sayette, Conklin, & Caggiula, 2003; Schlagintweit, Good, & Barrett, 2014) and the expectation of the subjective effects of alcohol consumption (Burton & Tiffany, 1997). Sensory factors include the sensory experience of tobacco consumption (e.g., inhaling smoke: Brauer et al., 2001; Rose, 2006). The second caveat of the studies that have examined the alcohol-tobacco relationship in humans, only a limited number have differentiated explicitly between tobacco consumption and nicotine consumption. This is an essential pharmacological distinction, as nicotine and non-nicotinic tobacco

factors affect separate and independent neurological pathways. For example, in a study by Rose and colleagues (2004), dependent smokers participated in four sessions where they were assigned to receive either a low dose of alcohol (0.5g/kg reaching an average BAC of 0.03%) or a placebo beverage across the four sessions. Before their beverage, they received either 10mg of the nicotinic antagonist mecamylamine hydrochloride or a placebo capsule. Participants then were given either a nicotine-containing or denicotinized cigarette to smoke through a smoking device (through a plastic tube extruding from an opaque screen, seen in Levin, Rose, & Behm, 1989), which limited the volume of the bolus participants could take. Each participant received each possible combination of capsule and cigarette over four separate sessions. After they received their capsule and consumed their cigarette, they could earn further boluses of the same type of cigarette over a two-hour period. Rose and colleagues' study revealed several useful findings. First, alcohol potentiated nicotine's effect on withdrawal-related cigarette craving. However, this distinction was made regarding alcohol potentiating nicotine-containing cigarettes', not about the effect of alcohol on tobacco or nicotine in isolation. Second, nicotine-containing cigarette puffs were more satisfying than denicotinized cigarette puffs. Third, mecamylamine reduced smoking satisfaction for nicotine-containing cigarettes, indicating that nicotine (or at least nAChR activation) plays an essential role in smoking satisfaction.

However, there are a few reasons to be cautious before generalizing Rose et al.'s (2004) findings to the alcohol-tobacco co-use phenomenon more broadly. First, the authors utilized a smoking device instead of allowing participants to smoke a cigarette as they usually would. Many sensory properties of smoking including taste (Lawrence,

Cadman, & Hoffman, 2011) and vacuum pull are known to influence liking of the act of smoking (Trtchounian, Williams, & Talbot, 2010). As well, while utilizing denicotinized cigarettes has the advantage of eliminating nicotine while retaining some chemicals found in cigarette smoke, denicotinized cigarettes are perceived differently (often as less reinforcing) than a smoker's brand of cigarettes (for a review, see Brauer et al., 2001). As well, the nicotine antagonist mecamylamine has different binding affinities to various nicotinic receptor subtypes (Loiacono, Stephenson, Stevenson, & Mitchelson, 1993), as well as agonist effects on other receptors (e.g., Zambrano, Short, Salamander, Grady, & Marks, 2015), so it is tenuous to say that nicotine delivered via tobacco smoke directly influences ratings of satisfaction from smoking. A strength of Rose et al.'s (2004)'s study is that it utilized both subjective ratings of craving (self-report) and a behavioral measure of self-administration, necessary in measuring the pharmacological effect of a substance on craving and drug-seeking behavior, respectively. Subjective ratings of craving are necessary to assess whether an individual is craving a cigarette because of a strong desire to smoke, with smoking perceived as rewarding (positively reinforcing) versus an urgent desire to smoke for negative affect relief (negatively reinforcing) (Toll, Katulak, & McKee, 2006).

However, subjective cravings do not always predict subsequent smoking behavior (Germeroth & Tiffany, 2015). Smokers can report their subjective craving using self-report pen-and-paper tasks. However, to measure smoking behavior, a task which can observe smoking behavior is required. Barrett's progressive ratio (PR) task (Barrett, 2010) is such a behavioral measure of drug use motivation. The PR task is an adaptation of PR tasks used in animal studies to measure the degree to which an animal desires a

substance. With both humans and animals, there are three indices that are observed during a PR task. The first is the latency between the initial opportunity to consume a substance and when the first unit of a substance is consumed. Latency is typically considered a measure of how deprived an individual is of a substance (Henningfield & Griffiths, 1979), and can be influenced by other motivational factors such as incentive salience, expectancies, the presence or absence of drug cues. Moreover, level of deprivation would not be expected to yield the same level of importance for dependent vs. non-dependent individuals (Barrett, Campbell, Roach, Stewart, & Darredeau, 2013; Shiffman, 1989). The second index is how much of a substance is consumed during an experimental trial. The amount estimates how much of a substance is required to reach satiation throughout the trial. In smoking studies, this is often recorded as the number of puffs an individual has consumed over a standardized timeframe. The third indicator is how hard a participant is willing to work for additional units of a substance as they become increasingly difficult to obtain (i.e., require more actions to earn). This index is called "breakpoint," and while it is contingent upon a participant's satiation of a target substance, it also examines the strength of the participant's drive to consume units of the substance. Without utilizing a PR task and only counting the total number of puffs taken, as in Rose and colleagues' (2004) study, it is difficult to understand the meaning of their behavioral effects.

Dermody and Hendershot's (2017) meta-analysis of the alcohol and nicotine co-administration research literature was critical of the varied methods utilized across experimental studies, especially since consuming two (or more) substances increases the complexity of the experimental design. The timing of substance administration also

influences substance absorption. The route of administration (e.g., oral, dermal, mucosal, smoking) along with the conditions for delivery (e.g., pH of a substance, solubility) both affect the pharmacokinetics of substance absorption. Both alcohol (Baraona et al., 2001) and nicotine (Gourlay & Benowitz, 1997; Tønnesen, Lauri, Perfekt, Mann, & Batra, 2012) absorption are affected by the route and conditions of substance absorption.

Alcohol is almost exclusively ingested orally and is absorbed passively through the gastrointestinal tract (Chan & Anderson, 2014) by passive diffusion. The higher the concentration of ethanol consumed, the higher the rate of absorption. As ethanol enters the body, passive diffusion begins in the stomach. However, absorption is more rapid in the duodenum and jejunum. Gastric emptying of the stomach expedites ethanol absorption (Holt, Stewart, Adam, & Heading, 1980; Holt, 1981), and there are factors that influence this gastric emptying. For example, stress increases the rate of gastric emptying, while concurrent food consumption decreases the rate, especially with foods high in fat content. Typically, the psychopharmacological effects of ethanol begin about 15 minutes post-consumption.

For nicotine, the rate of absorption depends on how the product is administered. Nicotine is a weak base ($pK_a = 8.0$). Therefore, oral preparations such as chewing tobacco and nicotine gum need to be buffered with an alkaline product to ensure nicotine remains unprotonated so it can absorb into the buccal mucosa rapidly (Benowitz, 2008). When tobacco smoke is inhaled, nicotine is rapidly absorbed by the lungs and then is circulated throughout the body without first-pass or hepatic metabolism, with levels peaking after 10 minutes. This bypassing of first-pass and hepatic metabolism allows smoking tobacco to increase venous nicotine levels more rapidly than administering

nicotine intravenously, which causes it to peak after 30 minutes (Gourlay & Benowitz, 1997). Other oral tobacco products have a rate of nicotine absorption comparable to cigarette smoke inhalation, with peak nicotine loading occurring 10 minutes after absorption has begun (Benowitz, Porchet, Sheiner, & Jacob, 1988). The primary difference between smoking and oral absorption of a tobacco product is that nicotine levels drop rapidly after a cigarette is consumed and with no more considerable increase in absorbed nicotine after 12 minutes. Most oral tobacco products, however, have nicotine loading throughout the product's absorption, up to 90 minutes after beginning to use the product. The more rapidly nicotine is absorbed into the user's system, the quicker the desired pharmacological effect occurs, which increases the acute reinforcing value of the nicotine delivery product (Schnoll et al., 2010).

These rates of absorption temporally affect the metabolism of these drugs. Absorption rates then alter the rate of psychoactive metabolite production. Both alcohol and nicotine have relevant psychoactive metabolites, as acetaldehyde is a metabolite of alcohol (Rodd-Henricks et al., 2002) and nornicotine is a metabolite of nicotine (Clemens, Caillé, Stinus, & Cador, 2009). Therefore, how substances are absorbed affects their subjective experience. Ethanol catabolism occurs throughout the body, including in the stomach itself, but most catabolism of ethanol occurs in the liver. After ethanol is absorbed either through the stomach or small intestines, it flows through the portal vein to the liver. There, alcohol dehydrogenase (ADH) breaks down alcohol into acetaldehyde through oxidative metabolism (Edenberg, 2007). Other enzymes such as cytochrome P450 2E1 (CYP2E1) and catalase break down ethanol into acetaldehyde. Acetaldehyde is primarily metabolized rapidly into acetate by aldehyde dehydrogenase (ALDH2) in

mitochondria. Acetaldehyde is highly reactive and known to bind to many other proteins in the body if not immediately metabolized. When it has the opportunity, acetaldehyde forms adducts with neurotransmitters, which causes the formation of new psychoactive molecules by combining a highly reactive form of acetate with a neurotransmitter. Acetate is then metabolized by acetyl CoA into carbon dioxide either in the liver, or in other tissues found in the brain, skeletal muscle, or heart. The rate at which ethanol is metabolized is highly dependent on the health of the individual and the genetic polymorphisms of ADH and ALDH2 (Thomasson, Beard, & Li, 1995). For nicotine, the liver enzyme CYP2A6 is the enzyme primarily responsible for nicotine's metabolism to cotinine (Benowitz, 2008). Typically, the half-life of nicotine is 2 hours, although genetic polymorphisms of CYP2A6 can alter this length of time. As well, low CYP2A6 activity in some individuals can cause glucuronidation – the metabolism of a substance such as nicotine by drugs instead of endogenous enzymes – to be a major metabolic pathway for nicotine metabolism.

The order and timing of substance co-administration have implications for their subjective experience and pharmacology. Individuals implicitly learn their preferred substance-administration order through experience (Barrett, Gross, Garand, & Pihl, 2005). Substance administration order is important when considering the timing of alcohol and tobacco use, as alcohol primes the administration of tobacco as well as other abused substances (McKay, Alterman, Rutherford, Cacciola, & McLellan, 1999). The timing of when alcohol is administered relative to another drug in experimental studies might impact the conclusions drawn, as alcohol has known biphasic effects depending on whether blood alcohol concentration (BAC) levels are rising or falling. When BAC levels

are rising, participants consume more cigarettes (Epstein et al., 2007; Mitchell, de Wit, & Zacny, 1995) and also report greater cigarette craving (Kouri, McCarthy, Faust, & Lukas, 2004) compared with when BAC is decreasing. In Kouri and colleagues' study, they found that the desire to smoke a cigarette peaked 30 minutes after beginning to consume 0.7g/kg alcohol in occasional alcohol consumers, regardless of any nicotine or placebo patch pretreatment. This increased desire to smoke disappeared as BAC levels began to fall immediately afterward. However, there is mixed evidence that the phase of alcohol intoxication a heavy drinker is experiencing influences their cigarette craving and consumption. Kahler and colleagues (2014) found that heavy alcohol users' smoking urge was consistent across both limbs of the BAC in their lab-based study regardless of receiving 0.4g/kg or 0.8g/kg alcohol, which suggests that the degree of dependence on alcohol may influence how alcohol affects tobacco craving. Variability in the degree of alcohol dependence across samples is one reason why Dermody and Hendershot (2017) were unable to conclude whether alcohol increases nicotine administration. In their review, alcohol increased nicotine use in four of seven studies, while three studies found no effect of alcohol on nicotine administration. These mixed results are likely due, in part, to the timing of alcohol administration, along with other moderating variables such as sex, level of dependence on nicotine and alcohol, and cigarette use frequency.

A final and challenging experimental consideration when examining the alcohol-tobacco co-use mechanism is how to minimize the subjective expectations of alcohol and tobacco consumption. Placebo effects have been observed with alcohol use where individuals report feeling intoxicated (Burton & Tiffany, 1997; Peloquin et al., 2014) when consuming a beverage that appears intoxicating but does not contain sufficient

alcohol to have a physiological effect (Kushner et al., 1996). Moreover, exposure to alcohol cues (imagery, scripts) alone is known to increase tobacco consumption, suggesting strong memory associations between the two substances such that exposure to cues of one substance elicits increased consumption of the other (Erblich et al., 2009). Placebo effects have also been observed in tobacco studies (Perkins et al., 2003). However, it is important to note that nicotine replacement products do not have the same sensory properties (see Rose, Behm, Westman, Bates, & Salley, 2003) and do not result in the same subjective effects as tobacco consumption; therefore, they cannot be used to make claims about the effects of tobacco. Regardless, alcohol-tobacco research requires the use of placebos for both alcohol and tobacco products to differentiate physiologically-induced effects from expectancy-induced effects of each of these drugs.

It is understandable that no single experimental study of co-administered alcohol and tobacco use in humans has been able to conclude why alcohol increases tobacco use. Confounding biological factors such as heredity, the role of nicotine versus non-nicotinic tobacco constituents, and the rates of absorption and metabolism of alcohol, tobacco, and nicotine influence the alcohol-tobacco co-use phenomenon. Confounding psychological issues such as substance expectancies, and methodological issues such as how to record both physiological changes and subjective affective states including craving, as well as observable substance use motivation, also need to be considered. As well, the impact of social phenomena such as appropriateness to smoke and drink in a given context is also relevant. The more closely an experimental session can resemble a naturalistic setting in which individuals consume both alcohol and tobacco, the more generalizable the results are likely to be. Ideally, studies should provide as much experimental control as possible

over the stimulus expectancies of alcohol and tobacco, while maintaining as much ecological validity as possible. Studies with improved methodology may lead to a better psychological theory for the alcohol-tobacco use phenomenon.

Furthermore, if a substance could deliver chemicals found within tobacco along with nicotine and not contain any of the chemical by-products of tobacco pyrolysis, this substance could be used in alcohol-tobacco co-use experiments to infer what effect tobacco itself has on alcohol-induced cigarette craving and consumption. A form of tobacco called snus does satisfy these requirements. It contains un-pyrolyzed tobacco and is not smoked, minimizing expectations of craving reduction compared to smoking a cigarette or other nicotine-delivery device. Without the same expectations as other tobacco products familiar to North American smokers, the results of experimentation utilizing snus could be said to be free of the cigarette expectancies that have confounded previous research studies. Snus also has many of the bioavailable components of tobacco with a similar loading profile to a cigarette, making it an ideal product to use in alcohol-tobacco experimentation.

INTRODUCTION TO SNUS

Swedish snus – moist oral Swedish snuff – is finely ground tobacco with high moisture content. Snus is blended with an alkali salt to reach a pH between 8 and 9 to allow for the absorption of chemicals found in tobacco, including nicotine (Houezec, McNeill, & Britton, 2011; Nordgren & Ramström, 1990; Rutqvist, Curvall, Hassler, Ringberger, & Wahlberg, 2011). It is prepackaged into sachets and placed under the upper lip. Traditionally it was sold loose, and the user would pinch the moist tobacco and place and hold it under their upper lip. Many brands of Swedish snus add flavorants to

the tobacco to achieve a brand-specific flavor (Rutqvist et al., 2011). Some brands add flavorants to create mint, fruit, or herbal notes.

Snus has been the dominant smokeless tobacco product in Sweden since the 19th century (ENVIRON International Corporation, 2010; Nordgren & Ramström, 1990; Rutqvist et al., 2011). After waning in popularity from the 1920s to 1960s, the Swedish Tobacco Company (the government-owned sole producer of snus in Sweden at the time) launched a successful marketing campaign to rebrand snus. Snus was rebranded from a tobacco product mainly used by older, less educated males, to an exciting new product for young people as an alternative to cigarettes. The marketing campaign was highly successful, and snus use rose in popularity from the late 1960s into the 1980s with 19% of Swedish men aged 16-74 years using snus daily and another 5% using snus occasionally (Nordgren & Ramström, 1990). Thirty-one percent of 16-24-year-olds used snus daily and an additional 8% used snus occasionally, with only 11% of adults 35 to 70 years old using snus. Since the 1980s, Swedish cigarette use rates have been decreasing, while snus use rates have been increasing (Digard, Errington, Richter, & McAdam, 2009; Furberg, Lichtenstein, Pedersen, Bulik, & Sullivan, 2006; Pedersen & von Soest, 2014; Rodu, Jansson, & Eliasson, 2013; Stegmayr, Eliasson, & Rodu, 2005). As of 2009, 24.1% of men aged 25-64 years reported using snus, with 8.8% endorsing cigarette use and 2% using both snus and cigarettes, compared with 1986 when only 18% of similarly-aged men reported using snus but 19% reported smoking cigarettes, and 4% reported using both substances. Interestingly, the rate of snus use for women aged 25-64 years in Sweden has also increased over the same span. In 1986, 27% percent of women were cigarette smokers and none reported using snus; in 2009, only 11.1% of women were

cigarette smokers and 8.2% of women used snus, with 0.9% using both. For adolescents aged 16-17 years, snus rates increased significantly between 2002 and 2010, from 4.3% in 2002 to 11.9% in 2010, with significantly more boys than girls using snus at both time points. Over the same period, daily cigarette use dropped from 23.6% to 6.8% in adolescents, and overall daily use of any tobacco product fell from 26.8% to 17.6% in adolescents (Pedersen & von Soest, 2014).

One explanation for this trend in the prevalence of Swedish snus use and the decline of cigarette use across the lifespan is the marketing of snus as a healthier alternative to cigarette smoking (Gartner et al., 2007; Nordgren & Ramström, 1990; Rutqvist et al., 2011). Snus users have no higher risk of periodontal diseases (Hugoson & Rolandsson, 2011) or diabetes (Eliasson, Asplund, Nasic, & Rodu, 2004) than the average person, as well as a lower incidence of cancer than cigarette smokers (Nordenvall, Nilsson, Ye, & Nyrén, 2011; Rodu & Cole, 2002; Roosaar, Johansson, Sandborgh-Englund, Nyrén, & Axéll, 2006; Zendehdel et al., 2008). Snus users have only a slightly increased risk of myocardial infarction or stroke relative to non-tobacco users (Boffetta & Straif, 2009). The primary body of carcinogens found in tobacco and tobacco smoke is tobacco-specific nitrosamines (TSNAs) (Schmeltz & Hoffmann, 1977), produced as a by-product of the pyrolysis of tobacco. American Snus (Caraway & Chen, 2013; Gerardi, Coleman III, & Phillips, 2008; Stepanov et al., 2014), chew, dipping tobacco, and cigarette tobacco are either fermented or cooked with propane flames during production and therefore have TSNAs. TSNA also are created when cigarettes, cigarillos, and both pipe or hookah tobacco are smoked (Schmeltz, Tosk, & Hoffmann, 1976). Nitrosamine levels in Swedish snus are considerably lower than in other forms of tobacco

(Digard, Gale, Errington, Peters, & McAdam, 2013; Foulds, Ramstrom, Burke, & Fagerström, 2003; Stepanov, Jensen, Hatsukami, & Hecht, 2008) due to internal industry standards of Swedish snus preparation (Rutqvist et al., 2011). However, no study to date has directly compared nitrosamine biomarkers in snus and cigarettes.

Many individuals claim that they have successfully used snus to reduce or quit cigarette consumption (Gilljam & Galanti, 2003; Lindström, 2007; Lund, Scheffels, & McNeill, 2011; Lund, McNeill, & Scheffels, 2010; Scheffels, Lund, & McNeill, 2012). Lab-based studies have found that snus use increased intentions to quit smoking cigarettes in smokers without prior intention to quit smoking (Burris, Carpenter, Wahlquist, Cummings, & Gray, 2014). Snus has reduced smoking behavior in people wanting to reduce or quit cigarette use (Fagerstrom, Rutqvist, & Hughes, 2012; Joksić, Spasojević-Tišma, Antić, Nilsson, & Rutqvist, 2011), and has reduced smoking in smokers who did not disclose their intentions to quit (Caldwell, Burgess, & Crane, 2010). These findings are all the more impressive given that snus users are also known to consume more alcohol than cigarettes smokers, and many continue to use snus instead of reverting to previous cigarette consumption levels (Larsen, Rise, & Lund, 2013; Lund, Tefre, Amundsen, & Nordlund, 2008).

Snus' efficacy at reducing cigarette consumption lies in the fact that Swedish snus contains many of the same pharmacologically active chemicals found in cigarette smoke. Snus contains nornicotine, anatabine, anabasine, myosmine, 2,3'-dipyridyl, acetaldehyde, and cotinine, along with nicotine (Digard, Gale, et al., 2013; ENVIRON International Corporation, 2010; Stepanov et al., 2008). All these chemicals have been implicated in the reinforcing properties of cigarette smoke, as previously described. However, certain

MAOIs such as harman and norharman, which are condensation products of acetaldehyde and are believed to be reinforcing (Herraiz, 2004), have not been identified in snus. The lack of harman and norharman in snus comes as no surprise given that acetaldehyde levels in snus are approximately 35.7µg/g, or 23.9µg per snus portion, whereas they are 0.6 – 2.1 mg/cigarette, meaning that acetaldehyde concentration is approximately 25-90-fold lower in snus. Acetaldehyde levels are likely lower in snus because it is pasteurized and not combusted when manufactured (Stepanov, Jensen, Hatsukami, & Hecht, 2008). As a result, Swedish snus is an ideal tobacco product to examine the alcohol-tobacco relationship without the confound of the many different chemicals created through tobacco pyrolysis (Church & Pryor, 1985).

As previously stated, an ideal product to examine the alcohol-tobacco relationship would require a similar chemical loading profile to other tobacco products and minimize any tobacco expectancies in research participants. Snus meets both criteria in Canada. Nicotine absorption rates into blood plasma peak 5 minutes after either snus and cigarette use (Benowitz et al., 1988). The overall level of nicotine absorbed with snus is more similar to smoking a cigarette than other oral NRTs (Benowitz et al., 1988; Lunell & Lunell, 2005).

Furthermore, no snus of any kind has never been advertised in any Canadian market, nor has Swedish snus been commercially available in Canadian markets as of 2018. Therefore, most Canadians would never have experienced nor have known about this product. Smokeless tobacco products like chewing tobacco and dipping tobacco do exist in Canada but are unpopular, with only 4.4% of youths aged 15-19 reporting having

ever tried them (Health Canada, 2013b). Fewer than 0.5% of individuals 15 years and older have used an oral tobacco product in the last 30 days (Reid, 2013).

An added benefit of snus is that a tobacco-free product with the same sensory properties as Swedish snus exists, and previous studies have validated it as a placebo product for snus in experimental studies (Coffey & Lombardo, 1998; McChargue, Collins, & Cohen, 2002). Therefore, snus can be effectively utilized in double-blind placebo-controlled experiments to examine the alcohol-tobacco co-use relationship as placebo products exist for both substances.

Because both alcohol and tobacco products with experimentally-validated placebos exist, the alcohol-tobacco co-use phenomenon can be examined in a laboratory setting, with results that can differentiate between the pharmacological effects of alcohol and tobacco on alcohol-induced cigarette craving and consumption. Tobacco dependence can also be accounted for by recruiting both dependent and non-dependent cigarette smokers. As well, the order of administration can be easily altered to determine how relative administration order of alcohol and tobacco and absorption timeframes influence cigarette craving and smoking behavior. Creating an experimental paradigm that accounts for these variables will allow us to not only better understand the alcohol-tobacco co-use phenomenon, but also provide insight into when pronounced increases in cigarette craving occur, and whether specific product administration orders increase or reduce craving and consumption given the opportunity to smoke. Having a clear understanding of what factors influence alcohol-induced cigarette craving and consumption will benefit those creating tobacco cessation interventions, especially for smokers who drink.

PROLOGUE

This dissertation comprises three individual manuscripts and a general discussion. The first paper describes an experiment that examined the effect of alcohol and snus on cigarette craving and consumption with daily dependent smokers (DDS) who were not trying to quit smoking. Participants consumed either an alcoholic or taste-matched placebo beverage, followed by either a 1g (8mg nicotine) sachet of snus or a taste-matched placebo product. After both products were absorbed, participants reported their affective and cigarette craving states, then completed a progressive ratio (PR) task where they could earn puffs of their preferred brand cigarettes over a 60-minute timeframe. Participants completed two sessions, with the same beverage condition in both. In the experiment described in the second paper, participants consumed either snus or the taste-matched placebo product followed by a 30-minute absorption period. After reporting their affective and cigarette craving states, participants consumed their assigned beverage. After waiting 15 minutes for their beverage to absorb, they completed another set of affective and cigarette craving questionnaires, and then began their PR task as in Study 1. This second experiment was intended to examine further the effect product administration order would have on cigarette craving and consumption. The third paper describes an experiment that examined the effect of alcohol and a 0.5g (4mg nicotine) snus sachet on cigarette craving and consumption in both dependent and non-daily non-dependent smokers (NNS) who were also not trying to quit smoking. This study aimed to expand upon the first two studies by utilizing a smaller portion of snus and a more extended tobacco abstinence period to determine whether half the dose of snus would still produce the changes in cigarette craving and smoking behavior after alcohol consumption

that was seen in the first two studies with tobacco-dependent smokers. As well, the third study recruited NNS in order to determine whether an individual's degree of dependence on tobacco influences snus' efficacy in reducing cigarette craving and consumption. The design of this third study was otherwise similar to that of Study 1, with the exception that each participant was assigned to complete each of the four possible product and beverage conditions on four separate occasions. The implications of these three studies for clarifying the alcohol-tobacco co-use phenomenon, as well as the nature of tobacco craving, are discussed, and suggestions for future alcohol and tobacco research are outlined in the final chapter.

CHAPTER 2: THE EFFECT OF SNUS ON ALCOHOL-INDUCED CIGARETTE CRAVING AND CONSUMPTION

This chapter contains an unpublished research study. My role included the design of the experiment, running participants, analyzing the results, and writing the attached paper. This research took place in Dr. Sean Barrett's Substance Use and Addictions Lab with research funds granted to him. Drs. Sean Barrett, Sherry Stewart, Kim Good, and Natalie Rosen provided feedback on the writing of the attached paper. Ari Franklin assisted in running research participants.

ABSTRACT

Alcohol and tobacco are frequently co-administered. Numerous lab-based studies have shown that alcohol consumption increases both cravings for cigarettes and cigarette consumption; however, the extent to which nicotine or tobacco administration impact these effects is unknown. The present study examined the effect that moist Swedish snus had on cigarette craving and consumption when administered following an alcoholic beverage to snus-naïve users. In a mixed model design, 25 dependent smokers (12 female) who were also moderate drinkers attended two experimental sessions and were given either an alcoholic or a placebo beverage in both sessions, followed by either a snus sachet or a placebo product to absorb, counterbalanced between session. Participants were asked to rate their cigarette craving before beginning a 60-minute progressive ratio task (Barrett, 2010) where they could earn cigarette puffs of their preferred brand of cigarettes. No changes in cigarette craving following beverage and product absorption were found relative to baseline, which was unexpected. However, participants consumed

fewer puffs (p = .049) and worked less hard to earn puffs (p = .037) after snus relative to placebo product absorption, regardless of beverage condition. Beverage consumption did not influence cigarette smoking behavior. These findings show that snus can attenuate cigarette smoking, even following alcohol consumption, but that snus does not appear to impact subjective cigarette craving.

INTRODUCTION

Some of the most challenging cigarettes to abstain from are those a person has after consuming alcohol (McKee et al., 2006; Toll, Leeman, McKee, & O'Malley, 2008). Alcohol potentiates both cigarette craving (Burton & Tiffany, 1997; Glautier et al., 1996; King et al., 2009; Sayette et al., 2005) and consumption (McKee et al., 2006; Mello et al., 1980; Mintz et al., 1985) in dependent smokers. Nicotine replacement therapy (NRT) products do not abate these effects (e.g., Kouri, McCarthy, Faust, & Lukas, 2004), suggesting that alcohol-induced cigarette craving and increased smoking may in part be due to a drive to consume other tobacco components beyond nicotine.

Swedish snus, a moist oral tobacco product, has been marketed as a less harmful alternative to cigarettes (Boffetta & Straif, 2009; Britton, 2003; Gartner et al., 2007; Hansson et al., 2009; Hatsukami et al., 2004; Krautter, Chen, & Borgerding, 2015; Ramström, 2011; Rodu & Cole, 2002). Snus users have anecdotally reported that snus works as a smoking cessation aid (Lindström, 2007; Lund et al., 2010; Scheffels et al., 2012). It appears to reduce both cigarette craving (Caldwell et al., 2010) and consumption in experimental studies (Burris et al., 2014; Caldwell et al., 2010; Fagerstrom et al., 2012). Individuals who have used snus to reduce their cigarette consumption typically do so despite continuing their alcohol consumption (Larsen et al., 2013; Lund et al., 2008), raising the possibility that snus may also reduce alcohol-induced cigarette craving and smoking behavior.

It is currently unknown how snus may reduce alcohol-induced cigarette craving and consumption, although several mechanisms have been suggested. First, snus contains a number of the same reinforcing chemicals found in cigarette smoke beyond

nicotine, such as nornicotine, anatabine, anabasine, myosmine, 2,3'-dipyridyl, and cotinine (ENVIRON International Corporation, 2010; Stepanov et al., 2008). All of these chemicals are known to be independently reinforcing and may reduce alcohol-induced cigarette craving and consumption (Digard, Gale, et al., 2013; Harris et al., 2015; Hoffman & Evans, 2013; Van Den Eijnden et al., 2003). Second, snus also has a similar nicotine loading profile to smoking a cigarette (Benowitz et al., 1988; Lunell & Curvall, 2011; Lunell & Lunell, 2005). The rapid rate of nicotine loading into blood plasma may make it as reinforcing as a cigarette, or even moreso. Third, snus may be better tolerated than oral NRT products, as found by Caldwell and colleagues (2010), although subsequent studies suggest otherwise (Barrett, Campbell, Temporale, & Good, 2011; Barrett & Wagner, 2011). The relative lack of adverse side effects of snus may cause some smokers to prefer it to cigarettes, and may also explain why some smokers prefer snus to NRTs when attempting to reduce their smoking behavior.

The purpose of this study was to determine if snus reduces alcohol-induced tobacco craving and consumption by administering snus after alcohol was consumed. I predicted that alcohol would increase cigarette craving and consumption, and that snus would reduce cigarette craving and consumption regardless of alcohol use. As well, I intended to record any subjective effects that either alcohol or snus induced in participants to further understand the subjective mood effects of snus.

METHODS

PARTICIPANTS

Non-treatment seeking daily dependent smokers (DDS) (i.e., daily tobacco use for a minimum of one year; score ≥ 3 on the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991)) were recruited from the Halifax Regional Municipality in Nova Scotia. All were regular heavy consumers of alcohol, having consumed a minimum of 4 drinks for women (5 drinks for men) at least once/week during the previous month. All participants were non-problem drinkers, scoring 2 or less on the short version of the Michigan Alcoholism Screening Test (SMAST; Selzer, Vinokur, & Rooijen, 1975). Potential participants were told that the study would consist of two experimental sessions that would involve the administration of beverages that may vary in alcohol content followed by the administration of substances that may vary in their contents of ingredients typically found in cigarettes (e.g., tar, ammonia, menthol, nicotine, sucrose). All participants reported that they were medically healthy, and all had reached the minimum age to consume alcohol and tobacco in Nova Scotia legally; none of them intended to quit smoking over the subsequent 30 days, and none were using NRT products. All participants were found to be naïve to snus before the study when interviewed upon completion of the study. The study adhered to guidelines from the Declaration of Helsinki and was approved by a local research ethics board.

Design

The protocol consisted of two double-blind, randomized sessions with a 2 (beverage condition: alcohol or placebo) x 2 (product condition: snus or placebo) between-within subjects design. All sessions were identical in procedure except that participants were randomly assigned to one beverage condition (alcohol or placebo) for both sessions, and product condition changed between sessions.

Beverages

In the alcohol conditions, participants received 2.28 ml 50% USP units of alcohol per kilogram of body weight for women and 2.73 ml 50% USP units of alcohol per kilogram of body weight for men (MacDonald, Baker, Stewart, & Skinner, 2000). These ratios of consumed alcohol for men and women target a peak blood alcohol content (BAC) of 0.06%. Drinks were mixed 1:4 parts vodka to cranberry juice. The placebo beverage was made up of 5 parts cranberry juice with a small amount of alcohol applied to the rim of the glasses and on the drink tray to ensure the odor and taste of alcohol (Kushner et al., 1996).

Products

In the snus condition, participants received a 1g Phantom brand Swedish-style snus regular portion containing 8mg of nicotine and a manufacturer reported pH of 8.5 (V2 Tobacco; Silkeborg, Denmark). Snus has a nicotine loading timeframe of 30 minutes (Foulds et al., 2003; Lunell & Lunell, 2005). In the placebo condition, participants received a BaccOff brand non-tobacco placebo portion (V2 Tobacco; Silkeborg, Denmark) which mimics the sensory properties of snus (Coffey & Lombardo, 1998).

BLINDING

Participants were blind to the contents of the beverages and products received during each session. Participants were informed that the products might vary between sessions in their content of ingredients usually found in cigarettes, but they were not informed that the products might vary in nicotine content specifically. Similarly, participants were also informed that the alcohol content of the beverages might vary, but not that the doses were selected to produce either mild or no intoxication. To maintain the integrity of the blind, research personnel not otherwise involved with data collection prepared all beverages, administered the oral product, and recorded all breath alcohol measurements.

SUBJECTIVE ASSESSMENT

Subjective Rating Scales

An author-compiled Subjective Rating Scale (SRS) was used to assess subjective state (i.e., “relaxed”, “pleasant”, “head rush”, “stimulated”, “jittery”, “dizzy”, “irritable”, “trouble concentrating”, “anxious”, “satisfied”, “high”, “alert”, “frustrated”, “sedated”, “intoxicated”, “enjoy taste”, and “crave cigarette”). Each item was rated on a 10-cm horizontal line labeled with integers 1-10 and anchored with the endpoints “Not at all” and “Extremely.” Similar scales have been widely used to assess subjective drug effects, and have been shown to be both reliable (e.g., Wewers & Lowe 1990) and sensitive to the acute effects of alcohol and tobacco (e.g., Barrett, Campbell, Roach, Stewart, & Darredeau, 2013; Barrett, Tichauer, Leyton, & Pihl, 2006). Positive affect items (“relaxed”, “pleasant”, “head rush”, “stimulated”, “satisfied”, “high”, and “alert”) were combined to create a positive affect factor, and negative affect items (“jittery”, “dizzy”,

"irritable", "trouble concentrating", "anxious", "frustrated", and "sedated") were combined to create a negative affect factor. The positive affect factor had a good internal item consistency of Cronbach's alpha of .80, and the negative affect factor had a good internal item consistency of Cronbach's alpha of .85, in the present sample. "Intoxicated" and "enjoy taste" were analyzed separately.

Questionnaire of Smoking Urges-Brief

The Questionnaire of Smoking Urges-Brief (QSU-B; Cox, Tiffany, & Christen, 2001) is a 10-item self-report measure used to assess tobacco craving across two dimensions. Each question is rated on a scale of 1 to 7, with 1 indicating "strongly disagree," 4 "neutral," and 7 "strongly agree." Five items grouped as factor 1 reflect a strong desire and intention to smoke, with the perception that smoking will be rewarding. These include items such as "I have a desire for a cigarette right now" and "If it were possible, I probably would smoke now." The remaining five items reflect anticipation of relief from negative affect with an urgent desire to smoke and are known as factor 2. These include items such as "I could control things better right now if I could smoke" and "I would do almost anything for a cigarette right now." Item scores were totaled into index scores for factors 1 and 2, each ranging from 5 to 35. Internal item consistency for factors 1 and 2 in the present sample was Cronbach's alpha = .97 for both factors, similar to the original factors found in the Questionnaire of Smoking Urges (Tiffany & Drobes, 1991).

Brief Biphasic Alcohol Effects Scale

The Brief Biphasic Alcohol Effects Scale (B-BAES; Martin, Earleywine, & Musty, 1993) is a 6-item self-report measure used to assess the subjective stimulant

effects of alcohol associated with a rising BAC (factor 1), as well as the subjective sedative effects associated with a descending BAC (factor 2) (Rueger, McNamara, & King, 2009). Factor 1 items include "energized", "excited", and "up", whereas factor 2 items include "sedated", "slow thoughts", and "sluggish". Each item was rated on a 10-cm horizontal line labeled with integers 1-10 and anchored with the endpoints “Not at all” and “Extremely” similar to the scale used with the author-compiled Subjective Rating Scales. Internal item consistency for factor 1 ranges between Cronbach’s alpha of .89 to .93, and .90 to .91 for factor 2, in the current sample across measurement occasions. Factor 1 on the B-BAES correlates with the original BAES factor 1 by $r = .92$, and factor 2 correlates with the original BAES factor 2 by $r = .93$ ($ps < .001$) (Martin, Earleywine, Musty, & Swift, 1993).

Behavioral measures

Heart Rate

The average and maximum heart rates of participants were collected alongside subjective assessments (RS-100 Polar Heart Rate Monitor; Polar Electro Canada; Lachine, Canada), as alcohol (Brunelle, Barrett, & Pihl, 2007) and nicotine (Perkins et al., 1995) are known to induce increased heart rate relative to sober baseline.

Progressive Ratio Task

Participants could earn puffs of their preferred brand of cigarette (supplied by the lab) using a computerized progressive ratio (PR) task over 60 minutes. Ten key presses were required to earn the initial puff, and the requirement increased at a ratio of 1.3 for each subsequent puff. Participants were not required to earn any puffs but were required to remain seated in front of the cigarette until the end of the session. The latency to start

smoking, the total number of puffs earned, and the breakpoint – the number of key presses completed to earn the last puff – were recorded for each session. The PR task has been demonstrated to be sensitive to pharmacological manipulations in human tobacco self-administration studies (e.g., Barrett et al., 2013).

PROCEDURE

Participants arrived for each testing session having abstained from smoking and alcohol for a minimum of 12 hours and from food and caffeine for a minimum of 2 hours. A breath CO reading of 15 ppm or less, and/or a 50% reduction in CO from the non-abstinent baseline, confirmed abstinence from smoking (Vitalograph; Lenexa, KS). Abstinence from alcohol was confirmed using an Alcomate Premium breath alcohol analyzer (AK Solutions; Lansdale, PA) with a cutoff of 0.00%. At this time, participants were provided with a cigarette of their preferred brand, asked to smoke the cigarette, and then waited one hour in the experimental chamber before the task began. The purpose of having participants smoke a preferred brand cigarette and then wait an hour was to harmonize the degree of tobacco withdrawal both between sessions and across participants. Typically, DDS will have consumed a cigarette within the first hour after waking (Shiffman et al., 2002; 2014) and otherwise would be experiencing intense tobacco withdrawal symptoms at the beginning of the experiment. A timeline outlining the sequence of procedures is presented in Table 1.

TABLE 1

Procedure	Time (minutes)	Total time (minutes)
Informed consent/ participant reminded of right to withdrawal		
Confirmation of alcohol and smoking abstinence	5	5
Smoke cigarette	5	10
Wait time	60	70
Heart rate recording and subjective assessment	7	77
Administration of beverage	15	92
Administration of product	30	122
Disposal of product, heart rate recording, breath alcohol and subjective assessment	10	132
PR task	60	192
Sobering period	60	252

Table 1. Timeline of experimental procedures for Study 1

After completing a baseline subjective assessment (SRS, QSU-B, B-BAES) and heart rate recording, participants consumed their assigned beverage (alcohol or active placebo) over 15 minutes. Afterward, participants were given their product and instructed to place it between their upper gum and lip for 30 minutes while they waited alone in the testing room. A post-product subjective assessment and a breath alcohol and heart rate

recording were conducted. Participants could then earn cigarette puffs over the following 60 minutes on the PR task. Following the PR task, the session concluded with a "sobering period" of at least one hour during which participants were provided with a light snack and rested until their BAC was below 0.04%. All participants completed this sobering period in each session to maintain the blind of the experiment.

STATISTICAL ANALYSIS

Data were analyzed using linear mixed models in SPSS version 20.0 for Windows (SPSS Inc.; Chicago, IL). Linear mixed models account for unequal sample sizes by producing adjusted degrees of freedom and estimated marginal means. An appropriate covariance structure was selected for each variable based on model simplicity and the likelihood ratio test. The behavioral measures were the latency (time in seconds) to start smoking on the PR task, the breakpoint (key presses needed to earn the last puff), and the total number of puffs self-administered. Behavioral data were analyzed using Product (snus vs. placebo snus) conditions as fixed and repeated factors, Beverage condition (alcohol vs. placebo beverage) as a fixed factor, and Subject as a random factor. The residuals were screened for normality. Shapiro-Wilk and Kolmogorov-Smirnov tests indicated that normality assumptions were best met following an inverse transformation for latency. Both number of puffs and breakpoint variables remained untransformed. The effects of interest were the main effects of Beverage and Product. Subjective, BAC, and heart rate data were analyzed using Product as a fixed and repeated factor, Beverage as a fixed factor, and Subject as a random factor. Baseline scores [T1] were used as a time-varying covariate for post-beverage and product absorption scores [T2]. The effects of interest were the main effects of Beverage and Product. For interactions, the simple

effects of variables within each level combination of the other variable(s) were tested. An experimental alpha of .05 was selected for all analyses as other studies have found significant pharmacological effects with a similar sample size with fewer participants (e.g. King and Epstein, 2005; Mckee et al., 2010).

RESULTS

PARTICIPANTS

Twenty-five (twelve female) DDS enrolled in the study, with all participants completing two experimental sessions. No differences were found between participants randomly assigned to the alcohol or placebo beverage condition with respect to their age, age of first tobacco or alcohol use, number of days in the past week when alcohol or tobacco was consumed, or how many alcoholic beverages or cigarettes were consumed the week before testing (Table 2).

TABLE 2

	Alcohol	Placebo	*p*	Total
N	15	10		25
Sex	9 males, 6 females	4 males, 6 females		13 males, 12 females
Age	24.8 (5.0)	21.8 (1.7)	.08	23.6 (4.2)
FTND score	4.5 (1.6)	4.1 (1.4)	.482	4.4 (1.5)
What age did you first try cigarettes?	14.7 (3.1)	16.3 (2.4)	.192	15.4 (2.9)
Total # of cigarettes this past week	98.3 (45.7)	80.2 (17.5)	.246	91.1 (37.6)
What age did you first try drinking alcohol?	14.5 (2.2)	15.0 (2.5)	.610	14.7 (2.3)
Total # of alcoholic drinks in the past week	26.7 (29.1)	25.6 (14.3)	.916	26.2 (23.9)

How many days in the past week did you try consuming alcohol?	2.9 (1.8)	3.3 (1.3)	.587	3.1 (1.6)

Table 2. Demographics for participants. Means scores reported with standard deviations in brackets. No significant differences with $p \leq .05$ were detected.

HEART RATE

No significant effects of either Product or Beverage or their interaction were observed on either average or maximum recorded heart rate 30 minutes post-product absorption (*ps* > .10).

ALCOHOL ADMINISTRATION VERIFICATION

All BAC levels were 0.00% at baseline. Alcohol increased BAC level 45 minutes post beverage, $t(15)$ = BAC of 0.055% (*SE* = .003%), $p <$. 001, which did not vary significantly between product conditions ($p = .246$).

SUBJECTIVE EFFECTS

No main effects or interactions of Beverage or Product conditions were detected for either QSU-Brief factor 1 or factor 2, nor for "crave cigarette" ratings (*ps* > .204). This was unexpected, as alcohol typically increases cigarette craving and snus was expected to decrease cigarette craving.

Subjective mood effects were assessed using the positive and negative SRS factors as well as ratings of intoxicated and enjoy taste, and the B-BAES scale factors.

Alcohol increased the prototypical stimulating effects of alcohol (B-BAES Factor 1 scores), $F(1,20.547) = 13.48$, $p <. 001$, as well as ratings of "intoxicated" $F(1,24.67) = 14.163$, $p < .001$, relative to the placebo beverage. A Beverage X Product interaction for B-BAES Factor 2 scores $F(1,23.754) = 8.624$, $p = .007$ showed that the placebo product and placebo beverage lowered sedation levels compared to snus ($p = .001$) (Figure 1). Neither Beverage nor Product influenced positive or negative SRS factor scores ($ps >$ .093).

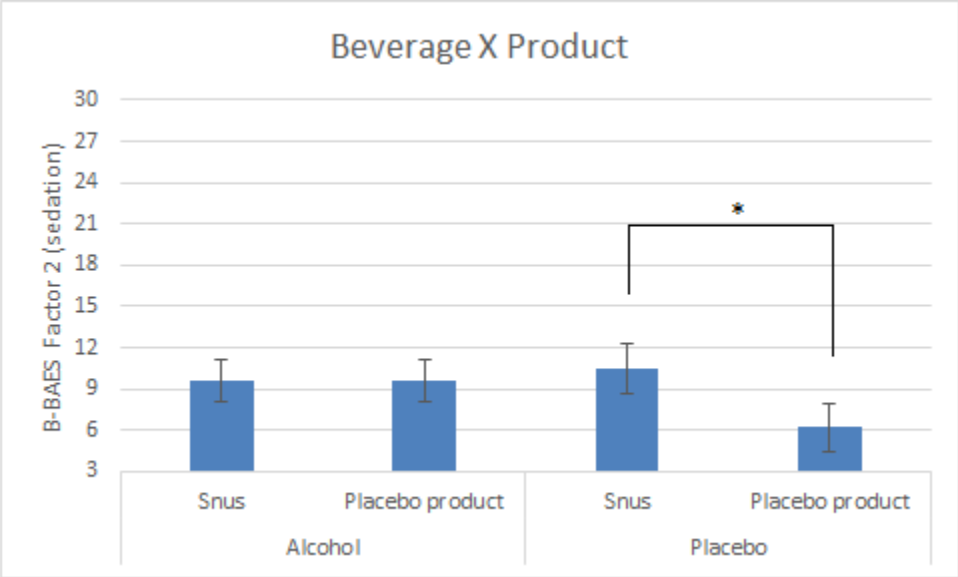


Figure 1 B-BAES Factor 2 (sedation) scores decreased when participants consumed the placebo product compared to the snus when consuming the placebo beverage. Estimated marginal means are shown, and error bars represent standard errors.

SELF-ADMINISTRATION

One female participant assigned to the alcohol beverage condition did not consume any tobacco after absorbing the product in the active snus condition. Behavioral

data for this participant was excluded due to a lack of data to compare against other participants.

No differences in latency to start smoking were detected between beverage conditions (p = .829), between snus and placebo product sessions (p = .805), nor interaction between both factors (p = .494). However, a main effect of Product was detected for the total number of puffs that participants took, $F(1,21.433) = 4.34$, p = .049; participants took fewer puffs when they consumed snus than when they consumed the placebo product (M = 18.63, SE = 0.74 vs. M = 19.80, SE = 0.73 puffs). As well, a main effect of Product was found for breakpoint, $F(1,21.16) = 4.943$, p = .037, where participants in the snus condition worked less hard for their last puff compared to when they were in the placebo product condition (M = 1473.42, SE = 233.60 vs. M = 1860.29, SE = 230.60 keypresses) (Figures 2a – c). These main effects remained for puffs (p = .043) and breakpoint (p = .024) if the excluded participant remained in the analyses. No effect of Beverage was detected for total puffs $F(1,23.66 = 1.09$, p = .31) or breakpoint $F(1,23.42) = .40$, p = .533, nor any Beverage X Product interactions for puffs ($F(1,21.43) = 3.04$, p = .096) or breakpoint $F(1,21.16) = 2.39$, p = .14)

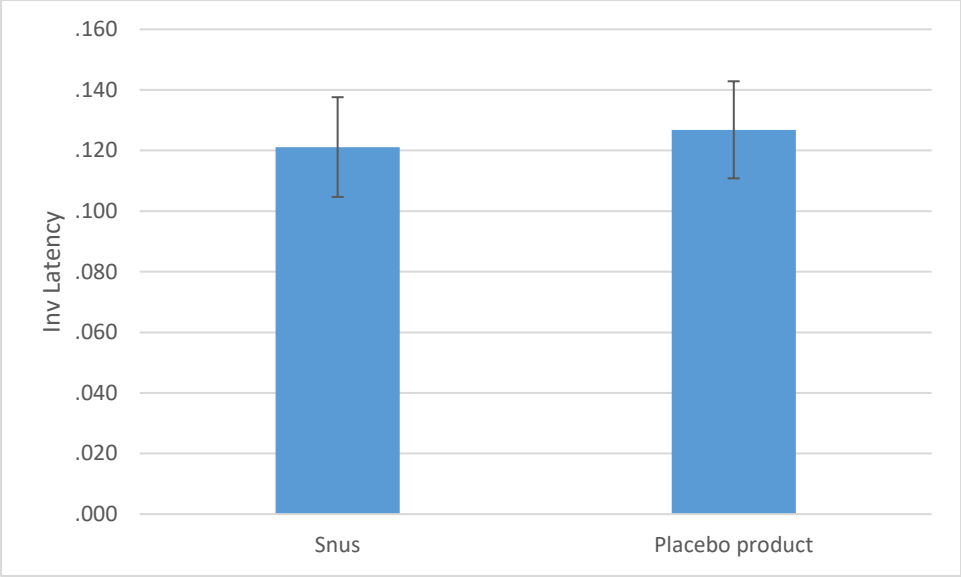


Figure 2a

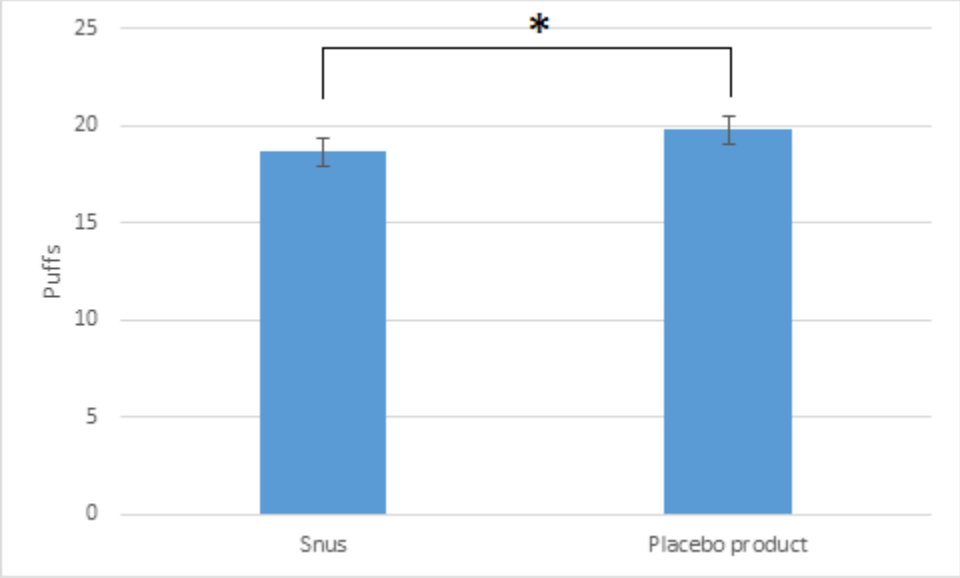


Figure 2b

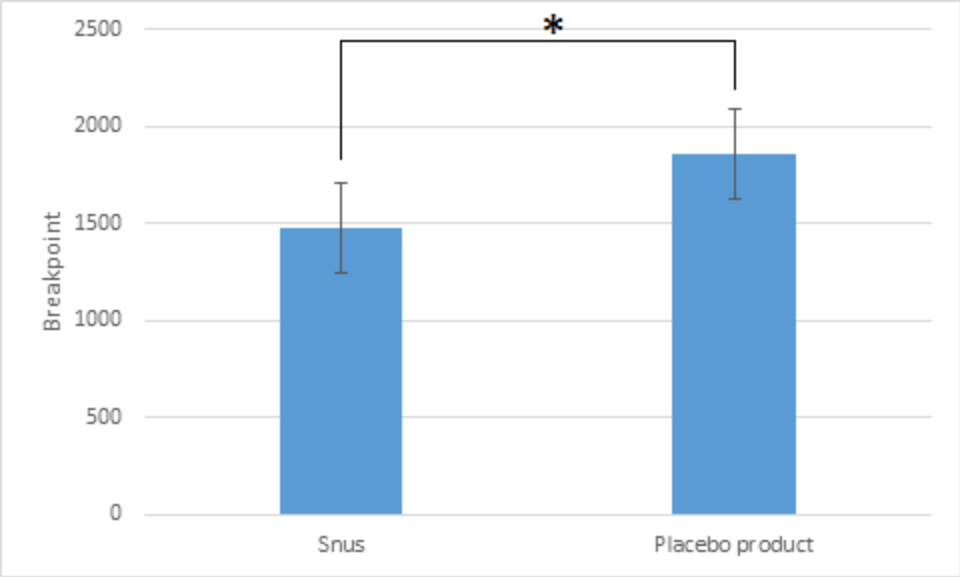


Figure 2c

Figures 2a-c Average latency (inversed), number of puffs, and breakpoint values between snus and placebo product sessions. Significant differences in puffs and breakpoint, but not in latency, were detected between product sessions. Error bars represent standard errors.

DISCUSSION

The results from the present study support the theory that snus reduces cigarette-consuming behavior in snus-naïve tobacco dependent cigarette smokers (Barrett, Campbell, Temporale, & Good, 2011; Barrett & Wagner, 2011; Lunell & Curvall, 2011). Furthermore, snus was able to reduce tobacco consumption in those participants who drank alcohol. Snus reducing alcohol-induced cigarette consumption fits with the assumption that snus contains tobacco factors that smokers seek when drinking. When snus is absorbed after alcohol, it reduced cigarette consumption, and this effect is not

seen with NRTs (e.g., Kouri et al., 2004), as these latter agents do not appear to be effective in reducing cigarette consumption when individuals consume alcohol.

Although snus did reduce smoking, there were a few counterintuitive effects seen in this study. First, snus absorption did not reduce subjective cigarette craving nor alter the latency to begin smoking at the start of the progressive ratio task. Latency to begin substance use is considered a similar construct to craving (Sayette et al., 2000), as higher craving is strongly correlated with shorter latency to begin substance use (Tiffany, 1990).

We can rule out the lack of an opportunity to smoke as an explanation for why snus did not affect cigarette craving or latency to start smoking. All participants were aware of the upcoming PR task and how they could earn cigarette puffs. It is possible that by the time craving and latency were measured, the chemicals within snus had not been fully absorbed. The bioavailability and pharmacokinetics of most of the chemicals in snus are unknown. Only the pharmacokinetics of nicotine in snus is established, and the rate of nicotine absorption is known to peak after 5 minutes (Benowitz et al., 1988). Nicotine concentration continues to rise for at least an hour following snus use (Digard, Proctor, Kulasekaran, Malmqvist, & Richter, 2013). The lack of an effect of snus on cigarette craving and latency to start smoking may be due to a lag in plasma levels of nicotine or other chemicals typically delivered after 30 minutes. The lack of psychopharmacologically significant absorption of the chemicals within snus after 30 minutes may be due to a change in pharmacokinetic properties in the mouth which the snus was absorbed. Snus is slightly alkaline (V2 Tobacco; Silkeborg, Denmark), and consuming an acidic cranberry beverage (Reddy, Norris, Momeni, Waldo, & Ruby, 2016) immediately before snus absorption occurred may have either reduced the bioavailable

nicotine and other chemicals typically absorbed from snus. This explanation is also consistent with the reduction in puffs taken and lowered breakpoint score seen during the PR task, as they occur later relative to snus administration. Snus' sedative effect seen in this study may also have influenced how hard individuals were willing to consume cigarette puffs. It remains conceivable that snus reduces cigarette craving in addition to consumption while individuals are drinking alcohol, but snus may take more than 30 minutes to have a pharmacologically significant effect.

There remains the possibility, albeit less parsimonious, that snus had a more complicated effect on alcohol-induced cigarette craving and smoking. Snus may have been adequately absorbed by the participants and may have reduced cigarette craving without participants' knowledge. Two weak tenets support this tentative explanation. The first is that previous studies have demonstrated that snus is pharmacologically active within 5 minutes (Lunell & Curvall, 2011), 15 minutes (Cobb, Weaver, & Eissenberg, 2010), and at 30 minutes (Kotlyar et al., 2007). These studies did not account for placebo effects, but it would be surprising if snus were not pharmacologically active within the current study's time frame if multiple studies detected an effect of snus on craving and consumption. None of these studies administered an acidic beverage, however, which could have interfered with the absorption of chemicals found in snus in the present study.

Nonetheless, there are limits to the duration of snus-induced craving reduction found in these experimental snus studies. Barrett and Wagner (2011) found that snus reduced cigarette craving after 10 minutes into product absorption but did not significantly affect craving after 40 minutes. The participants in the present study rated their cigarette craving within a 30-40 minute timeframe, meaning the maximal effect of

snus on cigarette craving may have occurred and passed. As well, Cobb, Weaver, and Eissenberg (2010) found that two different brands of snus reduced cigarette craving during an initial session but not during subsequent sessions, and only after 30 minutes of absorption. The different biological composition between brands of snus may affect the level of bioavailable nicotine or other chemicals in snus. Differences in chemical composition between different brands of snus might play a role in cigarette craving reduction.

A second possibility is that a reduction in craving does not necessarily indicate a reduction in smoking behavior and vice versa, as previously discussed (Germeroth & Tiffany, 2015). Substance craving and consuming behavior are multifactorial (Sayette et al., 2000). The specific mechanisms by which snus may reduce cigarette consumption and not craving may have to do with snus differentially reducing the "want"/urge to consume nicotine without participants expecting a reduction in craving (Berridge, Robinson, & Aldridge, 2009; Robinson & Berridge, 2001). Snus reduced participants' appetite for tobacco, as evidenced by reduced consumption of cigarette puffs on the PR task. However, both their intention to smoke (QSU-B factor 1) and expectation of withdrawal/negative affect relief (QSU-B factor 2) ratings remained unchanged. While the most reasonable explanation is that snus' effect was not pharmacologically significant until after the PR task started, it is also possible that participants believed they retained their desire to smoke as if they had received a placebo. Without the awareness that they had consumed a tobacco product, their "want"/urge to smoke might have remained regardless of whether or not they received a pharmacologically-active snus portion. Their continued urge to smoke could be due to both products (snus and placebo product)

being novel to the participants. Consuming a new substance would not trigger any cigarette satiation expectancies (e.g., Schlagintweit, Good, & Barrett, 2014). Moreover, assessment of cigarette craving preceded tobacco consumption on the PR task, so participants would not have been cued to evidence of their reduced drive to consume tobacco.

The expectation that snus will affect cigarette craving may be responsible for the reduction in cigarette craving seen in some previous studies, regardless of any pharmacological effect of snus absorption. For example, in Kotlyar and colleagues' (2007) study, participants reported that snus reduced tobacco withdrawal. However, they were told that their product contained tobacco, and therefore a placebo effect can not be ruled out. In Lunell and Curvall 's (2011) study, they found that snus did reduce cigarette craving similarly to nicotine chewing gum, but once again they did not use a placebo product or hide the nature of their product from participants.

In the present study, participants received no information regarding how their product and beverage should affect cigarette craving. They were informed that beverages may vary between sessions in the amount of alcohol they contained and that their product may vary between sessions and might contain components typically found in cigarettes such as tar, ammonia, nicotine, sucrose, menthol, and carbon monoxide. No statements directly related to an effect of either their beverage or product on cigarette craving or consumption were made, and statements were consistent across sessions. The rationale for this omission is that explanations influence beliefs, as instructional sets for NRTs play a significant role in how effective they are at reducing cigarette craving (Kelemen & Kaighobadi, 2007). Schlagintweit and colleagues (2014) found that manipulating the

expectancy of receiving nicotine versus receiving a placebo product has a significant effect on conscious cigarette craving regardless of actual product contents.

Even the sensorimotor aspects of smoking appear to be essential in reducing cigarette craving (Barrett, 2010; Rose, Behm, Westman, & Johnson, 2000). Behm, Schur, Levin, Tashkin, and Rose (1993) found that using a tobacco-flavored citric acid aerosol when experiencing a cigarette urge reduced participants' cigarette craving over a three week period. Levin and colleagues (1993) found that mimicking the sensations and actions from inhaling tobacco smoke with inhaling ascorbic acid reduced subsequent smoking behavior when cigarettes were available. Mimicking the sensorimotor aspects of smokeless tobacco products also reduces tobacco craving among smokeless tobacco consumers. For example, Gray, Breland, Weaver, and Eissenberg (2008) found that placebo chewing tobacco reduced urge to consume further chewing tobacco as well as intentions to smoke (QSU-B factor 1 cigarette craving) in regular smokeless tobacco users who were unaware they were receiving a placebo product. McChargue, Collins, and Cohen (2002) similarly found that when smokeless tobacco users were given the placebo product BaccOff but were unaware that it was a placebo product, their tobacco withdrawal symptoms were reduced after administration. As well, the previously discussed Cobb, Weaver, and Eissenberg (2010) study found that different brands of snus differentially reduced cigarette craving. The difference in effects of the brand of snus on craving may, in fact, be due to differences in sensorimotor factors between brands, although it is also possible that each brand provided different doses of nicotine and other tobacco factors which could not be accounted for in the study.

Furthermore, the belief that smoking will or will not be permitted during a timeframe is also known to modulate craving (Dar et al., 2010; Dar, Stronguin, Marouani, Krupsky, & Frenk, 2005). If there is no upcoming smoking opportunity, regular smokers report less cigarette craving than if smoking opportunities are to be available (Dar et al., 2005). Cigarette craving after a period of abstinence increases when smoking opportunities are anticipated shortly (Dar et al., 2010). In the present study, participants knew they would be allowed to smoke shortly after product administration. However, they were not directly informed about the nature of the product and what the product would do to their cigarette craving. It stands to reason that their conscious level of craving could remain high with an upcoming smoking opportunity while physiologically they would experience a reduced drive to smoke cigarettes after snus was absorbed.

In summary, some factors weakly support the alternative hypothesis that snus was adequately absorbed. Knowing that the PR task contained an upcoming smoking opportunity could have influenced participant's cigarette craving and consumption, although it is likely that belief would increase their craving instead of reducing it (Dar et al., 2010). Participants may have also held beliefs regarding what effect snus would have on their tobacco craving and consumption, but since all participants were naïve to snus, it is unlikely. However, it possible that the beverage altered the pharmacokinetics of snus absorption, such that snus did not alter cigarette craving. For further reviews of placebo effects and tobacco expectancies, see Dar & Barrett, (2014), Juliano et al. (2011), Perkins, Sayette, Conklin, & Caggiula, (2003), and Sutton, (1991).

It was also surprising that alcohol did not cause the prototypical increase in cigarette craving and smoking (Burton & Tiffany, 1997; Glautier, Clements, White,

Taylor, & Stolerman, 1996; McKee, Harrison, & Shi, 2010; McKee et al., 2006; Mello, Mendelson, & Palmieri, 1987; Mello, Mendelson, Sellers, & Kuehnle, 1980; Mintz et al., 1985). However, as previously stated, participants' BAC levels would have plateaued and begun descending when cigarette craving was sampled 45 minutes after alcohol was first consumed. The average breath alcohol reading 45 minutes after alcohol consumption was 0.055%, suggesting that BAC levels had plateaued and were starting to fall from the peak as the targeted peak was 0.06%. Rising BAC is predictive of increased cigarette craving compared to a falling BAC (e.g., Epstein, Sher, Young, & King, 2007; Kahler et al., 2014). The same is true for actual tobacco consumption, which tends to be enhanced only as BACs are rising (Epstein et al., 2007; Kouri et al., 2004; Mitchell et al., 1995). Moreover, participants' heart rates seemed unaffected by alcohol after 45 minutes. The lack of an effect of alcohol on heart rate is surprising, given that participants' heart rate would be expected to be above baseline value after 45 minutes of alcohol absorption according to the results of Conrod, Peterson, Pihl, and Mankowski (1997). However, Brunelle and colleagues (2007) found that when social drinkers of unknown smoking status were given 0.75g/kg of alcohol to consume over 15 minutes, there was no effect of alcohol on heart rate after 40 minutes. Their participants were given a higher alcohol dose than those in the present study, and their BAC levels had plateaued at 40 minutes and were beginning to drop.

It is possible that the timing of alcohol administration was too early relative to when cigarette craving was measured to notice any alcohol-induced cigarette craving in the present study. Altering the order of the beverage and product administration would verify whether a rising BAC before the PR task would increase cigarette craving and if

snus can act as a prophylactic against alcohol-induced cigarette craving and consumption. It is also possible that the alcohol dose selected for this experiment was too low to produce the prototypical effect of alcohol consumption on cigarette craving as seen in studies that utilize a higher BAC level (e.g., McKee et al., 2010 utilizing a target BAC of 0.08%). However, alcohol-induced cigarette craving has been observed in studies utilizing alcohol doses as low as 0.4g/kg and 0.5g/kg (Glautier et al., 1996; Kahler et al., 2014). Moreover, participants did endorse feeling intoxicated when under the influence of alcohol compared with those in the placebo beverage condition, suggesting that the dose of alcohol participants consumed was sufficiently psychoactive.

Additionally, the only reported subjective mood state snus produced was an increase in feeling sedated, and only when consuming the placebo beverage. Increased sedation is unlike the positive emotional states reported in other studies such as increased levels of satisfaction after snus-naïve individuals have used snus (Caldwell et al., 2010; Hatsukami, Zhang, O'Connor, & Severson, 2013; Lunell & Curvall, 2011). Since alcohol increases subjective ratings of stimulation, it is possible that combining alcohol and snus is reinforcing because the alcohol-induced stimulation counteracts the sedative properties of snus. The lack of other subjective effects is possibly due to the timing of absorption of snus. Also, as previously described, participants were naïve to snus and were not explicitly told they were consuming a tobacco product. It is possible that this increase in sedation was a psychological reaction to the product, but this is unlikely as it did not occur when participants consumed the placebo product BaccOff along with the alcoholic beverage.

This study, therefore, addressed one aspect of the alcohol-tobacco phenomenon; that the administration of non-pyrolyzed tobacco immediately after alcohol (or placebo beverage) consumption reduces cigarette smoking. BAC levels were dropping before the start of the PR task. The beverage could have interfered with the absorption of tobacco constituents, causing the blood plasma levels of tobacco constituents to continue to rise and affect cigarette consumption during the PR task. It is also possible that the tobacco constituents were not sufficiently absorbed before the PR task to influence participants' experience of craving (Figure 3)

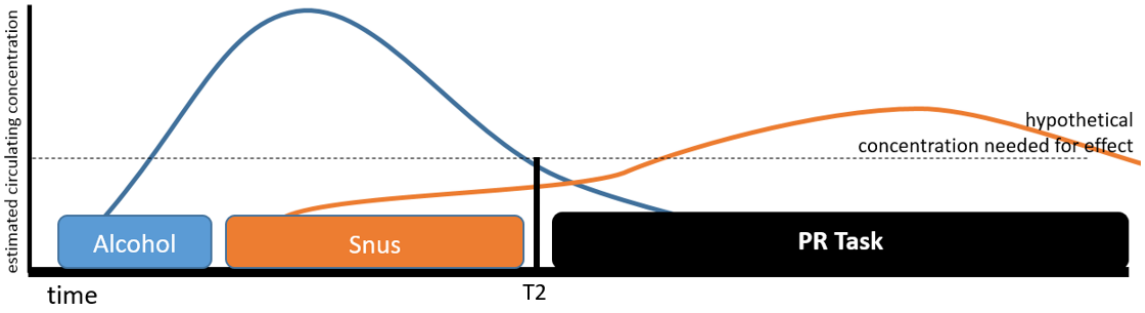


Figure 3 Null effects of both alcohol and snus absorption on craving immediately before (at T2) the progressive-ratio task may have been due to insufficient levels of alcohol and tobacco chemicals absorbed by participants. This graph demonstrates how continued absorption and distribution of tobacco factors throughout the task might explain the effect snus had on both puffs taken, and effort to earn puffs (breakpoint).

The next aspect of the alcohol-tobacco co-use phenomenon worth examining is whether tobacco administration before alcohol consumption produces the same reduction in cigarette consumption and if cigarette craving would be reduced immediately following snus absorption, regardless of whether the individual has consumed alcohol or not. This different order of administration would indicate whether snus could be used

prophylactically against alcohol-induced cigarette consumption, similar to how oral NRTs are used to protect against anticipated cigarette cravings (Shiffman et al., 2003).

CHAPTER 3: SNUS MODERATES ALCOHOL-INDUCED CIGARETTE CRAVING AND CONSUMPTION

This chapter contains an unpublished research study. My role included designing the experiment, running participants, analyzing the results, and writing the attached paper. This research took place in Dr. Sean Barrett's Substance Use and Addictions Lab with research funds granted to him. Drs. Sean Barrett, Sherry Stewart, Kim Good, and Natalie Rosen provided feedback on the writing of the attached paper. Parisa Asadnejad assisted in running research participants.

ABSTRACT

Moist Swedish snus has been found to reduce cigarette craving in experimental studies and by self-report of former cigarette smokers. The mechanisms by which snus functions appear to be related to nicotine absorption. In Study 1 of this thesis, snus reduced cigarette consumption in dependent smokers even when participants had consumed alcohol, but neither snus nor alcohol affected cigarette craving. This lack of an effect of snus on cigarette craving was hypothesized to be because alcohol slowed snus absorption, while alcohol's lack of effect on craving was thought to be related to the fact that blood alcohol concentration levels were falling when cigarette craving was measured. The present study (Study 2) examined the role of alcohol and how the beverage influences snus absorption by administering snus before alcohol consumption. The purpose was to determine whether snus can prevent alcohol-induced cigarette craving. Twenty-two daily dependent smokers were recruited and, using a between-

within design, participants were unknowingly assigned to either the placebo or alcoholic beverage condition. On either day, a 1-gram snus portion containing 8mg of nicotine or a placebo product was administered before either the intoxicating dose of alcohol (BAC 0.06%) or a placebo beverage, delivered on two experimental days. Craving was assessed before a cigarette self-administration task. The latency to start smoking, the number of puffs earned, and the number of keypresses for the last puff earned were collected during this one-hour progressive ratio (PR) cigarette self-administration. Snus increased the latency to start smoking on the PR task ($p = .046$). As well, alcohol increased cigarette craving across two cigarette craving measures before the PR task (*ps* $\leq .024$) and increased how hard participants worked to consume cigarette puffs on the PR task ($p = .024$). This study demonstrates that snus can reduce smoking behavior even in the context of alcohol-induced smoking.

INTRODUCTION

Swedish snus has been shown to reduce cigarette craving and consumption in smokers in experimental studies (Burris et al., 2014; Caldwell et al., 2010; Fagerstrom et al., 2012; Joksić et al., 2011) and by individuals' self-report (Gilljam & Galanti, 2003; Lindström, 2007; Lund et al., 2011; Lund et al., 2010; Scheffels et al., 2012). Many snus users report that they consume fewer cigarettes than they previously did since beginning using snus (Lund et al., 2011). Therefore, snus can be conceptualized as a nicotine replacement product for smokers, with snus replacing cigarette smoke as a source of nicotine, the primary alkaloid on which smokers become dependent (Watkins et al., 2000).

Snus and alcohol use patterns suggest that snus affects alcohol-induced cigarette consumption patterns in cigarette consumers in countries where both substances are permitted. Snus and alcohol are often co-administered (Norberg, Malmberg, Ng, & Broström, 2015) and, in Swedish and Norweigan samples, snus users tended to be more substantial drinkers than their snus-abstaining counterparts (Larsen et al., 2013; Lund et al., 2008; Norberg et al., 2015). It presently is unknown at this time whether snus directly increases alcohol craving and consumption. Regarding nicotine in tobacco, to my knowledge, there is no evidence that nicotine replacement therapies (NRTs), which contain no other tobacco products, reduce alcohol-induced cigarette craving and consumption. Discontinuing smoking while drinking is considered challenging for smokers trying to quit (McKee et al., 2006; Toll et al., 2008). This lack of evidence of NRTs reducing alcohol-induced cigarette craving and consumptions may be due to the dearth of studies examining smokers utilizing NRTs who are also problematic drinkers

(Kouri et al., 2004). Because snus users consume more alcohol than do cigarette smokers, and there is a lack of evidence demonstrating that NRTs reduce alcohol-induced cigarette craving and consumption, it is possible that chemicals within snus beyond nicotine moderate alcohol-induced cigarette consumption. It also remains possible that alcohol increases snus craving and consumption more than cigarette craving and consumption. This, in turn, might cause individuals who use both substances to discontinue smoking and remain snus users. However, because snus users report that snus has helped them reduce their previous cigarette craving and consumption (Scheffels et al., 2012), is it possible that snus dampens alcohol-induced cigarette consumption. Snus contains additional reinforcing chemicals in addition to nicotine including nornicotine, anatabine, anabasine, myosmine, 2,3'-dipyridyl, and cotinine (Digard, Gale, et al., 2013; ENVIRON International Corporation, 2010; Stepanov et al., 2008). It is reasonable to conclude that snus may be more effective in curbing cigarette craving and smoking relative to NRTs in the presence of alcohol because of the additional tobacco factors found in snus that smokers who drink are craving.

Study 1 of this thesis examined the effect that alcohol administration immediately followed by snus administration had on subsequent cigarette craving and consumption in snus-naïve dependent cigarette smokers. The study demonstrated that snus administration did reduce cigarette consumption but not cigarette craving. The most parsimonious explanation for this phenomenon was that the beverage consumed before using snus altered the rate of absorption of the chemicals within snus, causing a lag in the expected timeframe when snus should have altered cigarette craving. The rate of nicotine absorption from snus is greatest after 5 minutes (Benowitz et al., 1988) and blood serum

levels of nicotine continue to rise for at least 30 minutes of continuous use (Digard, Proctor, et al., 2013). If drinking an acidic beverage interferes with snus' nicotine absorption into the body, then snus' peak effect after drinking may be later than when it is singly administered (Cobb et al., 2010; Kotlyar et al., 2007; Lunell & Curvall, 2011). If snus can reduce the drive to consume cigarette smoke after alcohol consumption but requires more than 30 minutes to be effective at reducing cigarette craving, then snus administration before a drinking episode may reduce both subsequent cigarette consumption and subsequent craving. This question has ecological validity as it would address the practical question of whether snus can be used prophylactically in advance of a drinking session to curb cigarette craving and consumption.

The purpose of this study was to examine the alcohol-tobacco phenomenon by reversing the order of administration from Study 1, to further clarify the order effects of snus administration while consuming alcohol. It was predicted that snus use would acutely reduce both cigarette craving and consumption. If snus is absorbed before alcohol administration, the reduction of cigarette craving and consumption should continue after alcohol absorption. Since blood alcohol concentration (BAC) levels would be near their peak both when cigarette craving is reported and when the PR task occurs, so it was predicted that alcohol would increase cigarette craving and consumption. Since snus reportedly reduced cigarette craving and consumption by drinkers who were trying to quit smoking (Scheffels et al., 2012), I predicted that snus would continue to reduce cigarette craving and consumption regardless of alcohol administration. Lastly, I predicted that both snus and alcohol would increase positive subjective states beyond their effect on cigarette craving and consumption.

METHODS

PARTICIPANTS

Non-treatment seeking daily dependent smokers (DDS) (i.e., daily tobacco use for a minimum of one year; score ≥ 3 on the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991)) were recruited from the Halifax Regional Municipality in Nova Scotia. All were regular heavy consumers of alcohol. Each had consumed a minimum of 4 drinks for women (5 drinks for men) at least once/week during the previous month. Each was a non-problem drinker, scoring 2 or less on the short version of the Michigan Alcoholism Screening Test (SMAST; Selzer, Vinokur, & Rooijen, 1975). Potential participants were told that the study would consist of two experimental sessions that would involve the administration of substances that may vary in their contents of ingredients typically found in cigarettes (e.g., tar, ammonia, menthol, nicotine, sucrose) followed by the administration of beverages that may vary in alcohol content. All participants reported that they were medically healthy, all had reached the minimum age to legally consume alcohol and tobacco in Nova Scotia, none intended to quit smoking over the subsequent 30 days, and none were using NRT products. All participants were found to be naïve to snus before the study when interviewed upon completion of the study. The study adhered to guidelines from the Declaration of Helsinki and was approved by a local research ethics board.

DESIGN

The protocol consisted of two double-blind, randomized sessions with a 2 (beverage condition: alcohol or placebo) x 2 (product condition: snus or placebo)

between-within subjects design. All sessions were identical in procedure except that participants were randomly assigned to one beverage condition (alcohol or placebo) for both sessions, and product condition was counterbalanced between sessions.

Beverages

In the alcohol condition, participants received 2.28 ml 50% USP units of alcohol per kilogram of body weight for women and 2.73 ml 50% USP units of alcohol per kilogram of body weight for men to target a peak blood alcohol concentration (BAC) of 0.06% (MacDonald et al., 2000). Drinks were mixed 1:4 parts vodka to cranberry juice. The placebo beverage was made up of 5 parts cranberry juice with a small amount of alcohol applied to the rim of the glasses and on the drink tray to ensure the odor and taste of alcohol (Kushner et al., 1996).

Products

In the snus condition, participants received a 1g Phantom brand Swedish-style snus regular portion containing 8mg of nicotine and a manufacturer reported pH of 8.5 (V2 Tobacco; Silkeborg, Denmark). Snus has a nicotine loading timeframe of 30 minutes (Foulds et al., 2003; Lunell & Lunell, 2005). In the placebo condition, participants received a BaccOff brand nontobacco placebo portion (V2 Tobacco; Silkeborg, Denmark), which mimics the sensory properties of snus (Coffey & Lombardo, 1998).

Blinding

Participants were blind to the contents of the beverages and products received during each session. Participants were informed that the products might vary between sessions in their content of ingredients typically found in cigarettes, but they were not

specifically informed that the products might vary between sessions in nicotine content. Similarly, participants were informed that the alcohol content of the beverages might vary, but not that the doses were selected to produce either mild or no intoxication. To maintain the integrity of the blind, research personnel not otherwise involved with data collection prepared all beverages, administered the oral product, and recorded all breath alcohol concentration measurements.

SUBJECTIVE ASSESSMENT

Subjective Rating Scales

An author-compiled Subjective Rating Scale (SRS) was used to assess subjective state (i.e., "relaxed", "pleasant", "head rush", "stimulated", "jittery", "dizzy", "irritable", "trouble concentrating", "anxious", "satisfied", "high", "alert", "frustrated", "sedated", "intoxicated", "enjoy taste", and "crave cigarette"). Each item was rated on a 10-cm horizontal line labeled with integers 1-10 and anchored with the endpoints "Not at all" and "Extremely." Similar scales have been widely used to assess subjective drug effects, and this method of assessment has been shown to be both reliable (e.g., Wewers & Lowe 1990) and sensitive to the acute effects of alcohol and tobacco (e.g., Barrett, Campbell, Roach, Stewart, & Darredeau, 2013; Barrett, Tichauer, Leyton, & Pihl, 2006). Positive items ("relaxed", "pleasant", "head rush", "stimulated", "satisfied", "high", and "alert") were combined to create a positive affect factor, and negative items ("jittery", "dizzy", "irritable", "trouble concentrating", "anxious", "frustrated", and "sedated") were combined to create a negative affect factor. As calculated in Study 1, the positive affect factor had a good internal item consistency Cronbach's alpha of .80, and the negative affect factor a good internal item consistency Cronbach's alpha of .85. "Intoxication" was

analyzed separately.

As well, the SRS item "enjoy taste" was administered only following product administration, the item "like drink" was administered only after beverage administration, and the item "want alcohol" was administered after both.

Questionnaire of Smoking Urges-Brief

The Questionnaire of Smoking Urges-Brief (QSU-B; Cox, Tiffany, & Christen, 2001) is a 10-item self-report measure used to assess tobacco craving across two dimensions. Each question is rated on a scale of 1 to 7, with 1 indicating "strongly disagree," 4 "neutral," and 7 "strongly agree." Five items grouped as factor 1 reflect a strong desire and intention to smoke, with the perception that smoking will be rewarding. These include items such as "I have a desire for a cigarette right now" and "If it were possible, I probably would smoke now." The remaining five items reflect anticipation of relief from negative affect with an urgent desire to smoke and are known as factor 2. These include items such as "I could control things better right now if I could smoke" and "I would do almost anything for a cigarette right now." Item scores were totaled into index scores for factors 1 and 2, each ranging from 5 to 35. Internal item consistency for both factors 1 and 2 from Study 1 was Cronbach's alpha = .97, similar to the reliability of the original factors found in the Questionnaire of Smoking Urges (Tiffany & Drobes, 1991).

Brief Biphasic Alcohol Effects Scale

The Brief Biphasic Alcohol Effects Scale (B-BAES; Martin, Earleywine, & Musty, 1993) is a 6-item self-report measure used to assess the subjective stimulant effects of alcohol associated with a rising BAC (factor 1), as well as the subjective

sedative effects associated with a descending BAC (factor 2) (Rueger, McNamara, & King, 2009). Factor 1 items include "energized", "excited", and "up", whereas factor 2 items include "sedated", "slow thoughts", and "sluggish". Each item was rated on a 10-cm horizontal line labeled with integers 1-10 and anchored with the endpoints “Not at all” and “Extremely” similar to the scale used with the author-compiled Subjective Rating Scales. Internal item consistency for factor 1 ranges between Cronbach’s alpha of .89 to .93, and .90 to .91 for factor 2 from Study 1. Factor 1 on the B-BAES correlates with the original BAES factor 1 by $r = .92$, and factor 2 correlates with the original BAES factor 2 by $r = .93$ ($ps < .001$) (Martin, Earleywine, Musty, & Swift, 1993).

BEHAVIORAL MEASURES

Heart Rate

The average and maximum heart rates of participants were collected alongside subjective assessments (RS-100 Polar Heart Rate Monitor; Polar Electro Canada; Lachine, Canada), as alcohol (Brunelle et al., 2007) and nicotine (Perkins et al., 1995) are known to increase heart rate.

Progressive Ratio Task

Participants could earn puffs of their preferred brand of cigarette (supplied by the lab) using a computerized progressive ratio (PR) task over 60 minutes. Ten key presses were required to earn the initial puff, and the requirement increased at a ratio of 1.3 for each subsequent puff. Participants were not required to earn any puffs but were required to remain seated in front of the cigarette until the end of the session. The latency to start smoking, the total number of puffs earned, and the breakpoint – the number of key presses completed to earn the last puff – were recorded for each session. The PR task has

been demonstrated to be sensitive to pharmacological manipulations in human tobacco self-administration studies (e.g., Barrett et al., 2013).

PROCEDURE

Participants arrived for each testing session having abstained from smoking and alcohol for a minimum of 12 hours, and from food and caffeine for a minimum of 2 hours. A breath CO reading of 15 ppm or less and/or a 50% reduction in CO from the non-abstinent baseline confirmed abstinence from smoking (Vitalograph; Lenexa, KS). Abstinence from alcohol was confirmed using an Alcomate Premium breath alcohol analyzer (AK Solutions; Lansdale, PA) with a cutoff of 0.00%. Afterward, participants were provided with a cigarette of their preferred brand to smoke and then waited one hour. The purpose of having participants smoke a preferred brand cigarette and then wait an hour was to harmonize the degree of tobacco withdrawal both between sessions and across participants. Typically, DDS will have consumed a cigarette within the first hour after waking (Shiffman et al., 2002; 2014) and otherwise would be experiencing high tobacco withdrawal symptoms at the beginning of the experiment. Table 3 presents a timeline outlining the sequence of procedures.

TABLE 3

Procedure	Time (minutes)	Total time (minutes)
Informed consent/ reminded of right to withdrawal		
Confirmation of alcohol and smoking abstinence	5	5
Smoke cigarette	5	10
Wait time	60	70
Heart rate and subjective assessment	7	77
Administration of product	30	107
Disposal of product, and subjective assessment	7	114
Administration of beverage	15	129
Beverage absorption	20	149
Breath alcohol, heart rate, and subjective assessment	10	159
PR task	60	219
Sobering period	60	279

Table 3. Timeline of experimental procedures for Study 2

After completing a baseline subjective assessment and heart rate recording, participants were given their product and instructed to place it between their upper gum and upper lip for 30 minutes while they waited alone in the testing room. Afterward,

participants disposed of their product in a container such that the researcher could not see which product they received and completed a post-product subjective assessment. Participants then consumed their assigned beverage (alcohol or active placebo) over 15 minutes, followed by a 20-minute waiting period for their drink to absorb. Afterward, a post-beverage subjective assessment and heart rate and BAC recordings were conducted. Participants could then earn cigarette puffs over the following 60 minutes. Following the PR task, the session concluded with a "sobering period" of at least one hour during which participants were provided with a light snack and rested until their BAC was below 0.04%. All participants completed this sobering period in each session to maintain the blind of the experiment.

STATISTICAL ANALYSIS

Data were analyzed using linear mixed models in SPSS version 20.0 for Windows (SPSS Inc.; Chicago, IL). Linear mixed models account for unequal sample sizes by producing adjusted degrees of freedom and estimated marginal means. An appropriate covariance structure was selected for each variable based on model simplicity and the likelihood ratio test. The behavioral measures were the latency (time in seconds) to start smoking on the PR task, the breakpoint (key presses needed to earn the last puff), and the total number of puffs self-administered. Behavioral data were analyzed using Product (snus vs. placebo snus) condition as a fixed and repeated factor, Beverage condition (alcohol vs. placebo beverage) as a fixed factor, and Subject as a random factor. Shapiro–Wilk and Kolmogorov–Smirnov tests screened for and confirmed normality assumptions were met for these variables. Subjective data were analyzed using Product as a fixed and repeated factor, Beverage as a fixed factor, Time as a repeated factor, and Subject as a

random factor. Baseline scores [T1] were used as a time-varying covariate for product absorption [T2] and post-beverage [T3] scores. For interactions, the simple effects of variables within each level combination of the other variable(s) were tested. SRS items "enjoy taste" and "like drink" were analyzed without a time-varying covariate as they were sampled only at a single time point. Family-wise Bonferroni corrections were applied to subjective analyses to account for multiple testing in Study 2 ($\alpha = .05*.67 = .033$) as it contained an additional timepoint in the analyses. Behavioral analyses retained an α of .05 as in Study 1 as other studies have found significant pharmacological effects with a similar sample size with fewer participants (e.g. King and Epstein, 2005; McKee et al., 2010).

RESULTS

PARTICIPANTS

Twenty-two (ten female) DDS enrolled in the study, and twenty (eight female) completed both experimental sessions. No differences were found between participants randomly assigned to the alcohol or placebo beverage condition with respect to age, age of first tobacco or alcohol use, and total alcoholic beverages and total cigarettes consumed in the previous week (Table 4).

TABLE 4

	Alcohol	Placebo	*p*	Total
N	11	11		22
Sex	6 males, 5 females	6 males, 5 females	1.0	12 males, 10 females
Age	24.4 (4.7)	25.5 (8.1)	.702	24.9 (6.5)
FTND score	4.6 (1.9)	5.1 (1.4)	.529	4.9 (1.6)
What age did you first try cigarettes?	14.0 (3.3)	15.6 (1.9)	.193	14.7 (2.7)
Total # of cigarettes this past week	83.4 (43.2)	93.0 (41.3)	.606	88.1 (41.5)
What age did you first try drinking alcohol?	14.9 (2.4)	14.3 (2.2)	.526	14.5 (2.3)
Total # of alcoholic drinks in the past week	10.9 (10.1)	15.3 (16.4)	.464	13.0 (13.3)

How many days in the past week did you try consuming alcohol?	2.5 (1.6)	2.1 (1.6)	.608	2.3 (1.6)

Table 4. Demographics for participants. Means scores reported with standard deviations in brackets. No significant differences with $p \leq .05$ were detected.

ALCOHOL ADMINISTRATION VERIFICATION

All BAC levels were 0.00% at baseline. Alcohol increased BACs 20 minutes post ingestion (45 minutes after starting to consume their first beverage) reaching the target BAC of 0.06% ($M = .059$, $SE = .004$), and did not vary significantly by participant product condition ($p > .39$).

HEART RATE

Heart rate was not affected by alcohol or snus consumption or their interaction (*ps* > .055).

SUBJECTIVE EFFECTS OF CIGARETTE CRAVING

For QSU-Brief factor 1 and factor 2 variables as well as SRS item "crave cigarette", a main effect of Time ($F(1,46.60) = 17.117$, $p < .001$, $F(1,35.45) = 14.098$, $p = .001$, and $F(1,57.36) = 14.080$, $p < .001$, respectively) revealed that cigarette craving increased following the administration and absorption of the beverage ($M = 23.1$, $SE = 1.07$ vs. $M = 27.7$, $SE = 1.07$; $M = 13.3$, $SE = 0.76$ vs. $M = 16.4$, $SE = 1.02$; and $M = 5.5$,

SE = 0.43 vs. *M* = 7.1, *SE* = 0.43, respectively). A Beverage X Time interaction, $F(1,35.40) = 6.081$, $p = .019$, for QSU-B factor 2 was found as craving increased after participants received and absorbed the alcoholic beverage (*M* = 12.4, *SE* = 1.08 vs. *M* = 17.6, *SE* = 1.45 vs.; $p < .001$), which was not seen in the placebo beverage condition (*M* = 14.1, *SE* = 1.07 vs. *M* = 15.2, *SE* = 1.43 ; $p = .363$). A similar interaction was seen for "crave cigarette", $F(1,54.350) = 5.419$, $p = .024$, where craving increased post alcoholic beverage (*M* = 5.2, *SE* = 0.61 vs. *M* = 7.8, *SE* = 0.61, $p > .001$) and not post placebo beverage (*M* = 5.9, *SE* = 0.61, vs. *M* = 6.5, *SE* = 0.61, $p = .313$) (Figures 4a – c). There was no significant interaction for Beverage X Time for QSU-B factor 1 ($F(1,46.63) = 2.345$, $p = .132$). No effects of Product on subjective cigarette craving were detected.

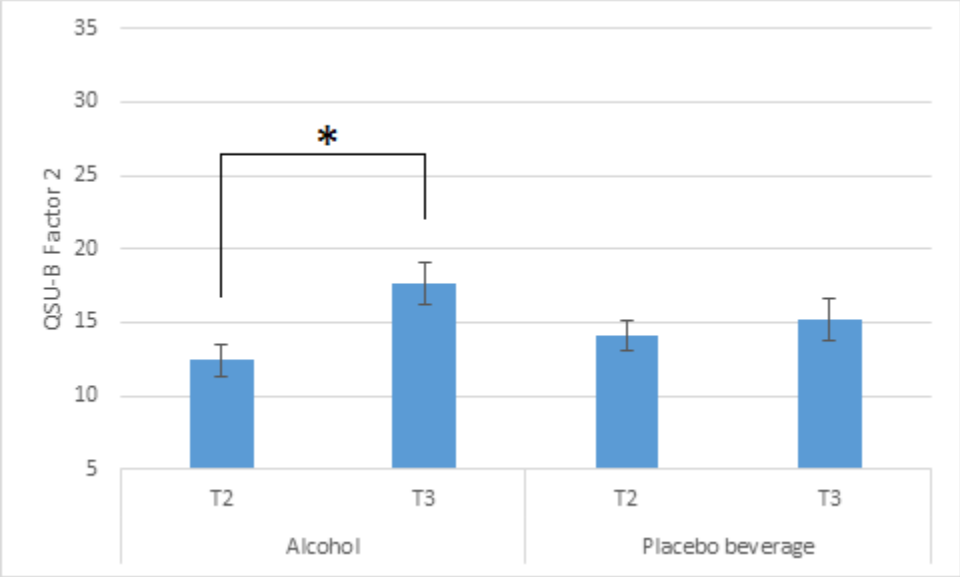


Figure 4a

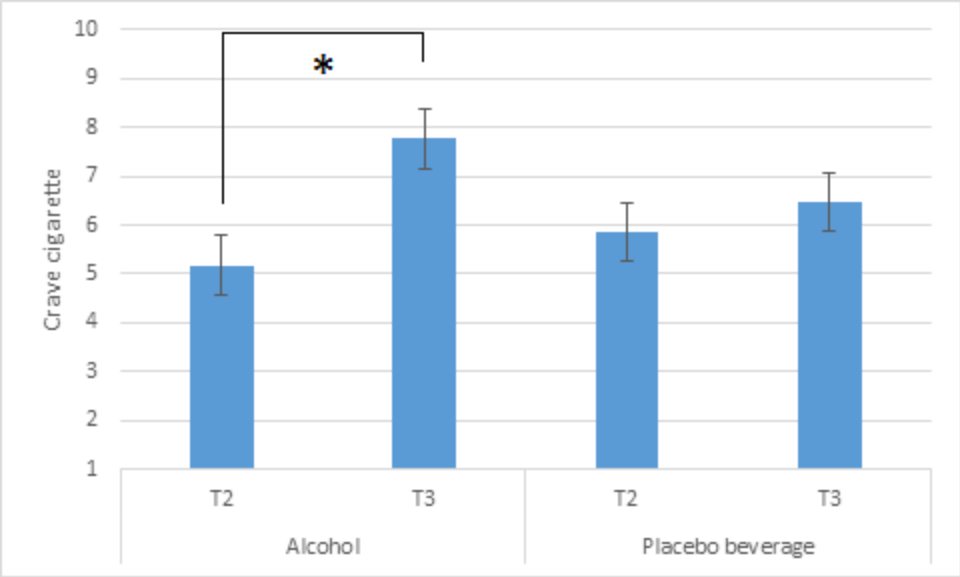


Figure 4b

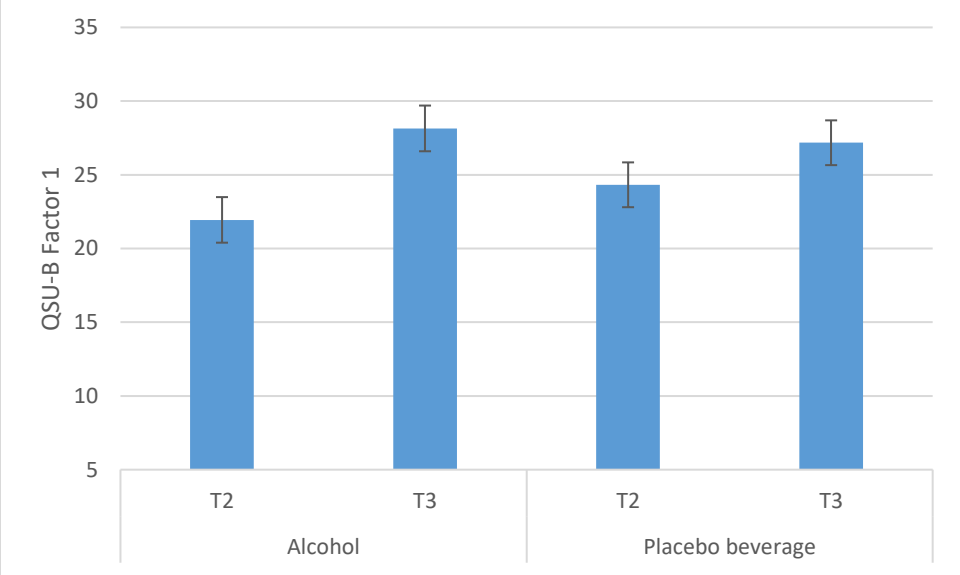


Figure 4c

Figures 4a-c. Covariate adjusted for time 1 (baseline levels) estimated marginal means of QSU-B factor 2 and "crave cigarette" demonstrate significant increases in cigarette craving following alcohol consumption from time 2 - time 3. Alcohol did not affect QSU-B factor 1 cigarette craving.

SELF-ADMINISTRATION

A main effect of Product was detected for participants' latency to start smoking, $F(1,37) = 4.24$, $p = .046$, where those who received snus took longer to start smoking than those who received placebo product ($M = 13.8$, $SE = 1.35$ vs. $M = 9.9$, $SE = 1.32$ seconds) (Figure 5a). A main effect of Beverage on breakpoint, $F(1,37) = 5.53$, $p = .024$, revealed that participants in the alcoholic beverage condition worked harder to earn puffs than those in the placebo beverage condition ($M = 2174.4$, $SE = 283.29$ vs. $M = 1243.2$, $SE = 276.78$ keypresses) (Figure 5b). No differences in puffs taken were detected between those in the alcohol or placebo beverage condition, $F(1,19.001) = .219$, $p = .645$ ($M = 18.9$, $SE = 1.24$ vs. $M = 18.1$, $SE = 1.24$), nor between those in the snus or placebo product condition, $F(1,16.44) = .834$, $p = .374$ ($M = 18.28$, $SE = .92$ vs. $M = 18.76$, $SE = .91$). There were no other main or interactive effects.

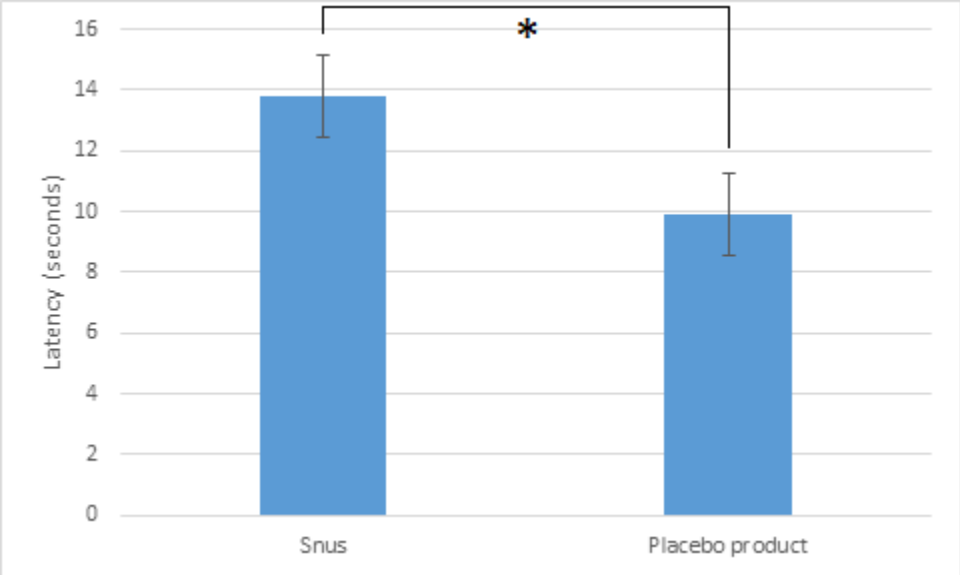


Figure 5a

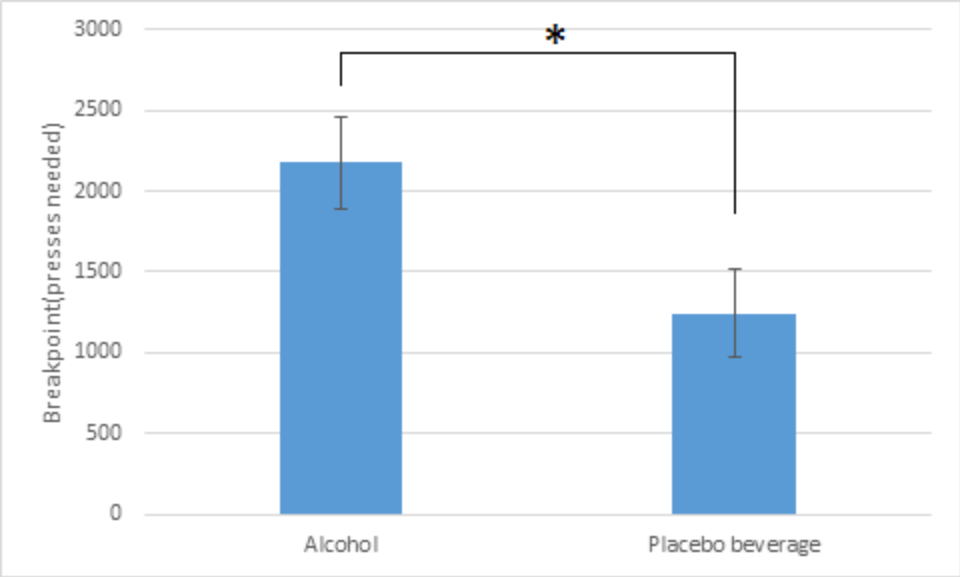


Figure 5b

Figures 5a and b. Figure 5a Main effect of product (snus vs. placebo product) on the latency to start smoking. Figure 5b Main effect of beverage condition (alcohol vs. placebo beverage) on breakpoint on the progressive ratio task. Participants who consumed snus took longer to begin the progressive ratio task than those who consumed the placebo product. As well, participants who consumed alcohol worked significantly harder to earn cigarette puffs than those who consumed the placebo beverage.

ADDITIONAL SUBJECTIVE EFFECTS

The remaining subjective mood effects were assessed using the positive and negative affect SRS factors, the B-BAES scale, and the SRS items "intoxicated", "like taste", "want alcohol", and "enjoy taste". A Beverage X Time interaction $F(1,18.749) = 20.143$, $p < .001$ revealed that alcohol increased ratings of intoxication after consumption of the alcoholic beverage ($M = 1.4$, $SE = .26$, vs. $M = 5.7$, $SE = .56$, $p < .001$) but not after consumption of the placebo beverage ($M = 1.4$, $SE = .26$, vs. $M = 2.3$, $SE = .56$, $p =$

.114). A Beverage X Time interaction was also found for positive SRS items, $F(1,19.790) = 4.51$, $p = .046$, with alcohol increasing positive affect post-alcoholic beverage *(*$M = 31.6$, $SE = 2.00$, vs. $M = 35.8$, $SE = 2.09$, $p = .044$), an effect that was not seen with the placebo beverage *(*$M = 31.8$, $SE = 1.99$, vs. $M = 30.1$, $SE = 2.09$, $p = .408$). As well, a Beverage X Time interaction was found for the prototypical stimulating effect of alcohol consumption (B-BAES Factor 1), $F(1,29.697) = 6.733$, $p = .015$. Participants reported a greater degree of the prototypical stimulating effects of alcohol after consuming the alcoholic beverage ($M = 14.3$, $SE = 1.18$, vs. $M = 18.3$, $SE = 1.09$, $p = .007$) whereas no such change was seen with the placebo beverage ($M = 14.6$, $SE = 1.17$ vs. $M = 13.8$, $SE = 1.07$, $p = .837$).

A main effect of Product revealed that participants who received snus reported higher positive affect SRS factor scores, $F(1,18.735) = 5.60$, $p = .029$, relative to those who consumed the placebo product *(*$M = 34.3$, $SE = 1.94$, vs. $M = 30.3$, $SE = 0.95$). A Product X Time interaction was found for negative SRS factor scores $F(1,21.414) = 16.10$, $p < .001$. For those participants who used snus, negative SRS factor scores remained constant from post-product to post-beverage consumption ($M = 16.5$, $SE = 1.46$, vs. $M = 14.6$, $SE = 1.46$, $p = .210$) whereas there was an increase in negative affect over this period for participants who consumed the placebo product *(*$M = 15.1$, $SE = 1.44$, vs., $M = 18.3$, $SE = 1.44$, $p = .002$).

DISCUSSION

Study 2 allowed the examination of the alcohol-tobacco co-use phenomenon with a different order of administration than in Study 1. Here snus was administered before alcohol consumption, allowing participants more time for snus absorption before bringing

the beverage on board. Using this order of administration, participants' craving was sampled while their BAC was continuing to ascend. Under these conditions, snus increased latency to begin smoking, and alcohol increased cigarette craving prior to the PR task and participant breakpoint during the PR task.

Due to the results of Study 1, I expected that earlier absorption of snus would cause an observable reduction in cigarette craving and cigarette consumption peaking after the 30 minutes of absorption. These expected effects were only partially observed. No reduction in cigarette craving occurred with snus, and only the latency to start smoking was increased by snus. Latency to begin substance use is considered a similar construct to craving (Sayette et al., 2000), as higher craving is strongly correlated with shorter latency to begin substance use (Tiffany, 1990). Latency to begin substance use is an especially useful index in experiments involving administration of substances that may satiate craving and distort further cognitive appraisals of craving (Griffiths & Henningfield, 1982; Juliano, Fucito, & Harrell, 2011; Perkins et al., 2008).

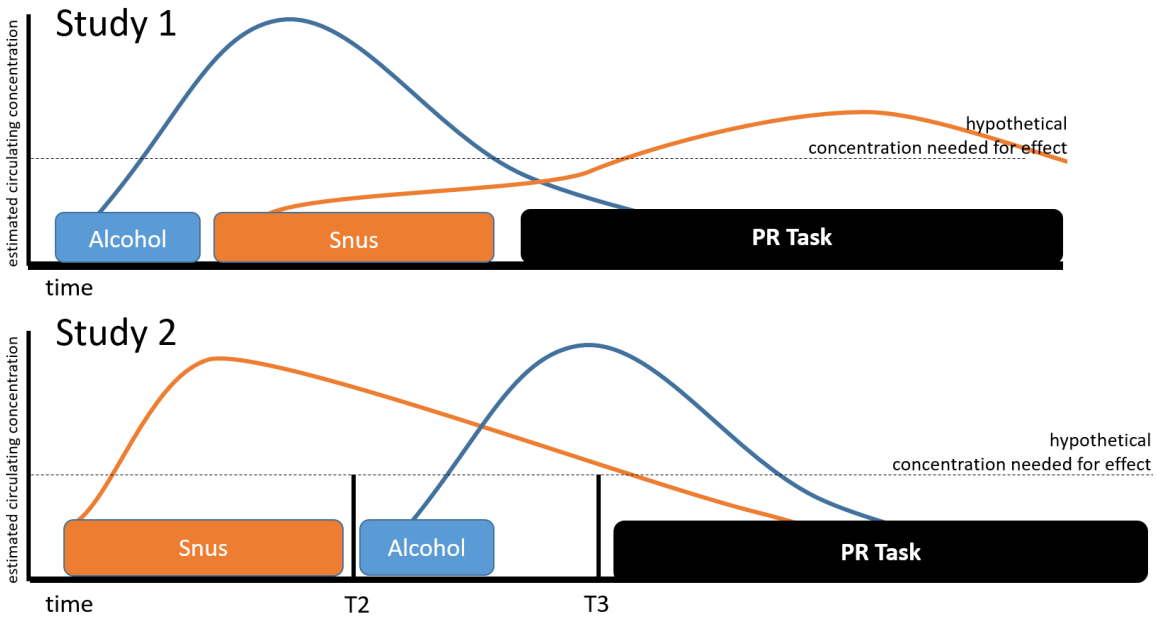
However, while increased craving for a substance might lead to a decreased latency to begin consuming a substance, this is not always true. The absence of, or a barrier to, an opportunity to smoke would moderate the craving-latency relationship. For example, a person may strongly crave a substance but not engage in substance consumption immediately if they perceive a barrier to consuming the substance. They may also be distracted by their environment or thoughts, causing them to delay satisfying their craving. As well, a person may quickly consume a substance while experiencing a minimal level of substance craving if the opportunity to consume the substance is readily available. A person may be motivated to engage in another behavior entirely when

experiencing an intense craving which competes for the individual's attention. A negative affective state could signal that satisfying their craving should be postponed until they seek relief from their aversive subjective state. Thus, there are many differences between latency to start consuming and the subjective craving a person experiences. Therefore latency to start smoking and craving should be considered separate constructs (Sayette, Wertz, & Martin, 2003).

Snus reduced motivation to consume cigarettes because it increased the latency to begin smoking. However, because all participants were naïve to snus in this study, it remains possible that snus reduced their desire to consume cigarettes without reducing their conscious cigarette craving (Miller & Gold, 1994). This reduction in desire to smoke caused by snus (as observed on the PR latency variable) may have been short-lived, which may be why the total number of puffs and breakpoint were left unaffected by snus.

The primary hypothesis in Study 1 for why snus did not influence cigarette craving was that the acidity of the beverage influenced the pH in participants' mouths, reducing absorption of the chemicals in snus. However, the alternative hypothesis made in Study 1 for the lack of effect of snus on cigarette craving was that because participants were naïve to snus, there was no expectation that their product would reduce cigarette craving. Participants were unfamiliar with the product. In Study 2, snus once more did not affect conscious cigarette craving despite affecting at least some aspect of cigarette consumption behavior. Snus did not reduce cigarette craving even immediately after product absorption, prior to receiving the beverage. A lack of an effect of snus on cigarette craving at T2 and T3 is surprising, given that snus has been found to be

psychoactive within 5 to 30 minutes of use (Cobb et al., 2010; Kotlyar et al., 2007; Lunell & Curvall, 2011). If snus reduced conscious cigarette craving, this reduction should have been captured at T2 (Figures 6a and b). A lack of effect of snus on cigarette craving even under these improved conditions in Study 2 where alcohol could not have interfered with snus absorption, strengthens the alternative hypothesis from Study 1. Specifically, the lack of effect of snus on cigarette craving in both studies is most likely due to a dissociation between a conscious reduction of cigarette craving and snus' pharmacological reduction of the drive to consume further nicotine.



Figures 6a and b In Study 1 (Figure 6a), the leading hypothesis is that the acidic beverage influenced the pharmacokinetics of snus absorption, protracting the absorption of tobacco chemicals. In Study 2 (Figure 6b), the beverage was administered after snus, therefore rendering it unable to influence the pharmacokinetics of snus absorption. The

lack of an effect of snus on cigarette craving in both Studies, therefore, is likely due to factors other than pharmacokinetics.

The fact that snus increased latency to start smoking in Study 2 further supports the dissociation between craving and consumption hypothesis from Study 1. The study most similar to Studies 1 and 2 neither supports nor refutes this interpretation. As previously discussed, Barrett and Wagner (2011) found that snus was able to reduce cigarette craving for 10 minutes, but was no longer capable of reducing cigarette craving after 40 minutes. However, this was with individuals who were not also consuming a placebo beverage or placebo product on different sessions. Their participants also did not engage in a PR task to measure whether snus influenced smoking behavior. If the alternative hypothesis that snus did not affect cigarette craving because participants were naïve to snus and therefore did not expect a reduction in cigarette craving is correct, then it is possible that snus' effect on cigarette consumption is, in fact, different than the pharmacological and psychological effect it has on naïve users. Snus reduces cigarette consumption through a pharmacological mechanism, but only affects craving through a psychological mechanism in naïve users. If the participants were familiar with snus, it is likely that snus would have reduced their cigarette craving, as seen in a study conducted by Gray and colleagues (2008) where smokeless tobacco users reported a reduction in cigarette craving after being administered snus. Therefore, it is possible that the hypotheses involving beverage-interference and the dissociation of craving and consumption are both valid.

As well, alcohol increased breakpoint and cigarette craving in the current study. It is not surprising that alcohol increased cigarette craving when BAC levels were rising, as

found in other studies. Mitchell, de Wit, and Zacny (1995) found that a rising BAC increased cigarette smoking in a lab-based study with dependent smokers who were moderate drinkers. King and Epstein (2005) found that social smokers who drink increased their QSU-B factor 1 cigarette craving during the first 15 minutes of the ascending limb of the BAC curve. Their study was similar to the present experimental design, except that in King and Epstein's experiment participants did not have an opportunity to smoke cigarettes.

Alcohol increasing breakpoint was consistent with our prediction that an earlier BAC curve, closer to the PR task, would increase how actively participants worked towards earning puffs. It was surprising, however, that alcohol did not influence earlier smoking behavior such as latency, nor did it influence the number of puffs participants consumed. As previously discussed in Study 1, upcoming smoking opportunities are known to influence cigarette craving (Dar et al., 2010, 2005). It is possible that the participants in Study 2 were already optimally motivated to consume cigarette puffs, such that alcohol did not further reduce their initial latency to start smoking. However, the lack of an increase in puffs while an increase in breakpoint occurred while intoxicated likely indicates that the alcohol created a greater urgency to consume cigarette puffs early on in the PR task but was not sufficient to create a measurable increase in effort later on in the task when a difference in overall puffs consumed would be observed (Hodos & Kalman, 1963). As BAC levels began to drop, the number of cigarette puffs earned between beverage conditions likely became similar over time. This early drive to consume puffs influenced the effort during the task to consume puffs but ultimately did not increase participants' need for greater satiation from puffs. Alcohol only affected the drive to

consume puffs, as evidenced by the increase of breakpoint in the alcohol vs. placebo beverage conditions.

Alcohol also had some other subjective effects in Study 2. Alcohol increased ratings of intoxication, positive affect, and stimulation (B-BAES Factor 1). Intoxication, stimulation, and increased positive affect are expected effects of a rising BAC (Hendler et al., 2013). Alcohol also increased withdrawal-related urges to smoke (QSU-B factor 2), as well as overall cigarette craving, but did not increase craving to smoke for positively reinforcing reasons (QSU-B factor 1) as per King and Epstein's (2005) study. The increase in withdrawal-related craving is a common effect of alcohol on cigarette craving for dependent smokers (Barrett et al., 2013; Heffner et al., 2011), whereas alcohol is known to increase positive reinforcement cigarette cravings predominantly for non-dependent smokers (McKee et al., 2010). It is possible that the lack of an increase in cigarette craving for positively reinforcing properties may also be because participants' craving increased regardless of beverage condition, as the upcoming smoking opportunity already increased their positive reinforcement craving.

Snus may have also caused changes in subjective experience. Snus users reported an increased positive affect in the current study from 30 minutes into absorption when the product was initially disposed of (T2) until at least 72 minutes after the product was first used (T3). This increase in positive affect is similar to that seen in other previously mentioned snus studies (Caldwell et al., 2010; Hatsukami, Zhang, O'Connor, & Severson, 2013; Lunell & Curvall, 2011). This increase in positive affect in Study 2 is unlike the increase in sedation found in Study 1, even though participants in both studies were naïve to snus and unaware of the content of either product. This difference could be

due to differences in snus absorption, with the beverage increasing the acidity of participants' mouths during snus consumption in Study 1 but not Study 2. Alternatively, participants may have been more attentive to changes in affect caused by snus since it was administered prior to the beverage, which all participants would have thought would have the psychoactive properties of alcohol.

Study 2 is also the first study to our knowledge that has examined the subjective effects of snus taken before alcohol consumption. In lab-based studies not using an alcohol challenge, Swedish snus is not typically enjoyed upon the first use (Hatsukami et al., 2013); however, use is reported as satisfying after a week of use by smokers trying to quit (Caldwell et al., 2010). A protracted liking of snus aligns with the epidemiological evidence that individuals who use snus regularly also consume alcohol and report enjoying snus' subjective effects. As well, snus users who drink also report snus' utility as a cigarette replacement for those wishing to quit smoking (Larsen et al., 2013; Loukas et al., 2012; Lund et al., 2008). Familiarity with a similar tobacco product may also expedite liking of snus, as seen in a study conducted by Gray and colleagues (2008), which found that participants who were already smokeless tobacco users (but not necessarily snus users) endorsed some positive subjective mood states ("head rush", "like feel", "relax", "alert") after snus administration. This familiarity did not exist with our participants.

Furthermore, the placebo product increased negative affect at T3, whereas snus maintained the affective state of users. The maintenance of negative affect scores in comparison to the increase in negative affect without snus in Study 2 is also a novel finding. Nicotine is known to reduce negative affect in dependent smokers (Watkins et

al., 2000). Nicotine delivered through nicotine lozenges reduces negative affect (Barrett et al., 2011). Snus appears to deliver nicotine and should therefore cause a decrease in negative affect regardless of alcohol consumption, similar to how cigarettes reduce negative affect when drinking (e.g., King & Epstein, 2005; Oliver et al., 2013). This could be due to both the nicotine and non-nicotinic tobacco factors found within snus. This was observed in this study, with negative affect increasing over time in the absence of snus. The increase in negative affect is likely due to participants' desire to smoke, nicotine withdrawal throughout the study, and possibly boredom, all of which would be satiated by snus.

When compared to Study 1, the findings of Study 2 also highlight that differences in the order of alcohol and snus administration affect craving, cigarette consumption, and subjective affect states. When alcohol precedes tobacco use, cigarette craving is often increased in daily smokers immediately before a smoking opportunity in lab-based studies (e.g., Glautier et al., 1996; Kahler et al., 2014; McKee et al., 2006). For example, Glautier and colleagues found that when daily smokers (between 5 and 20 cigarettes daily) consumed 0.5g/kg of alcohol over 15 minutes with a 5-minute rest immediately before a smoking opportunity, participants reported an increased cigarette craving relative to those who consumed a placebo beverage. This increased cigarette craving included a greater desire to smoke (similar to QSU-B factor 1), the anticipation of enjoyment from smoking, and anticipation of feeling better by smoking (similar to QSU-B factor 2). Those who consumed alcohol also increased the number of cigarette puffs they consumed in a fixed interval smoking task. Kahler and colleagues (2014) similarly found that 25 minutes after dependent smokers consumed a high dose of alcohol

(0.8g/kg), their latency to begin smoking was reduced relative to that of dependent smokers who received either a placebo beverage or a lower dose of alcohol (0.4g/kg). The amount of alcohol consumed is vital in understanding how alcohol affects subsequent cigarette smoking, as higher doses of alcohol are more likely to increase subsequent tobacco consumption than lower doses. As well, the Kahler et al. (2014) study also found that regardless of which dose of alcohol was consumed, alcohol-consuming participants reported an increased urge to smoke. There was an indirect relationship between alcohol use and latency to smoke, with the urge to smoke as a partial mediator of latency to smoke. Nonetheless, participants' alcohol-induced cigarette craving was to some degree independent of alcohol's effect on their latency to start smoking. Specifically, there was no effect of the low dose of alcohol on latency to start smoking. Thus, the lack of an effect of a lower dose of alcohol on latency to start smoking, together with its significant effect in increasing subjective craving, indicates that the latency to start smoking and cigarette craving must be, to some degree, separate constructs. In McKee and colleagues' (2006) study, they found that 5 minutes after daily smokers who were social drinkers consumed an alcoholic beverage to reach a target BAC 0.03% of alcohol, they demonstrated an increase in cigarette craving for positively reinforcing properties (QSU-B factor 1). Alcohol-consuming participants also experienced increased craving to manage nicotine withdrawal (QSU-B factor 2). Those who consumed alcohol consumed more tobacco puffs over a 60-minute ad-lib smoking session. During this time their BAC levels rose, plateaued, and began to decrease. This suggests that small increases in BAC that quickly plateau and fall over 60 minutes can increase total tobacco consumed over a 60-minute ad-lib smoking session. Given the result that participants in

Study 2 demonstrated an increased effort to earn puffs when given the alcoholic beverage, it is likely that alcohol increased their effort to consume puffs during the ascending BAC limb, which is reflected as an increased effort to earn future cigarette puffs compared to those who consumed the placebo beverage.

Unfortunately, there are no other known lab-based studies similar to Glautier et al.'s (1996), Kahler et al.'s (2014), or McKee et al.'s (2006) that have reversed the order of alcohol and tobacco administration as the present Study 2 where tobacco has been consumed immediately before alcohol consumption. A limited number of studies have demonstrated that tobacco use appears to increase future alcohol use. In an ecological momentary assessment study by Piasecki and colleagues (2011) with current smokers who drink, they found that individuals enjoyed their last drink of the night more if they were smoking. Two other studies where male smokers were pretreated with transdermal nicotine patches found that nicotine increased the amount of alcohol men consumed (Acheson, Mahler, Chi, & de Wit, 2006; Kouri et al., 2004). Another study found a similar result in women (McKee, O'Malley, Shi, Mase, & Krishnan-Sarin, 2008). Rats also self-administer more alcohol when injected with nicotine (Nadal, Chappell, & Samson, 1998). Furthermore, a study by Barrett and colleagues (2006) found that administration of nicotine-containing cigarettes increased alcohol self-administration compared to denicotinized cigarettes. Barrett and colleagues' (2006) study utilized as a control denicotinized cigarettes, which hold many of the same sensorimotor properties as typical cigarettes. Although cigarettes and nicotine appear to increase the drive to consume alcohol, Study 2 did not support this in the case of snus. While that study was not designed to capture the various facets of craving for alcohol, there was no indication

that participants who consumed snus were more motivated to consume alcohol on our single "want drink" item. As previously reported, snus' lack of similar sensory properties to a cigarette may explain why the increased drive for alcohol was not detected.

Study 2 is the first experimental study to our knowledge that specifically examined the effect of a non-pyrolyzed tobacco product on later alcohol-induced cigarette craving and consumption. Therefore, it is the sole basis for understanding how pre-treatment with snus before alcohol consumption affects alcohol-induced cigarette craving.

Although several aspects of the alcohol-tobacco co-use phenomenon were elucidated in both Studies 1 and 2, neither of these studies examined whether the degree of dependence on tobacco an individual has modifies the alcohol-tobacco co-use relationship since both studies used daily dependent smokers as participants. Non-daily and intermittent smokers show a more considerable increase in tobacco consumption while consuming alcohol than do dependent smokers (Shiffman, Dunbar, et al., 2012). Therefore, the alcohol-tobacco co-use phenomenon should be different between subtypes of tobacco users. As well, altering the dose of snus can help reveal the extent to which the dose of nicotine and other chemicals within snus influence cigarette craving and consumption.

As discussed in the general introduction, the predominant theory is that non-nicotinic tobacco factors are the primary source of reinforcement during tobacco experimentation, which comes to be replaced by dependence on nicotine as the primary motivation to consume tobacco after chronic administration. Therefore, to determine whether a similar reduction in cigarette consumption occurs despite snus containing less

nicotine, the next study in this dissertation reduced the amount of snus, thus reducing the amount of nicotine both dependent and non-dependent smokers received during the alcohol-challenge. As well, Study 3 was designed to help determine whether the non-pyrolyzed chemicals within snus affect cigarette craving and consumption in non-dependent cigarette smokers, including when they consume alcohol.

CHAPTER 4: THE EFFECT OF SNUS ON ALCOHOL-RELATED CIGARETTE ADMINISTRATION IN DEPENDENT AND NON-DEPENDENT SMOKERS

Sections of this chapter are taken from Peloquin, M. P. J., Hecimovic, K., Sardinha, J., Stewart, S. H., & Barrett, S. P. (2013). The effect of snus on alcohol-related cigarette administration in dependent and non-dependent smokers. *Pharmacology, Biochemistry, and Behavior*, *114–115*, 97–102. http://doi.org/10.1016/j.pbb.2013.08.011. See Appendix G for the article.

ABSTRACT

Alcohol has been found to increase tobacco smoking in both dependent daily smokers (DDS) and non-dependent non-daily smokers (NNS). Yet examining how different treatments/products modify drinking-related smoking behavior has received little attention. This study examined the acute effects of snus (4mg of nicotine) on alcohol-related smoking responses in 18 DDS and 17 NNS. During each of four double-blind sessions, participants were randomly assigned to receive one of the following combinations: alcohol and snus, alcohol and placebo product, placebo beverage and snus, or placebo beverage and placebo product. Participants consumed their assigned beverage before absorbing their session's product, and after 30 min participants could self-administer puffs of their preferred brand of cigarette over a 60-minute period using a progressive ratio (PR) task. Alcohol significantly increased tobacco craving across two craving scales ($ps < .011$) and tended to decrease latency to start smoking ($p = .015$) but only among NNS. In contrast, snus tended to decrease the number of puffs earned and how hard DDS worked for puffs in both beverage conditions ($ps \leq .019$), but it did not

alter the smoking behavior of NNS. Snus did not significantly impact craving in either type of smoker. These findings raise the possibility that different processes mediate alcohol and cigarette co-use in NNS and DDS and that snus may be useful in reducing cigarette use in DDS regardless of alcohol consumption.

INTRODUCTION

It is well established that alcohol consumption increases cigarette use among those who smoke (e.g., Falk, Yi, & Hiller-Sturmhöfel, 2006). Alcohol-induced cigarette consumption occurs in both dependent and non-dependent smokers (e.g., Shiffman & Paty, 2006). Alcohol also plays a significant role in smoking initiation (e.g., O'Loughlin, Karp, Koulis, Paradis, & Difranza, 2009), smoking maintenance (Glautier, Clements, White, Taylor, & Stolerman, 1996; Kahler et al., 2010), and relapse to cigarette use among smokers trying to quit (Shiffman, 1986). Few if any treatments are known to affect alcohol-related smoking. Kouri, McCarthy, Faust, and Lukas (2004) found that a nicotine patch decreased smokers' subjective tobacco craving, but that this effect diminished when smokers consumed alcohol. Alcohol consumption is typically not restricted in smoking cessation trials, and most smokers intending to quit smoking do not simultaneously abstain from alcohol (e.g., Bobo, Mcilvain, Lando, Walker, & Leed-Kelly, 1998). It is possible that drinking may affect individuals' efforts to quit smoking either by altering smokers' motivation to quit (Burton & Tiffany, 1997) or by reducing the effectiveness of nicotine replacement therapy (NRT) (Kouri et al., 2004).

Both Studies 1 and 2 of this thesis demonstrated that Swedish snus alters cigarette consumption in dependent smokers. When snus is taken after a placebo or alcohol-containing beverage, it reduces the number of cigarette puffs earned and effort to earn future puffs during a PR task. When taken before either an alcoholic or placebo beverage, it increases the latency to start earning puffs during the same PR task. These results are consistent with the findings of epidemiological studies (Gilljam & Galanti, 2003; Lindström, 2007; Lund et al., 2011; Lund et al., 2010; Scheffels et al., 2012) that snus

may act as a smoking cessation aid that is superior to NRTs. Snus may be more effective than NRTs because it also provides other non-nicotinic tobacco factors such as nornicotine, anatabine, anabasine, myosmine, 2,3'-dipyridyl, and cotinine (ENVIRON International Corporation, 2010; Stepanov et al., 2008) to the user. Low rates of smoking in Sweden may be in part attributable to snus use (Norberg, Lundqvist, Nilsson, Gilljam, & Weinehall, 2011). Rates of alcohol use among Swedish snus users is high (Engström, Magnusson, & Galanti, 2010), implying that drinkers tolerate snus when it is co-administered with alcohol.

The purpose of this study was to examine whether the degree of dependence on cigarettes moderates the effect snus has on alcohol-induced cigarette craving and consumption. Both alcohol and nicotine consumption affect non-dependent and dependent smokers' subsequent tobacco consumption differently. Non-dependent and intermittent smokers are known to increase the consumption of cigarettes to a greater extent than dependent smokers when consuming alcohol (Barrett et al., 2013; Dierker et al., 2006; Epstein et al., 2007; King & Epstein, 2005; King et al., 2010; McKee et al., 2010; Mintz et al., 1985; Nichter, 2006; Shiffman et al., 2014; Shiffman, Dunbar, et al., 2012). Nicotine administration does not appear to be reinforcing in non-dependent cigarettes smokers (Eijnden, Spijkerman, & Fekkes, 2003). They do not self-administer sufficient nicotine for nicotine dependence to be the sole motivation for their tobacco consumption (Shiffman et al., 1992). It is likely that other chemicals in cigarettes are reinforcing for non-dependent smokers, but it is not known to what extent these chemicals affect non-dependent smokers' cigarette craving and consumption.

To examine the role of nicotine and dependence on nicotine in the alcohol-tobacco co-use phenomenon, Study 3 was designed similarly to Study 1, but with some modifications. In Study 3, the amount of snus administered was reduced for two reasons. One was to determine whether halving the amount of snus administered would reduce or eliminate snus' reduction in cigarettes consumed and effort to earn future puffs on a PR task, regardless of prior alcohol consumption. A lower dose of snus along with a lower dose of nicotine should still be reinforcing for a NNS as their drive to seek out nicotine is lower than DDS (Benowitz, 2008). The second reason was to determine whether snus would have any effect on the alcohol-induced cigarette craving and consumption of non-dependent smokers following alcohol consumption. Additionally, the requirement for participants to smoke a cigarette at the start of the study was removed to increase participants' cigarette craving further and increase the likelihood of observing any pharmacological effects of snus on cigarette craving and consumption in both groups of smokers.

As the order of beverage and snus administration was identical to that of Study 1, I predicted that snus would reduce the effort to consume puffs during the PR task as well as reduce cigarette craving for dependent smokers given the increased level of withdrawal these smokers would be experiencing. I also predicted that alcohol would not increase cigarette craving or smoking behavior for the dependent smokers, given the high level of cigarette craving the dependent smokers would already be experiencing before the PR task. For non-dependent smokers, I predicted that snus would not reduce either cigarette craving or consumption when consuming alcohol because snus does not contain the same amount or range of non-nicotinic tobacco factors as are found in cigarette

smoke. As well, I predicted that alcohol would increase both cigarette craving and consumption for non-dependent non-daily smokers.

METHODS

PARTICIPANTS

Non-treatment seeking daily dependent smokers (DDS) (i.e., daily tobacco use for a minimum of one year; score ≥ 3 on the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991)) and non-daily non-dependent smokers (NNS) (i.e., tobacco use on fewer than 25 days in the previous month; FTND = 0) were recruited from the Halifax Regional Municipality in Nova Scotia. All were regular heavy consumers of alcohol, having consumed a minimum of 4 drinks for women (5 drinks for men) at least once per week during the previous month. Participants were also non-problem drinkers, scoring 2 or less on the short version of the Michigan Alcoholism Screening Test (SMAST; Selzer, Vinokur, & Rooijen, 1975). Potential participants were told that the study would consist of an initial session to complete screening measures and collect a non-abstinent breath carbon monoxide (CO) sample, and four experimental sessions that would involve the administration of beverages that may vary in alcohol content followed by the administration of substances that may vary in their contents of ingredients typically found in cigarettes (e.g., tar, ammonia, menthol, nicotine, sucrose). Women who reported pregnancy, nursing, intention to become pregnant, or who screened positive on an elective urine pregnancy test were not permitted to participate. All participants reported that they were medically healthy, all had reached the minimum age to legally consume alcohol and tobacco in Nova Scotia, none intended to quit smoking over the subsequent 30 days, and none were using NRT products. All participants were naïve to

snus before the study. Participants were compensated CDN$10 per hour. The study was conducted in accordance with the Declaration of Helsinki and approved by a local research ethics board.

Design

The protocol consisted of four double-blind, randomized sessions with a 2 (dependence: DDS or NNS participants) x 2 (beverage condition: alcohol or placebo) x 2 (product condition: snus or placebo) mixed design. All sessions were identical in procedure except that participants received a different beverage–product combination during each session.

Beverages

In the alcohol condition, participants received 2.28 ml 50% USP units of alcohol per kilogram of body weight for women and 2.73 ml 50% USP units of alcohol per kilogram of body weight for men (MacDonald et al., 2000) to target a peak blood alcohol concentration (BAC) of 0.06%. Drinks were mixed 1:4 parts vodka to cranberry juice. The placebo beverage was made up of 5 parts cranberry juice with a small amount of alcohol applied to the rim of the glasses and on the drink tray to ensure the odor and taste of alcohol (Kushner et al., 1996).

Products

In the snus condition, participants received a Phantom brand snus mini portion containing 4mg of nicotine (V2 Tobacco; Silkeborg, Denmark). Snus has a nicotine loading timeframe of 30 minutes (Foulds et al., 2003; Lunell & Lunell, 2005). In the placebo condition, participants received a BaccOff brand nontobacco placebo portion (V2

Tobacco; Silkeborg, Denmark), which mimics the sensory properties of snus (Coffey & Lombardo, 1998).

BLINDING

Participants were blind to the contents of the beverages and products received during each session. Participants were informed that the products might vary between sessions in their content of ingredients usually found in cigarettes but were not specifically informed that they might vary in nicotine content. Similarly, participants were informed that the alcohol content of the beverages might vary, but not that the doses were selected to produce either mild or no intoxication. To maintain the integrity of the blind, research personnel not otherwise involved with data collection prepared all beverages, administered the oral product, and recorded all breath alcohol concentration measurements.

SUBJECTIVE ASSESSMENT

Subjective Rating Scales

Author-compiled Subjective Rating Scales (SRS) were used to assess subjective state (i.e., “relaxed”, “pleasant”, “head rush”, “stimulated”, “jittery”, “dizzy”, “irritable”, “trouble concentrating”, “anxious”, “frustrated”, “intoxicated”, and “crave cigarette”). Each item was rated on a 10-cm horizontal line labeled with integers 1-10 and anchored with the endpoints “Not at all” and “Extremely.” Similar scales have been widely used to assess subjective drug effects. This method of assessment has been shown to be both reliable (e.g., Wewers & Lowe, 1990) and sensitive to the acute effects of alcohol and tobacco (e.g., Barrett, Campbell, Roach, Stewart, & Darredeau, 2013; Barrett, Tichauer,

Leyton, & Pihl, 2006). Positive affect items ("relaxed", "pleasant", "head rush", and "stimulated") were combined to create a positive affect factor, and negative affect items ("jittery", "dizzy", "irritable", "trouble concentrating", "anxious", "frustrated") were combined to create a negative affect factor. As calculated in Study 1, the positive affect factor had a good internal item consistency Cronbach's alpha of .80, and the negative affect factor had a good internal item consistency Cronbach's alpha of .85. "Intoxicated" was analyzed separately.

Questionnaire of Smoking Urges-Brief

The Questionnaire of Smoking Urges-Brief (QSU-B; Cox, Tiffany, & Christen, 2001) is a 10-item self-report measure used to assess tobacco craving across two dimensions. Each question is rated on a scale of 1 to 7, with 1 indicating "strongly disagree," 4 "neutral," and 7 "strongly agree." Five items grouped as factor 1 reflect a strong desire and intention to smoke, with the perception that smoking will be rewarding. These include items such as "I have a desire for a cigarette right now" and "If it were possible, I probably would smoke now." The remaining five items reflect anticipation of relief from negative affect with an urgent desire to smoke and are known as factor 2. These include items such as "I could control things better right now if I could smoke" and "I would do almost anything for a cigarette right now." Item scores were totaled into index scores for factors 1 and 2, each ranging from 5 to 35. Internal item consistency for both factors 1 and 2 from Study 1 was Cronbach's alpha = .97, similar to the reliability of the original factors found in the Questionnaire of Smoking Urges (Tiffany & Drobes, 1991).

Brief Biphasic Alcohol Effects Scale

The Brief Biphasic Alcohol Effects Scale (B-BAES; Martin, Earleywine, & Musty, 1993) is a 6-item self-report measure used to assess the subjective stimulant effects of alcohol associated with a rising BAC (factor 1), as well as the subjective sedative effects associated with a descending BAC (factor 2) (Rueger, McNamara, & King, 2009). Factor 1 items include "energized", "excited", and "up", whereas factor 2 items include "sedated", "slow thoughts", and "sluggish". Each item was rated on a 10-cm horizontal line labeled with integers 1-10 and anchored with the endpoints “Not at all” and “Extremely” similar to the scale used with the author-compiled Subjective Rating Scales. Internal item consistency for factor 1 ranges between Cronbach’s alpha of .89 to .93, and .90 to .91 for factor 2 from Study 1. Factor 1 on the B-BAES correlates with the original BAES factor 1 by $r = .92$, and factor 2 correlates with the original BAES factor 2 by $r = .93$ ($ps < .001$) (Martin, Earleywine, Musty, & Swift, 1993).

BEHAVIORAL MEASURES

Heart Rate

The average and maximum heart rates of participants were collected alongside subjective assessments (RS-100 Polar Heart Rate Monitor; Polar Electro Canada; Lachine, Canada), as alcohol (Brunelle et al., 2007) and nicotine (Perkins et al., 1995) are known to induce increased heart rate.

Progressive Ratio Task

Participants were permitted to earn puffs of their preferred brand of cigarette (supplied by the lab) using a computerized progressive ratio (PR) task over 60 minutes. Ten key presses were required to earn the initial puff, and the requirement increased at a

ratio of 1.3 for each subsequent puff. Participants were not required to earn any puffs but were required to remain seated in front of the cigarette until the end of the session. The latency to start smoking, the total number of puffs earned, and the breakpoint – the number of key presses completed to earn the last puff – were recorded for each session. The PR task has been demonstrated to be sensitive to pharmacological manipulations in human tobacco self-administration studies (e.g., Barrett & Darredeau, 2012).

PROCEDURE

Participants arrived for each testing session having abstained from smoking and alcohol for a minimum of 12 hours and food and caffeine for a minimum of 2 hours. Abstinence from smoking was confirmed with a breath CO reading of 15 ppm or less and/or a 50% reduction in CO from the non-abstinent baseline (Vitalograph; Lenexa, KS). Abstinence from alcohol was confirmed using an Alcomate Premium breath alcohol analyzer (AK Solutions; Lansdale, PA) with a cutoff of 0.00%. Unlike in Studies 1 and 2 of this thesis, participants did not consume a cigarette at the beginning of the experimental session. I intended to ensure both DDS and NNS were experiencing higher levels of cigarette craving at the start of the experimental task than participants in Studies 1 and 2 as the previous results may have been influenced by having recently smoked a cigarette prior to the start of the experimental task. DDS typically consume a cigarette within the first hour after waking (Shiffman et al., 2002; Shiffman et al., 2014), as do some non-daily smokers (Shiffman et al., 2014). A timeline outlining the sequence of procedures is presented in Table 5.

TABLE 5

Procedure	Time (minutes)	Total time (minutes)
Confirmation of alcohol and smoking abstinence	5	5
Heart rate recording and subjective assessment	7	12
Administration of beverage	15	27
Administration of product	30	57
Disposal of product, heart rate recording, and subjective assessment	10	67
PR task	60	127
Sobering period	60	187

Table 5. Timeline of experimental procedures for Study 3

After completing a baseline subjective assessment (SRS, QSU-Brief, B-BAES) and heart rate recording (RS-100 Polar Heart Rate Monitor; Polar Electro Canada; Lachine, Canada), participants consumed their assigned beverage (alcohol or active placebo) over 15 minutes. Afterward, participants were given their product and instructed to place it between their upper gum and upper lip for 30 minutes while they waited alone in the testing room. Post-product subjective assessment and heart rate recording were then conducted. Participants could then earn cigarette puffs over the following 60 minutes during the PR task. Following the PR task, the session concluded with a "sobering period" of at least one hour during which participants were provided with a light snack and rested until their BAC was below 0.04%. All participants completed this sobering period in each session to maintain the blind of the experiment.

STATISTICAL ANALYSIS

Data were analyzed using linear mixed models in SPSS version 20.0 for Windows (SPSS Inc.; Chicago, IL). Linear mixed models account for unequal sample sizes by producing adjusted degrees of freedom and estimated marginal means. An appropriate covariance structure was selected for each variable based on model simplicity and the likelihood ratio test. The behavioral measures were the latency (time in seconds) to start smoking on the PR task, the breakpoint (key presses needed to earn the last puff), and the total number of puffs self-administered. Behavioral data were analyzed using Dependence level (NNS vs. DDS) as a fixed factor, Beverage (alcohol vs. placebo beverage) and Product (snus vs. placebo product) conditions as fixed and repeated factors, and Subject as a random factor. Shapiro–Wilk and Kolmogorov–Smirnov tests screened the residuals for normality and indicated that a logarithmic (log) transformation for latency and a square root (sr) transformation for breakpoint normalized the variables. The effects of interest were the main effects of Beverage, Product, and Dependence, as well as interactions of Beverage and Product, and Beverage and Product by Dependence. Subjective data and heart rate were analyzed using Beverage and Product as fixed and repeated factors, Dependence level as a fixed factor, and Subject as a random factor. Baseline scores [T1] were used as a time-varying covariate for post-beverage and product absorption scores [T2]. The effects of interest were the main effects of Beverage, Product, and Dependence, as well as interactions of Beverage and Product, as well as Beverage and Product with Dependence. For interactions, the simple effects of variables within each level combination of the other variable(s) were tested. An experimental alpha

of .01 was utilized for all analyses accounted for multiple testing, as participants in Study 3 participated in each condition four times, increasing the risk for type I error.

RESULTS

PARTICIPANTS

Eighteen (nine female) DDS and seventeen (seven female) NNS enrolled in the study. Sixteen (eight female) DDS and thirteen (six female) NNS completed all four experimental sessions, while the remaining two DDS and four NNS each completed three sessions. All sessions were retained for analysis. DDS had higher FTND levels, $t(33) = 12.20$, $p < .001$ ($M = 5.4$, $SE = 0.43$ vs. zero for NNS) and smoked more cigarettes in the previous week, $t(33) = 7.98$, $p < .001$ ($M = 122.3$, $SE = 13.35$ vs. $M = 11.3$, $SE = 2.22$) than NNS. No dependence group differences were detected in participants' age, age of initial tobacco use, age of initial alcohol use, or total alcoholic drinks in the previous week (Table 6).

TABLE 6

	DDS	NNS	*p*	Total
N	18	17		35
Sex	9 male, 9 female	10 male, 7 female		19 male, 16 female
Age	25.7 (8.3)	25.0 (4.2)	.788	25.3 (6.5)
FTND score	5.4 (1.8)	0	*< .001	
What age did you first try cigarettes?	13.8 (3.0)	15.2 (3.2)	.189	14.5 (3.1)
Total # of cigarettes this past week	122.3 (56.7)	11.2 (9.1)	*< .001	68.4 (69.4)
What age did you first try drinking alcohol?	14.4 (2.2)	15.1 (2.2)	.359	14.7 (2.2)
Total # of alcoholic drinks in the past week	20.6 (19.4)	15.7 (10.3)	.371	18.2 (15.7)
How many days in the past week did you try	3.2 (1.7)	3.6 (1.7)	.467	3.4 (1.7)

consuming alcohol?				

Table 5. Demographics for participants in Study 3. Means scores reported with standard deviations in brackets. * indicates a significant difference between DDS and NNS with a significance of $p \leq .05$.

ALCOHOL ADMINISTRATION VERIFICATION

All BAC ratings were 0.00% at baseline. No differences in BAC levels were detected 30 minutes following the absorption of the alcoholic beverage between those who received snus or placebo snus for NNS, $t(15) = 1.87$, $p = .083$ ($M = 0.041$, $SE = 0.010$ for snus; $M = .044$, $SE = 0.011$ for placebo product), or DDS, $t(16) = 1.33$, $p = .204$ ($M = 0.046$, $SE = 0.014$ for snus; $M = 0.049$, $SE = 0.014$ for placebo product). No significant differences in BAC levels occurred between NNS and DDS $t(28.87) = 1.21$, $p = .236$ ($M = 0.043$, $SE = 0.010$ for NNS; $M = 0.047$, $SE = 0.012$ for DDS). Participant BAC levels are lower than the target BAC as BAC levels had likely plateaued and were beginning to drop by 30 minutes post-absorption of beverages. BAC readings remained at 0.00% in both placebo beverage conditions.

HEART RATE

Alcohol increased average heart rate relative to the placebo beverage, $F(1, 106.7) = 7.22$, $p = .008$ ($M = 79.8$, SE = 1.00 vs. $M = 76.3$, $SE = 1.01$ beats per minute), as did snus relative to placebo snus, $F(1, 64.4) = 35.28$, $p < .001$ ($M = 81.3$, $SE = 0.95$ vs. $M = 74.8$, $SE = 0.92$), but these effects did not interact ($p = .38$).

SUBJECTIVE EFFECTS

Cigarette craving was assessed using the two factors of the QSU-Brief (factor 1: intention to smoke; factor 2: withdrawal/negative affect relief) and the SRS item "crave cigarette."

Main effects of Dependence showed that DDS had higher QSU-Brief factor 1, $F(1, 45.6) = 9.97$, $p = .003$ ($M = 27.5$, $SE = 0.99$ vs. $M = 22.6$, $SE = 1.01$), and factor 2, $F(1, 45.4) = 16.91$, $p < .001$ ($M = 29.8$, $SE = 1.41$ vs. $M = 20.5$, $SE = 1.45$) scores than NNS. A main effect of Beverage showed that alcohol also increased QSU-Brief factor 1, $F(1, 28.9) = 16.39$, $p = .002$ ($M = 26.0$, $SE = 0.78$ vs. $M = 24.0$, $SE = 0.78$), and factor 2, $F(1, 82.1) = 7.97$, $p = .006$ ($M = 26.1$, $SE = 0.94$ vs. $M = 24.2$, $SE = 0.94$) craving relative to placebo beverage in both types of smokers.

Examination of Dependence X Beverage interactions revealed significant effects on QSU-Brief factor 1 and factor 2 craving, along with a marginal interaction effect of Dependence X Beverage for SRS "crave cigarette". For factor 1 craving, $F(1, 29.1) = 16.39$, $p < .001$, when NNS received alcohol they reported greater craving than when they received a placebo beverage ($M = 24.8$, $SE = 1.19$ vs. $M = 20.4$, $SE = 0.98$; $p < .001$); however, this effect was not seen for DDS ($M = 27.3$, $SE = 1.00$ vs. $M = 27.7$, $SE = 0.96$; $p = .653$). Additionally, DDS reported greater factor 1 craving than NNS in the placebo beverage condition ($p < .001$), but not in the alcohol condition ($p = .168$). Similarly, for factor 2 craving, $F(1, 82.7) = 14.48$, $p < .001$, NNS reported higher craving in the alcohol than in the placebo beverage condition ($M = 22.8$, $SE = 1.52$ vs. $M = 18.2$, $SE = 1.55$; $p < .001$) and this effect was again not evident for DDS ($M = 29.50$, $SE = 1.8$ vs. $M =$

30.18, *SE* = 1.5; *p* = .483). Additionally, DDS reported greater factor 2 craving than NNS in both the placebo beverage (*p* < .001) and alcohol (p < .006).

For SRS "crave cigarette", *F*(1, 51.0) = 6.91, *p* = .011, NNS rated their craving higher in the alcohol than in the placebo condition (*M* = 6.2, *SE* = 0.37 vs. *M* = 5.1, *SE* = 0.35; *p* = .004); however, this effect was not found with DDS (*M* = 6.75, *SE* = 0.63 vs. *M* = 7.0, *SE* = .34; *p* = .504). Additionally, DDS showed higher SRS "crave cigarette" ratings than NNS in the placebo beverage condition (*p* = .002), but not in the alcohol condition (*p* = .300) (Figures 7a-c). Product condition was not found to affect subjective cigarette craving.

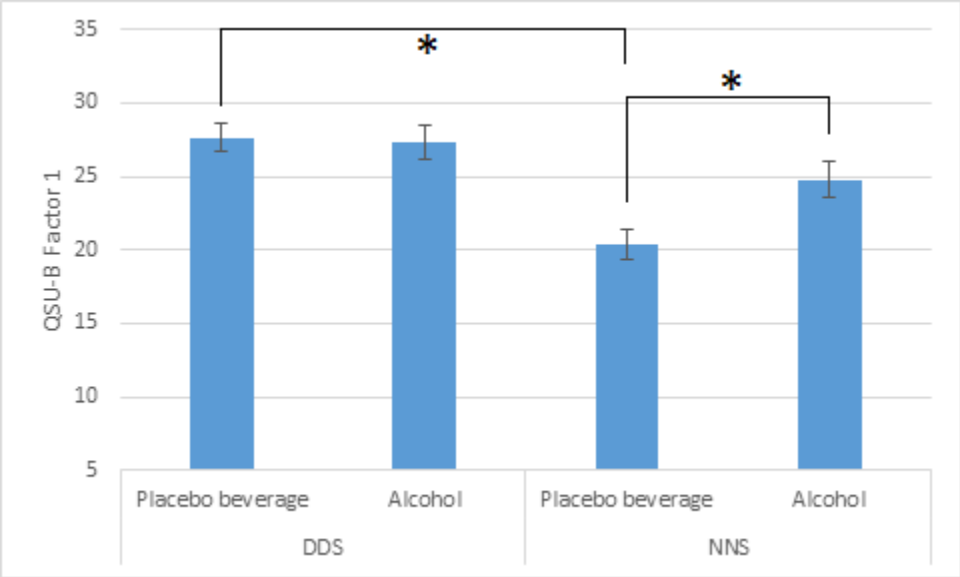


Figure 7a

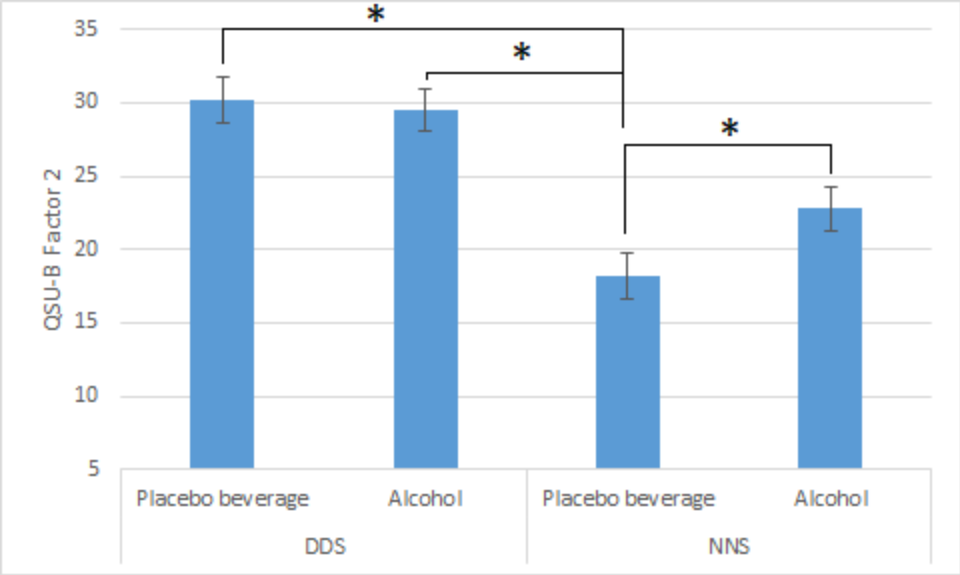


Figure 7b

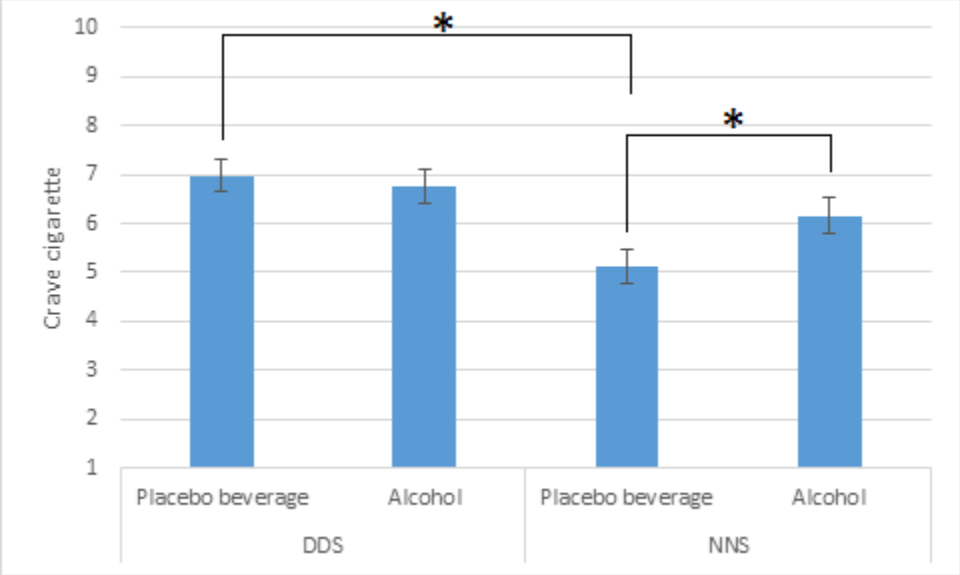


Figure 7c

Figures 7a-c. For non-dependent non-daily smokers' (NNS) QSU-B factor 1, factor 2, and "crave cigarette" estimated marginal means increased following alcohol consumption relative to consuming the placebo beverage. Alcohol consumption did not influence daily dependent smokers' (DDS) level of craving on all three indexies. As well, NNS showed

lower craving scores across all indexes than DDS in the placebo beverage conditions but not in the alcohol beverage conditions.

Subjective mood effects were assessed using two SRS affect factors, "intoxicated", and two B-BAES factors. A main effect of Beverage was detected for "intoxicated", $F(1, 37.1) = 52.01$, $p < .001$, with participants rating their subjective intoxication higher in the alcohol condition than in the placebo beverage condition (M = 4.7, SE = 0.37 vs. M = 2.1, SE = 0.22). A main effect of Beverage was also detected for B-BAES factor 1, $F(1, 82.4) = 9.35$, $p = .003$, where greater stimulating effects were detected post-alcohol beverage absorption than post-placebo beverage absorption (M = 15.1, SE = 0.61 vs. M = 13.6, SE = 0.61). No effects of Beverage for B-BAES factor 2 (sedative effects) were detected.

A main effect of Beverage was detected for SRS positive affect, $F(1,120.953) = 6.97$, $p = .009$, with participants endorsing higher levels of positive affect in the alcohol condition than in the placebo beverage condition regardless of level of nicotine dependence (M = 20.1, SE = 0.69 vs M = 18.0, SE = 0.69). Product condition did not influence subjective mood states.

SELF-ADMINISTRATION

Analyses revealed a main effect of Dependence for total number of puffs, $F(1, 29.0) = 13.69$, $p < .001$, and for squareroot breakpoint, $F(1, 29.0) = 21.71$, $p < .001$. DDS earned more puffs (M = 19.4, SE = 1.28 *vs*. M = 12.3 SE = 1.26 puffs) and worked harder for puffs (M = 38.5, SE = 2.91 *vs.* M = 19.5, SE = 2.85 square rooted keypresses) than NNS.

A marginal interaction effect of Dependence X Beverage was detected for log latency, $F(1, 81.4) = 6.16$, $p = .015$. NNS were marginally quicker to start smoking in the alcohol versus the placebo beverage condition ($M = 1.4$, $SE = 0.18$ vs. $M = 1.7$, $SE = 0.18$; p = .021), but beverage type made no difference in latency to start smoking for DDS ($M = 1.1$, $SE = 0.19$ for alcohol *vs.* $M = 0.9$, $SE = 0.19$ for placebo; $p = .248$) (Figure 8).

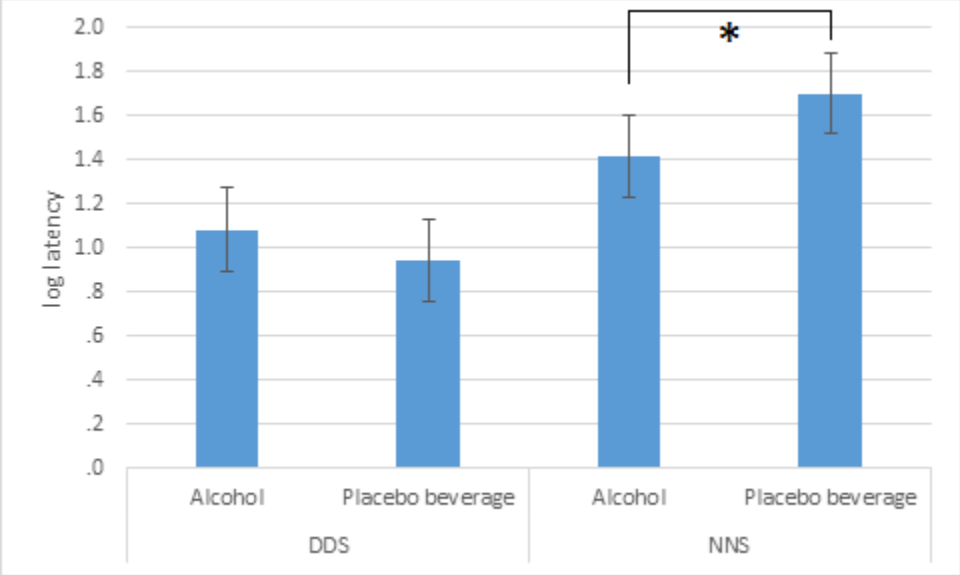


Figure 8. No difference was detected between daily dependent smokers (DDS) and non-daily non-dependent smokers (NNS) in how quickly they began the progressive ratio task ($p = .035$), but a trend was found that NNS, but not DDS started more quickly in the alcohol than in the placebo beverage condition ($p = .015$).

Finally, a Dependence X Product interaction effect was found for both puffs, $F(1, 81.2) = 7.54$, $p = .007$, and breakpoint, $F(1, 81.4) = 7.17$, $p = .009$. DDS tended to smoke fewer puffs ($p = .019$) and worked less hard to earn puffs ($p = .004$) in the snus versus the placebo snus condition; NNS did not show this effect ($ps > .1$) (Figures 9a and b).

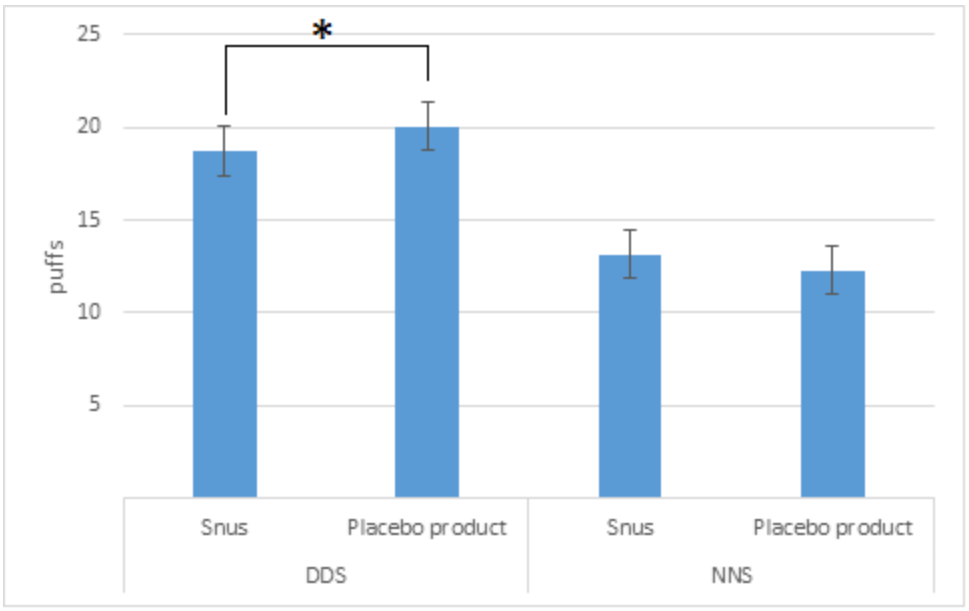


Figure 9a

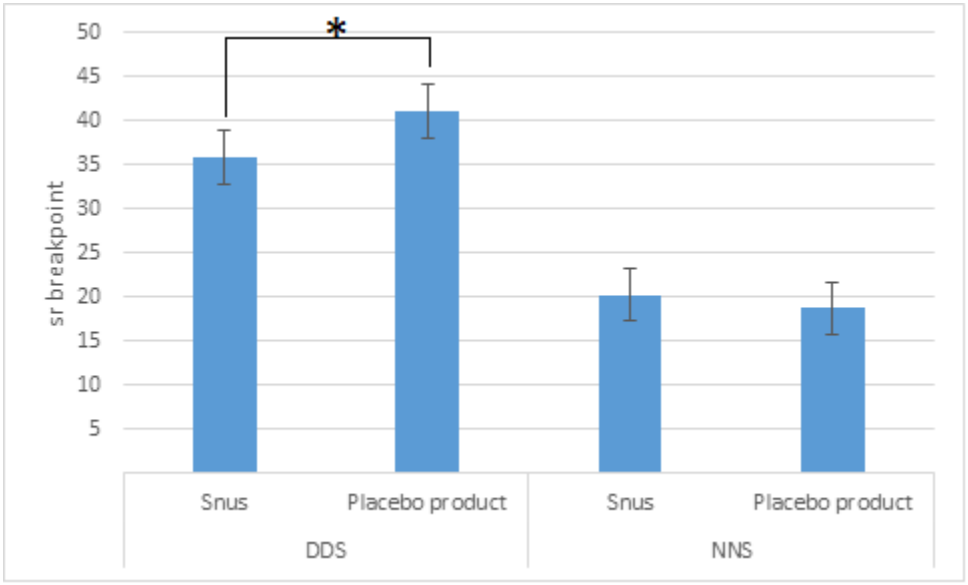


Figure 9b

Figures 9a & b. Daily dependent smokers (DDS) earned significantly fewer puffs and worked less hard for puffs when consuming snus vs. placebo product. Significant differences exist between DDS and non-daily non-dependent smokers (NNS) puffs

earned and square root breakpoint, with DDS great than NNS in both cases. DDS versus NNS main effects are omitted for visual clarity.

SUPPLEMENTARY ANALYSES

Comparisons of baseline cigarette craving were conducted between DDS from Studies 1 and 3 to determine if DDS in Study 1 had lower baseline craving scores than DDS in Study 3. The results showed that, on all three indexes, DDS in Study 1 had lower baseline levels of craving than those in Study 3 ["crave cigarette", $t(118) = -6.120$, $p < .001$, $M = 5.40$, $SE = 0.36$ vs. $M = 8.30$, $SE = 0.32$; QSU-B factor 1, $t(118) = -5.693$, $p < .001$, $M = 22.94$, $SE = 1.11$ vs. $M = 30.67$, $SE = 0.83$; QSU-B factor 2 $t(118) = -7.085$, $p < .001$, $M = 12.72$, $SE = 0.71$ vs. $M = 22.76$, $SE = 1.09$]. As well, the non-transformed latency, number of puffs earned, and breakpoint reached for DDS who received the placebo beverage and placebo product were compared between Study 1 and 3, with no differences found for latency ($t(27) = -.752$, $p = .458$, $M = 11.91$, $SE = 2.60$ vs. $M = 36.52$, $SE = 25.44$), puffs ($t(27) = 1.105$, $p = .279$, $M = 21$, $SE= 0.62$ vs. $M = 19.28$, $SE = 1.15$), or breakpoint ($t(27) = 1.184$, $p = .247$, $M = 2130.90$, $SE = 287.42$ vs. $M = 1736.11$, $SE = 193.00$). As well, baseline heart rates were compared between DDS from Study 1 and Study 3 and no differences were found ($t(120) = -.823$, $p = .412$, $M = 70.38$, $SE = 3.8$, $M = 73.63$, $SE = 15.7$).

DISCUSSION

Study 3 revealed some expected results. First, as expected, DDS craved cigarettes more and consumed more puffs than NNS. However, the study also produced unanticipated results given the modification to the design of Study1 to create Study 3. Like in Study 1, snus did not affect DDS' cigarette craving. It was expected that snus

would reduce cigarette craving and consumption because of the increased cigarette craving DDS experienced in Study 3 by being required to abstain from tobacco for 12 hours prior to the experimental task. The dose of snus utilized should have been sufficient to reduce cigarette craving, as nicotine in the form of 4mg quick-release lozenges reduces cigarette craving in dependent smokers within 30 minutes (Barrett & Wagner, 2011; Cobb, Weaver, & Eissenberg, 2010). Barrett, Campbell, Temporale, and Good's (2011) study also utilized smokers who abstained from nicotine-containing products overnight. Snus that is rated to contain 4mg of nicotine (versus the 1 gram weight/8mg of nicotine satchets) was shown to reduce craving and cigarette puff consumption in DDS who abstained from nicotine overnight (Barrett et al., 2011). Although nicotine replacement does not appear to be effective when co-administered with alcohol (Leeman et al., 2007), no effect of snus on craving was observed in either beverage condition in the present study. The lack of snus effect on cigarette craving likely was due to reasons hypothesized in the discussion of Study 1. The first was that the beverage interfered with snus absorption, delaying the effect of snus relative to when craving was sampled in the study. However, snus did not reduce cigarette craving in Study 2, suggesting that participants' lack of familiarity with the product may also be a reason that snus did not affect cigarette craving in any of the three studies in this thesis. The second possible explanation involved participants knowing there was an upcoming opportunity to smoke immediately following the assessment of cigarette craving. Knowing of the upcoming smoking opportunity may have contributed to the lack of a decrease in reported cigarette craving with snus in Studies 1 and 3 (Shiffman et al., 2013) by increasing craving across the board.

Interestingly, like in Study 1, snus reduced the number of puffs earned by DDS and how hard they worked to earn puffs regardless of beverage condition. The results related to puffs are similar to Barrett and colleagues' (2011) results. Differences in baseline craving between DDS from Studies 1 and 3 confirmed that participants in Study 3 had a significantly higher baseline level of cigarette craving, as intended. Study 3's results show that snus is still effective at reducing cigarette consumption among DDS when a smaller dose is administered following an increased period of tobacco abstinence. This reduction in cigarette consumption occurred regardless of alcohol consumption for DDS. Since nicotine alone does not appear to reduce alcohol-induced cigarette consumption (Leeman et al., 2007), it suggests that chemicals in snus beyond or in conjunction with nicotine reduce cigarette consumption when absorbed after alcohol consumption.

For NNS, alcohol increased their self-reported cigarette craving and marginally decreased their latency to begin smoking. It has been established that cigarette craving and consumption are more greatly affected by alcohol in NNS compared to DDS (Barrett et al., 2013). Since NNS are more sensitive to alcohol-induced tobacco craving than DDS (Epstein et al., 2007; King et al., 2010; McKee et al., 2010; Shiffman et al., 2014; Shiffman & Paty, 2006), it is not surprising that alcohol reduced their latency to start smoking. It is possible that alcohol-induced reduction to start smoking and increased cigarette craving may be more closely linked in NNS than for DDS, as outlined in Studies 1 and 2. However, the lack of an alcohol effect on increasing cigarette puffs and effort to earn more puffs was surprising. It is possible that the BAC level of NNS dropped throughout the PR task, as suggested by observed BAC levels immediately prior to the

PR task, causing them to be insufficiently intoxicated to experience alcohol-induced cigarette craving and consumption shortly beyond the start of the PR task. Later in the PR task, puffs become exponentially more difficult to earn, with NNS consuming 13 puffs on average during the PR task. A 14th puff would require 303 keypresses to earn, making earning significantly more puffs than participants receiving the placebo beverage unlikely unless the drive to consume puffs remained high near the end of the PR task. The lack of an increase in puffs earned by NNS who consumed alcohol could be because the alcohol dose utilized in Study 3 was too small to induce a substantial increase in smoking behavior. In a study conducted by Epstein and colleagues (2007), they recruited non-daily smokers with varying low levels of dependence on cigarettes (FTND score $M = 0.4$, $SE = 0.9$, cigarettes per day $M = 3.5$, $SE = 1.9$). They found that when they split their participants into "light" and "heavy" tobacco chippers and gave each group 0.4g/kg of alcohol, the light chippers reported an increase in cigarette craving for at least 45 minutes post beverage consumption when not allowed to smoke. "Heavy" chippers demonstrated no increase in cigarette craving post beverage at this dose of alcohol. It is possible that our NNS (FTND = 0, cigarettes per week $M = 11.3$, $SE = 2.22$) are more similar to Epstein and colleagues' "heavy" chippers rather than to their "light" chippers. In Epstein et al.'s task, when both groups received 0.8g/kg of alcohol instead of 0.4g/kg, participant cigarette craving increased and remained higher than baseline craving for at least 165 minutes.

As well, one would expect alcohol to increase DDS' craving and consumption of cigarettes as found in previous experimental studies (e.g., King, McNamara, Conrad, & Cao, 2009; Mitchell, de Wit, & Zacny, 1995). Kouri, McCarthy, Faust, and Lukas (2004)

found that DDS only demonstrated an increase in cigarette craving for 30 minutes after being given either 0.4g/kg or 0.7g/kg of alcohol. It is possible that the dose of alcohol chosen for Study 3 (i.e., 0.9g/kg for females, 1.08g/kg for males) was insufficient to produce a robust alcohol effect for the DDS as well; however, this is unlikely given the high dose. It is also possible that the lack of an alcohol effect on cigarette craving for DDS resulted from a ceiling effect. DDS' average score for "crave cigarette" was 8.3/10 before the start of the PR task. The average NNS' "crave cigarette" score was 5.4/10 at the same time point, possibly allowing the effect of alcohol on cigarette craving to be more readily detected for NNS as previously discussed.

One of the most exciting findings was that snus did not reduce cigarette craving or affect smoking behavior for NNS. NNS do not smoke to maintain nicotine blood plasma levels (Shiffman, Dunbar, et al., 2012), more likely smoking for other factors beyond nicotine, as evidenced by NNS finding denicotinized cigarettes just as reinforcing as typical cigarettes. Denicotinized cigarettes are reinforcing for NNS regardless of whether or not they are consuming alcohol or not (Barrett et al., 2013). There are at least three known chemicals in cigarette smoke beyond nicotine that have been shown to be reinforcing in animal studies. Acetaldehyde (Paschke et al., 2002; Seeman et al., 2002) and harman and norharman (Deitrich & Erwin, 1980) are known reinforcing chemicals that are found in pyrolyzed tobacco but that are not found in significant quantities in pasteurized tobacco. In contrast to the contribution of repeated exposure to nicotine in cigarettes to later nicotine dependence, such chemicals may be more important for reinforcing smoking behavior in non-dependent smokers. These tobacco factors, or others similarly missing due to snus not being pyrolyzed, may be necessary to influence

cigarette craving and consumption in NNS. Chapter 5 will expand upon the potential role these tobacco factors may play in tobacco dependence.

Snus did not induce any subjective effects in Study 3, whereas in Study 1 snus in the placebo beverage condition increased prototypical sedative effects typically seen during the descending limb of the BAC curve for DDS. It remains unclear why this difference occurred between Studies 1 and 3. It is possible that the lack of a sedative effect may be due to the smaller relative concentration of nicotine and non-nicotinic tobacco factors found in Study 3's smaller portion of snus. The level of nicotine withdrawal due to the increased tobacco abstinence period could also moderate whether snus causes a sedative effect in naïve snus users. Interestingly, in Study 3 both alcohol and snus increased participants' heart rate as expected (Conrod et al., 1997; Lunell & Curvall, 2011), in contrast to the lack of a cardiac effect in Study 1. Study 1 began with participants having a cigarette, which subsequently raised their baseline heart rate. The cigarette at the start of the study can explain the later lack of an effect of snus or alcohol on heart rate in Study 1. Alcohol and snus were able to increase heart rate in Study 3 because participants did not consume any nicotine within 12 hours before the start of the experiment.

Furthermore, alcohol caused subjective effects in Study 3 that were unlike those found in Study 1. In Study 3, alcohol increased positive affect, stimulation, and ratings of intoxication, similar to the alcohol effects found in Study 2. In Study 1, alcohol was intoxicating and stimulating to participants, but did not increase positive affect. Two factors might help explain why alcohol's effects on ratings of positive affect were variable across the three studies in this thesis. One potentially explanatory factor is that

the DDS in Study 1 were not sufficiently deprived of tobacco for alcohol to significantly increase ratings of positive affect. If this were true, the level of dependence a smoker has on nicotine might not be as important as how long it has been since one has consumed tobacco. However, this explanation would suggest that the lack of effect of alcohol on positive affect should have been seen in both Studies 1 and 2, and not in Study 3. The other potential explanatory factor relates to how recently alcohol consumption occurred relative to self-reporting of positive affect. Recent alcohol consumption might improve positive affect. This explanation would suggest that positive affect improvement from alcohol should have been detected in Study 2 and not in Studies 1 and 3. In Study 3, participants were deprived from consuming tobacco for at least 12 hours without a preliminary cigarette an hour prior to the experimental session. After this length of deprivation from cigarette smoke, both DDS and NNS report alcohol-induced increased positive affect and stimulation in Study 3. This indicates that alcohol's subjective effects are influenced by the duration of cigarette deprivation for both classes of smokers.

The current study demonstrated that snus still reduces cigarette consumption for dependent smokers with a lower dose and at least a 12 hour tobacco-abstinence period, but that snus does not appear to be useful for reducing non-dependent smokers' cigarette craving and consumption. Therefore, the main findings of this study were that snus reduces cigarette consumption with dependent daily smokers similarly to an NRT product, and that snus may outperform typical NRTs as this occurs regardless of alcohol consumption.

The following chapter will discuss the outcome of the preceding three studies in further detail. As well, the chapter will integrate the findings across the three studies and relate

these findings back to the broader literature. The chapter will then discuss the general limitations of the thesis and directions for future research.

CHAPTER 5: DISCUSSION

Utilizing snus with both dependent daily (DDS) and non-dependent non-daily smokers (NNS) who drink alcohol has allowed for study of previously unexamined aspects of the alcohol-tobacco co-use phenomenon. This particular perspective is due to snus' unique character containing both nicotine and non-nicotinic tobacco factors without the additional by-products produced by pyrolization of tobacco and without the act of smoking itself. There are four main areas of contribution of this dissertation: 1) effects of alcohol and snus; 2) order effects and the pharmacological properties of alcohol and snus co-administration; 3) how alcohol and tobacco co-use affect the development of tobacco dependence; and 4) whether craving and substance consumption are separate, similar, or overlapping constructs. Findings in each category are summarized and compared to previous research, including theories of why individuals consume alcohol and tobacco concurrently. As well, the clinical implications of utilizing snus as a smoking cessation product will be discussed, along with future directions for research into the alcohol-tobacco co-use phenomenon.

1. EFFECTS OF ALCOHOL AND SNUS USE

Among the few robust findings regarding alcohol and tobacco co-use with daily dependent smokers (DDS), the most established are that alcohol increases cigarette craving (e.g., Oliver et al., 2013). DDS also increase their cigarette consumption after drinking alcohol if smoking is permitted (Einstein et al., 1975; Falk et al., 2006; Harrison et al., 2009; Jackson et al., 2010; Piasecki et al., 2011; Witkiewitz et al., 2012).

However, DDS in both Studies 1 and 3 did not report an increase in cigarette craving or consumption following alcohol ingestion. Participants consumed sufficient alcohol to reach a peak BAC of 0.05-0.06% during each study, and prototypical subjective alcohol effects such as an increase in stimulating affect were observed (Cooper, Frone, Russell, & Mudar, 1995). Therefore, the dose of alcohol was sufficient to be intoxicating and was reported as intoxicating by participants, and should have been sufficient to increase cigarette craving and consumption. Mitchell, de Wit, and Zacny (1995) found that DDS increased their cigarette consumption when given as little as 0.4g/kg of alcohol compared to a placebo or 0.2g/kg alcohol beverage; the dose of alcohol in Studies 1 and 3 were higher than 0.4g/kg (i.e., 0.9g/kg for females, 1.08g/kg for males). The failure of alcohol to affect cigarette craving or consumption for DDS in both Studies 1 and 3 is thus surprising, and there are three potential reasons why this occurred.

First, alcohol administration may not have been optimally timed to elicit an increase in cigarette craving or consumption. In both Studies 1 and 3, beverage administration took 15 minutes. Cigarette craving assessment occurred between 30 and 40 minutes after alcohol consumption. In a study by Kouri, McCarthy, Faust, and Lukas (2004), DDS demonstrated an increase in cigarette craving for 30 minutes following alcohol consumption. This increase in craving occurred with alcohol doses both low (0.4g/kg) and moderate (0.7g/kg), and regardless of whether the participants were wearing a 21mg nicotine transdermal patch or a placebo patch. Kouri et al.'s participants did not have the opportunity to consume cigarettes in their task, so the knowledge that smoking would not occur may have reduced their craving in the absence of alcohol. In a

study by King, McNamara, Conrad, and Cao (2009), 0.8g/kg of alcohol increased cigarette craving 30 minutes post-beverage. However, King et al.'s methodology was different from that used in Studies 1 and 3 of the present thesis. King et al.'s participants consumed a nicotine or denicotinized cigarette puff both 15 minutes prior and 15 minutes after consuming their beverage. Regarding smoking behavior, King et al.'s study did not uniformly find that alcohol increased cigarette consumption, doing so for men but not for women. However, in Mitchell, de Wit, and Zacny's (1995) study, participants did consume significantly more cigarettes over a one hour period of free smoking after consuming 0.4g/kg of alcohol and were quicker to start smoking with this same dose. Unlike Studies 1 and 3, their participants did not have to wait 30-40 minutes before the free smoking period, so their cigarette craving and consumption were assessed while BAC levels were increasing. Since Studies 1 and 3 were methodologically different from the Kouri et al., King et al., and Mitchell et al. studies, direct comparisons of the timing and dose of alcohol on subsequent cigarette craving and consumption between studies are impossible. We can infer however that the dose of alcohol used in Studies 1 and 3 should have been sufficient to increase cigarette craving and consumption for DDS, but the time frame during which this occurs may be limited to a 30-minute or slightly longer time frame.

There then remain the two other, less likely possibilities to consider for why alcohol did not increase cigarette craving or smoking behavior of DDS in Studies 1 and 3. One is that snus nullifies alcohol-induced cigarette craving and consumption. Snus consumption immediately followed half of all sessions where participants consumed alcohol. If snus does neutralize alcohol-induced cigarette craving and consumption when

consumed after alcohol ingestion, no effect of alcohol on cigarette craving or consumption would occur in Studies 1 and 3. Alcohol did not influence cigarette craving or consumption in Studies 1 and 3. However, we can discount this theory because no interactions between beverage and product were detected for Studies 1 and 3. Alcohol would have significantly increased craving and altered cigarette consumption after placebo-product administration in these studies otherwise.

The other possibility is similar to the last. It is possible that both alcohol and snus exerted a pharmacological effect, but the effect of snus over-powered alcohol's effect on cigarette craving and consumption. Once more, without a significant Beverage by Product effect detected in either Study 1 or 3, this possibility is unlikely.

The effect of snus on subsequent cigarette use is less well understood. Snus is supposed to be pharmacologically active after either 5 (Lunell & Curvall, 2011), 15 (Cobb et al., 2010) or 30 minutes of absorption (Kotlyar et al., 2007). However, the time needed before snus efficiently reduces cigarette craving is unknown. Cobb, Weaver, and Eissenberg (2010) found that snus reduced cigarette craving when initially used, but not during subsequent sessions, and only after 30 minutes of absorption. Whether snus was novel to their participants was unknown. In a study by Barrett and Wagner (2011), participants who were naïve to snus found that snus reduced cigarette craving 10 minutes into product absorption. However, snus no longer reduced cigarette craving 40 minutes into product absorption, which represents the same time frame as craving assessment in Studies 1 and 3, immediately before the PR task. However, snus did reduce total cigarette puffs earned and effort to earn puffs in DDS in both Studies 1 and 3. Therefore, self-reported cigarette craving without the opportunity to smoke may not be predictive of

smoking behavior, especially when consuming an unknown substance. How craving and consumption are different will be elaborated in Section 4.

Since no alcohol and snus interactions occurred in Studies 1 and 3, it is unlikely that alcohol consumption before snus absorption causes a pharmacological interaction. However, consuming an acidic beverage may influence the absorption of snus by altering the pH of the mucosal lining in participants' mouths. The brand of snus used in these studies has a pH of 8.5 (V2 Tobacco; Silkeborg, Denmark). Nicotine itself is a weak base with a pKa of 8.0 on the pyrrolidine ring, and a pKa of 3.12 on the pyridine ring (Gorrod & Jacob III, 1999). As previously discussed in Study 1, consuming an acidic cranberry beverage with an estimated pH of 2.56 (Reddy et al., 2016) immediately before snus absorption may have reduced the bioavailable nicotine and other chemicals typically absorbed from snus. The pH within participants' mouths may have improved throughout snus absorption as new saliva increased the pH in the mouth. Participants were instructed to place the substance under the upper lip, so unlike chewing tobacco, minimal saliva would reach the unknown product in their mouth. Oral absorption may be a limitation of utilizing snus in alcohol and tobacco co-use research. However, nearly all alcoholic beverages have an acidic pH due to byproducts of the fermentation processes and additives added by manufacturers. Therefore, the order of product administration can influence how snus is absorbed and is necessary to understand the alcohol-tobacco co-use relationship better. Order effects are discussed in the following section.

2. ORDER EFFECTS AND THE PHARMACOLOGICAL PROPERTIES OF ALCOHOL AND SNUS CO-ADMINISTRATION

The order of alcohol and snus administration affected both cigarette craving and consumption behavior across Studies 1 through 3. This supports previous research concluding that alcohol-tobacco co-use has directional properties (Acheson et al., 2006; Barrett et al., 2006; Kouri et al., 2004; McGrath et al., 2015; McKee et al., 2008; Nadal et al., 1998; Oliver et al., 2013; Perkins et al., 1995, 2000; Piasecki et al., 2011; Reid, Mickalian, Delucchi, Hall, & Berger, 1998; Rose et al., 2004; Söderpalm et al., 2000; Zacny, 1989). Directional properties of alcohol and tobacco co-use appear to exist because the outcome on craving and cigarette consumption were different between Studies 1 and 2 when the order of administration of the two drugs were reversed. Moreover, these effects were different from the expected pharmacological impact of alcohol and snus consumption when singly administered.

The pharmacokinetics of snus is not fully understood, as summarised in Section 1 above. Previous research indicates that chemicals in snus are quickly absorbed through the mucosa lining, with noticeable psychotropic effects after 5 minutes (Cobb et al., 2010). Absorption continues over the following 25 minutes, with a slow tapering of nicotine levels over the following hours (Digard, Proctor, et al., 2013). There was no control group in either of those studies, so only plasma nicotine levels are established with snus, whereas the psychological effects are less well understood.

In comparison, alcohol absorption is well understood. Initial psychopharmacological effects begin 15 minutes after alcohol consumption (Holt et al.,

1980). Feeling stimulated and energized occur as BAC levels rise (Hendler et al., 2013; Rueger & King, 2013; Rueger, McNamara, & King, 2009), and heart rate increases (Brunelle et al., 2007). If BAC levels continue to rise past a level of 0.08% or begin to drop, subjective sedative effects such as feeling sluggish and having slow thoughts begin to occur (Pohorecky, 1977). Sedation occurs via the indirect effect of alcohol on a variety of neurotransmitter and neuropeptide systems (Vengeliene, Bilbao, Molander, & Spanagel, 2008). In Studies 1 and 3, participants consumed their beverage followed by snus absorption, so their BAC levels at the time of subjective sampling immediately before the PR task likely would have been plateauing, and thus alcohol would have been less stimulating for participants. This timing along with the relatively low amount of alcohol consumed may explain the lack of an effect of alcohol on craving and consumption even though alcohol consumption occurred. In Study 2, BAC levels were rising when participants reported their subjective mood and craving states immediately preceding the PR task. An increase in cigarette craving during a rising BAC is similar to Kouri and colleagues' (2004) findings. However, in Study 2 the general craving index "crave cigarette" and the urge to smoke for withdrawal/affect relief (QSU-B factor 2) increased following alcohol consumption, but the positively reinforcing desire to smoke a cigarette (QSU-B factor 1) did not. The lack of an increase in QSU-B factor 1 following alcohol consumption is a novel finding. Epstein, Sher, Young, and King (2007) found that alcohol increased both QSU-B factors 1 and 2 immediately following alcohol administration. However, their effect occurred in social (non-daily) smokers with a much lower average FTND score ($M = 0.4$, $SD = 0.9$), whereas Study 2's participants had a FTND of at least 3 ($M = 4.9$, $SD = 1.6$). This difference in alcohol-induced cigarette

craving may indicate that the more dependent a smoker is on nicotine, the higher their drive to consume tobacco for negatively reinforcing properties when BAC levels are increasing. The effect that dependence on nicotine has on negatively reinforcing craving while BAC levels are rising is a new addition to the alcohol-tobacco co-use knowledge base.

Similar to alcohol, snus' specific effects also appear to be dependent upon the timing of administration. Across all studies, snus either influenced participant affect, craving, or cigarette consumption. As previously discussed, snus reduced cigarette puff consumption and effort to earn additional puffs when administered after the beverage in Studies 1 and 3. Snus' effects in reducing puffs and effort to consume puffs without influencing earlier ratings of cigarette craving or latency to start smoking is likely because snus is alkaline, and the acidity of the beverage reduced the rate of snus absorption into the body. Consuming snus before an interfering acidic beverage in Study 2 would be expected to allow snus to absorb more optimally. The resulting reduction of cigarette craving and negative affect by snus in Study 2 were expected (Caldwell et al., 2010; Lunell & Curvall, 2011), and occurred approximately 82 minutes after the initial product was placed in the mouth, and by the start of the PR task. Since the pharmacological effects of snus are finite, it is reasonable to conclude that snus affected cigarette craving and consumption. The effect of snus on cigarette consumption may have waned throughout the PR task, resulting in no observable difference on puffs earned or effort to earn puffs during Study 2. These same effects could not occur in Studies 1 and 3 because snus absorption had not reached a sufficient threshold until later in the PR task.

Evaluating the various alcohol and tobacco co-use theories outlined in Chapter 1 is done by taking into account the effects of alcohol and snus found in these studies. First, snus reduces cigarette craving and consumption, but does not cancel alcohol-induced craving. There is anecdotal evidence that nicotine replacement therapies (NRTs) are not effective at reducing alcohol-induced cigarette craving (Hurt et al., 1995; Kalman et al., 2006; Leeman et al., 2007). Snus is pharmacologically similar to a cigarette, and a reduction in cigarette craving and consumption without a reduction of alcohol-induced cigarette craving aligns with the alcohol-tobacco use theory posited by Oliver and colleagues' (2013), that alcohol increases cigarette craving and consumption by decreasing tobacco satiety. Oliver and colleagues` also thought that tobacco could reduce the sedative effects of alcohol. Tobacco countering alcohol-sedation is also possible but cannot be determined in the present datasets since the BAC curve was descending during the PR task and subjective effects were not sampled at this time.

Glautier, Clements, White, Taylor, and Stolerman's (1996) theory that alcohol decreases the effect of cigarettes consumption upon cigarette craving is also possible. This theory does not correctly align with all the outcomes from Studies 1 through 3, however, as there were no significant Beverage by Product interactions, which would have showed that either alcohol or snus nullified the effect of the other. The only interaction which occurred in any of the three studies was in Study 1, where snus increased the rating of sedation, but only among participants who received the placebo beverage. It is possible that alcohol nullified the sedative effect, but this effect is poorly understood at this time.

McKee, Harrison, and Chi (2010) theorized that alcohol makes smoking less aversive, causing individuals to engage in more smoking behavior than typical. In Study 2, alcohol increased the desire to smoke for negatively reinforcing properties while snus reduced negative affect, and both substances increased positive affect. Alcohol consumption increased how hard participants worked to earn puffs, whereas snus administration increased latency to smoke. The change in affect and smoking behavior support the theory that alcohol makes tobacco smoking less aversive and more reinforcing, causing an increase in consumption (McKee et al., 2010). However, since the aversiveness of smoking was not directly assessed to disprove this theory, it cannot be steadfastly endorsed.

There are several other theories that are not supported by the present findings, including those of Rose and colleagues (2004), Field and colleagues (2005) and Kirchner and Sayette (2007). Rose and colleagues' (2004) theory is that alcohol increases the "liking" of a cigarette. In Study 2, alcohol increased the negatively reinforcing desire to smoke for the anticipation of relief from adverse affect with an urgent desire to smoke (QSU-B Factor 2), but did not significantly increase craving for the positively reinforcing properties of a cigarette (QSU-B Factor 1). Both motivations are unique. The QSU-B is a well-validated measure of smoking motivations (Toll et al., 2006), and endorsing a negatively reinforcing form of craving for cigarette consumption is different from a desire to smoke for positively reinforcing, or "liking", reasons. This view is similar to Kirchner and Sayette's (2007) theory that alcohol increases positive expectancy of smoking in DDS and negative expectancies in NNS. Both increases in positively and

negatively reinforcing craving occurred in NNS in Study 3, and alcohol did not selectively increase positively reinforcing craving in DDS.

Field and colleagues (2005) theorized that alcohol increases the expectation that tobacco use will be administered. This theory is the basis for cue-reactivity studies where alcohol is believed to increase the incentive value of smoking cues (i.e. Drobes, 2002; Duka & Townshend, 2004; Field et al., 2005; King, McNamara, Angstadt, & Phan, 2010; McGrath et al., 2015; Peloquin, McGrath, Telbis, & Barrett, 2014; Sayette, Martin, Wertz, Perrott, & Peters, 2005; Shiffman et al., 2013). However, our participants could not know when they were being given a tobacco versus a placebo product (see Coffey & Lombardo, 1998; McChargue, Collins, & Cohen, 2002, for validation of Bacc-Off as an acceptable snus placebo product). Theories that center around alcohol increasing tobacco expectancy are not supported by the results of Studies 1 through 3.

An additional theory, supported by Studies 1 through 3, is that alcohol may play a role in the development of tobacco dependence for drinkers who smoke. This will be discussed further in Section 3.

3. THE ROLE OF ALCOHOL IN TOBACCO DEPENDENCE

The third set of findings helps elucidate the role of alcohol and the role of alcohol-tobacco co-use in the development of tobacco dependence. In Study 3, alcohol increased non-dependent non-daily smokers' (NNS) cigarette craving and decreased their latency to begin smoking. NNS are known to demonstrate increased tobacco craving when their BAC is rising (King et al., 2002) and require less tobacco to satiate their tobacco cravings (Shiffman, Tindle, et al., 2012). What was surprising was that snus

administration did not influence their cigarette craving or consumption. Unlike for dependent smokers, the chemicals found in snus did not reduce cigarette consumption for NNS, regardless of alcohol use.

Smoking initiation often occurs in the context of drinking. Non-dependent smokers may become dependent on nicotine gradually through repeated concurrent consumption of cigarette while drinking (Harrison et al., 2009). Continued exposure to nicotine causes long-term changes in the function and number of nAChRs within the brain, causing dependence.

Although researchers have not demonstrated a direct link between alcohol use and nicotine dependence, alcohol and nicotine both activate nAChRs. Both ethanol and nicotine alter the pharmacological effects of the other, which may incentivize the user to administer more tobacco to achieve the desired effect while drinking. When drinking, nicotine's activation of nAChRs can prevent alcohol-induced neurotoxicity. Alcohol, in turn, can alter nicotine-induced signaling (Davis & De Fiebre, 2006; Narahashi et al., 2001), in addition to activating the same reinforcement system as nicotine in the brain (Markou, 2008). If both substances are similarly reinforcing and if concurrent administration increases the amount used of both substances compared to when taken alone, then both substances may strengthen dependence of each other within the user.

As well, there is one substance that is common to both alcohol and cigarette consumption. Acetaldehyde, a metabolite of ethanol, is also a component of cigarette smoke (or any tobacco which is flue-cured). Acetaldehyde is believed to be a highly reinforcing substance (Belluzzi et al., 2005), so smokers may mistake their desire for more acetaldehyde as a desire for more ethanol (Mascia et al., 2001). The presence of

acetaldehyde may explain why alcohol increases tobacco cue reactivity, with smokers primed to consume the acetaldehyde contained in of cigarettes.

As the need for nicotine increases over time, cigarette smokers may become highly dependent on nicotine in order to relieve withdrawal sensations and reduce negative affect. In Study 3, cigarette craving and cigarette consumption were not influenced by snus use for the NNS, but cigarette consumption was decreased for the DDS. The lack of an effect of snus on craving for smokers in Studies 1 and 3 is likely due to the acidic nature of the beverage consumed before snus administration, as noted above. However, snus did influence tobacco consumption for DDS in both Studies 1 and 3. Snus contains nicotine and non-nicotinic tobacco chemicals but contains only very low levels of acetaldehyde, harman, or norharman. The lack of a reduction in tobacco consumption by snus among NNS in Study 3 strongly suggests that acetaldehyde or other chemicals found in cigarette smoke but not in unpyrolyzed tobacco are reinforcing for non-dependent smokers. Thus, acetaldehyde and/or possibly other psychoactive chemicals such as harman and norharman may be relevant to the development of tobacco dependence in smokers that drink.

4. WHETHER CRAVING AND SUBSTANCE CONSUMPTION ARE SEPARATE, SIMILAR, OR OVERLAPPING CONSTRUCTS

There remains the possibility that snus did not influence cigarette craving due to psychological factors. The concept of craving is ambiguous in the literature, with the broadest definition including a personal need, urge, or strong desire to undertake a target behavior, such as consuming a target substance (Ferguson & Shiffman, 2013). There are two categories of craving: abstinence and cued cravings. Abstinence-related craving is

experienced during the time between substance administrations and increases over that period. Studies 1 and 2 controlled for abstinence-related cravings by asking smokers to abstain from tobacco a minimum of 12 hours before arriving and then giving them the opportunity to smoke a cigarette an hour before the experimental session. In Study 3, participants were asked to abstain for a minimum of 12 hours but began the experimental procedure immediately when they arrived at the lab. Study 3 DDS reported higher cigarette craving than DDS in Study 1 because of abstinence-related craving.

Cue-induced craving occurs when interoceptive or external stimuli that are conditioned either directly (e.g., thoughts or images of target substance) or indirectly (e.g., negative affect regulated through substance use; Veilleux, Conrad, & Kassel, 2013) appear and induce an appetite to consume the substance. Along with being influenced by the cueing stimuli, substance users are also able to report whether the induced cravings are for the positive or negative reinforcing properties of the substance. Positive reinforcement-related craving includes liking the substance and wanting to experience the pleasurable effects of the substance. Negative reinforcement-related craving relates to relief from negative affect or withdrawal sensations. Tiffany and Drobes' (1991) Questionnaire of Smoking Urges captures both positive and negative reinforcing properties of cigarette craving. In behavioral terms, these two categories represent two of the most basic motivations to use a substance or any other behavior, however, these two forms of craving cannot explain all substance use behavior (Tiffany & Carter, 1998). For example, many cigarette smokers experience cigarette craving throughout their day, and can report their level of craving. However, their level of craving is not a strong predictor of their real-world smoking behavior (Shiffman et al., 2015). Imaging studies also show a

disconnection between episodic craving and smoking behavior. Increased dopamine activity in limbic regions of the brain occurs during craving episodes (e.g., Volkow, Fowler, & Wang, 2004); however, many individuals attempting to abstain from substance use do not act on their cravings. Craving is a conscious phenomenon, about which individuals can have an awareness. However, compulsive substance use can be an unconscious process that occurs with little to no planning. Therefore, conscious and unconscious craving is in line with Tiffany and Carter's (1998) theory that compulsive substance use and craving are distinct constructs.

The purpose of using the progressive ratio (PR) task was to measure drug use motivation, which is an observable behavior, unlike self-reported subjective experiences of craving (Barrett, 2010). The PR does this by collecting three forms of substance using behaviors. In the PR task, the measure coded as latency is a behavioral marker for the urgency to consume a substance. The amount of substance earned throughout a progressively time-consuming task is another behavioral indication of drug use motivation. This represents the appetitive aspect of craving a substance; that, in turn, reflects the satiety of receiving units of the target substance on the craving experienced by the consumer. The third recorded behavior is breakpoint. In behavioral economic terms, breakpoint is the degree to which an individual is willing to work to earn units of a substance, marked by the number of keypresses on the PR task. Breakpoint shows that at a certain point, the expected outcome of further effort to consume a unit of substance is worth less than the work needed to achieve it. Each of these constructs attempts to map onto real-world behaviors. For example, someone could have a strong urge to smoke and begin smoking quickly yet reach satiation after only a few puffs. Another smoker could

desire smoking two cigarettes in sequence yet have little motivation to work for these puffs or find a suitable location to smoke and could have little urgency to begin smoking given the opportunity. The disconnection between each of these behavioral constructs and self-reported craving is crucial in understanding the alcohol-tobacco co-use phenomenon.

Both Studies 1 and 3 showed that snus administration reduced tobacco consumption and effort to earn additional puffs in DDS without affecting participants' cigarette craving before the PR task; in Study 2, snus caused an increase in the latency to begin smoking on the PR task in DDS. The most compelling explanation for this pattern of results across studies is that the acidic beverage negatively skewed the timeframe that snus has on tobacco craving and consumption, causing the pharmacological effect of snus absorption to occur while the PR task was already underway in Studies 1 and 3, so it only affected puffs consumed and breakpoint outcomes.

From a different perspective, one could argue that the reduction of cigarette consumption induced by snus over time is not entirely conscious, and not specific to whether the craving is for positively- or negatively-reinforcing aspects of cigarette consumption. It is unlikely that craving changed over the few minutes it would have taken to assess craving and begin the PR task, leading to the more likely possibility that participants were unaware that their craving for cigarette puffs had been reduced by snus, further bolstering the claim that craving and compulsive substance use are in fact separate constructs (Tiffany, 1990). This possibility is most evident in Study 2, as snus did not alter craving but did increase the latency to start smoking, which was measured immediately after assessment of craving.

Why might this disconnect between craving and substance use exist in a study where participants are not actively resisting consumption of the substance? One possible reason is an expectancy of a substance's effect can influence craving, as seen in previous tobacco research (Juliano & Brandon, 2002; Juliano et al., 2011; Kelemen & Kaighobadi, 2007; Perkins et al., 2003; Schlagintweit et al., 2014; Sutton, 1991). In a paper by Schlagintweit and colleagues (2014), it was found that the expectancy of receiving a nicotine-containing lozenge reduced withdrawal-related craving (QSU-B factor 2) regardless of nicotine content, and reduced their intentions to smoke (QSU-B factor 1) due to the pharmacological effect of the nicotine within the lozenge. However, these effects were lost following presentation with a smoking cue (a video of individuals smoking). These findings indicate that the belief that one is receiving nicotine reduces cigarette craving, and that nicotine consumption has a profound effect on abstinence craving, but not cue-induced craving. In our studies, we informed participants that their product might contain chemicals found in cigarettes, and that contents may vary between sessions. The product did not resemble a cigarette, nor did it provide the sensory properties of cigarettes, such as taste, or tactile sensations. Moreover, there were no placebo effects found for the placebo product. Thus, it is unlikely that snus and the placebo product held similar cigarette outcome expectancies as other NRTs or tobacco products known to our North American participants. The lack of a reduction in cigarette craving combined with the observed increase in latency to start smoking in Study 2 could be due to the pharmacological effects of snus without an expectancy of a reduction of craving. It is similarly possible that snus reduced smoking behavior but not cigarette craving for the same reason in Studies 1 and 3. Without the expectancy of a reduction in

craving and consumption from snus, participants' conscious self-reported craving for either positively or negatively reinforcing cigarette craving remained the same, although participants were less driven to begin consuming cigarette puffs in Study 2 and more satiated by previous nicotine delivered by snus in Studies 1 and 3.

If true, this phenomenon shows that craving is a conscious process, which aligns with Tiffany and Carter's (1998) theory that compulsive substance use and craving are distinct constructs. Individuals are unable to predict their substance use behavior without contextual cues. Such an inability to predict one's cigarette craving also falls in line with Koob's negative reinforcement model of drug addiction (Wise & Koob, 2014). Koob's model is primarily an opponent process model of addiction, where satiation of drives is the primary force of addictive behaviors. One of the three main stages of addiction, the withdrawal/negative affect stage (cravings), is activated and experienced by the user in the presence of drug cues through the activation of the incentive salience circuitry. Therefore, according to Koob's model of addiction, without smoking-related cues, cigarette craving should not increase (Wise & Koob, 2014).

It nonetheless remains reasonable that the beverage, regardless of content, would elicit a similar placebo response across participants, since alcohol is often co-administered with tobacco. In Study 2, where craving was measured after both product consumption and beverage, there was an increase in cigarette craving immediately following beverage consumption that occurred regardless of alcohol content. This can be explained in one of three ways: a placebo effect for beverage occurred, participants' abstinence-related craving increased over time and was correctly self-reported, or craving increased over time because participants knew a smoking opportunity would occur

shortly. To determine whether a cue-induced or abstinence-related craving occurred, one could sample craving immediately after the absorption of both substances in two separate studies, one with alcohol administered first and the other with tobacco first. Adding additional timepoints for self-reporting cigarette craving could be done in these future studies in order to help determine the extent to which craving was increasing over time, and to what degree it was due to our intervention.

If the acidic beverage did not influence the absorption of chemicals from snus, then the present studies suggest a disconnect between cigarette craving and actual cigarette consuming behavior given the opportunity to smoke. Real world smoking behavior is not compulsive, as smokers do not satisfy all cigarette cravings as they occur (Shiffman et al., 2015). While cue-reactivity is known to influence cigarette craving (Drobes, 2002; Duka & Townshend, 2004; Field et al., 2005; King, McNamara, Angstadt, & Phan, 2010; McGrath et al., 2015; Peloquin, McGrath, Telbis, & Barrett, 2014; Sayette, Martin, Wertz, Perrott, & Peters, 2005; Shiffman et al., 2013), it does not cause cigarette smoking itself. Studies that implicate craving as predictive of cigarette smoking behavior are not supported by the studies within this thesis, which show that there are circumstances under which unconscious cigarette craving and smoking behavior can occur in the absence of conscious craving.

STRENGTHS AND LIMITATIONS

A perceived limitation of these studies includes the selected sample size. Although the sample size limits the examination of small effects within multiple level interactions, additional subjects would have further increased the risk of Type II errors. Examining sex as a between-subject factor would further increase both risks. The studies

were placebo-controlled and double-blinded to minimize both demand characteristics and intra-individual differences between the two sessions in Studies 1 and 2 and across the four sessions for each participant in Study 3. Similar designs have been used by Barrett and colleagues (2005), Epstein and colleagues (2007), King and Epstein (2005) and McKee and colleagues (2010), and have found significant pharmacological effects of alcohol and tobacco in humans using fewer sessions.

As well, since snus is a novel product and given the cross-sectional design utilized, the authors of these studies were unable to comment on aspects of the alcohol-tobacco relationship that develops over time. Only snus' acute effects on naïve users could be analyzed, which is different from individuals who are frequent snus users. Frequent snus users are unlikely to be found in North America but could be recruited in areas such as Norway and Sweden.

Utilizing an acidic alcoholic beverage may have influenced the outcomes of the studies, as highlighted in Section 1 above. However, utilizing the cranberry-vodka cocktail recipe in Studies 1 through 3, as other published studies have used (e.g., Kushner et al., 1996), allowed for calculation of the proper dose of alcohol to administer to all participants based on their sex and body weight (Posey & Mozayani, 2007); it also allowed for the creation of a convincing placebo beverage. Few, if any, alcoholic beverages have a neutral or alkaline pH. One could be designed specifically for research use by adding a base to an acidic mixer. However, this would require testing to ensure that the product is palatable and can successfully pass as a placebo beverage when combined with alcohol.

Lastly, as previously discussed, selecting the timing of substance administration and self-report questionnaires limits our investigation into order effects that may occur at different intervals than those measured in this study. In contrast, in animal models, substances can be administered directly into the brain via cannula and researchers can immediately measure responses. Unfortunately, animal studies cannot observe cognitions like craving. Therefore our experimental human paradigm is the most reasonable choice, even with its unique limitations. As well, the timing of substance use in our experiments was meant to mimic natural substance use outside of the lab. However, concurrent overlapping substance administration is also ordinary (Dunbar, Scharf, Kirchner, & Shiffman, 2010; Shiffman et al., 2015; Witkiewitz et al., 2012), but difficult to study without quasi-experimental designs to assess individuals in settings where they usually drink and smoke. Indoor smoking is banned across all Canadian provinces in public places. There are limited locations where one can smoke and consume alcohol other than a personal dwelling or outside. Studying the effects of alcohol and tobacco use in participant's homes would increase the naturalistic validity of a similar experimental study, but would substantially compromise the level of experimental control afforded by a lab-based study. The strengths of the studies in the present thesis were that snus is a novel product for North American participants (Biener et al., 2014) and therefore would not elicit the same expectancies that would occur with a cigarette, an electronic cigarette, or any other familiar NRT product. This reduced the possibility of an expectancy that their product contained tobacco. We asked participants after the study if they were familiar with snus, and none reported that they knew of it. We did not query participants at the time they were administered their product as we did not wish to prime any

expectation that their product contained tobacco. The likely absence of an expectancy effect allowed for examination of the effects that tobacco alone and in combination with alcohol have on cigarette craving and consumption. Snus also allows for the comparison of the effects of tobacco with the effects of cigarette smoke, which are chemically different and often not differentiated between in the current literature. Although Studies 1 through 3 did not compare the effects by replacing snus with a cigarette across trials because of expectancy confounds, future studies can examine the subtle differences between the effects of both substances and compare their results against findings from the present set of studies. As well, the placebo product and beverage were reasonable facsimiles of their active counterparts and allowed us to compare pharmacological effects versus placebo effects.

IMPLICATIONS AND FUTURE RESEARCH

Ninety percent of smokers across Canada, the United States, the United Kingdom, and Australia regret that they ever began smoking (Fong et al., 2004). In the United States, approximately 68.8% of current smokers would like to quit smoking (Centers for Disease Control and Prevention, 2011). Approximately half of smokers attempt to quit each year, but only approximately 5% of smokers are successful in remaining tobacco-free each year (Health Canada, 2013a). As of 2001, it has been estimated that smokers utilize as much as 14% of all healthcare related costs in the United States (Wendy, 2001), and contribute to 16.6% of all deaths in Canada (Baliunas et al., 2006). With NRTs only increasing quit rates by 1.84 times (Cahill et al., 2013) and varenicline increasing quit rates by 2.88 times (Cahill et al., 2007, 2013), more effective smoking cessation methods are desperately needed. Furthermore, even if smokers are motivated to quit smoking and

utilize the best pharmacotherapy presently available, concurrent alcohol use places them at high risk to relapse into previous smoking behavior (Baliunas et al., 2006).

The primary purpose of the studies in this dissertation was to better understand the alcohol-tobacco co-use phenomenon in order to inform more effective smoking cessation interventions. Snus, a tobacco product with a low toxicity profile compared to cigarettes and other oral tobacco products, reduced cigarette consumption, even in the context of alcohol consumption, in DDS who have no intention to quit smoking. This reduction in cigarette consumption regardless of alcohol consumption is both a novel finding and one that provides a therapeutic option for both smokers who intend to quit smoking and those who merely wish to smoke fewer cigarettes. Snus appears to reduce cigarette consumption while drinking because it contains not only nicotine but also other non-nicotinic tobacco chemicals, unlike NRTs.

However, snus does not reduce cigarette consumption while drinking in NNS, possibly because snus does not contain the necessary levels of acetaldehyde or other chemicals which are reinforcing to non-dependent smokers (Digard, Gale, et al., 2013; ENVIRON International Corporation, 2010; Stepanov et al., 2008). It is possible that acetaldehyde or other condensation byproducts found in cigarette smoke and not in the tobacco itself may be implicated as significant motivators for smoking behavior and craving in early tobacco use. Without acetaldehyde or other condensation byproducts, snus is at least a less harmful tobacco option compared to cigarette use (Boffetta & Straif, 2009; Hatsukami et al., 2004; Krautter et al., 2015; Lee, 2013; Ramström, 2011; Rodu & Cole, 2002).

Although no randomized controlled trials have been conducted utilizing snus for quitting smoking among smokers who drink, our studies suggest that it shows promise to be even more effective than existing nicotine-only replacement therapy products. If smokers used snus, it is possible that the same effect of discontinuing or reducing cigarette use without prompting may be observed, as seen when electronic cigarettes become available to smokers (Polosa et al., 2011). As a bonus, snus produces no smoke and therefore poses little environmental risk to others if properly disposed of after use, thus reducing the second-hand harms of smoking (Öberg, Jaakkola, Woodward, Peruga, & Prüss-Ustün, 2011).

For tobacco researchers, snus is of great potential use because, as previously highlighted, it allows further investigation of the alcohol-tobacco co-use phenomenon in humans without many of the confounding psychological effects that cigarettes have. The present set of studies examined three sets of alcohol and tobacco use administration timings, but there are many more experimental paradigms that can be crafted to understand the alcohol-tobacco use phenomenon further. Snus remains a new substance in Canada, and therefore remains a viable research tool for experimental studies here. Direct comparison of the effects of nicotine absorption with NRTs, electronic cigarettes, and cigarettes themselves with alcohol can be conducted along with snus to determine whether the impact snus has on cigarette consumption is significantly higher than that of NRTs. At the time of this thesis, there is a dearth of experimental research examining the efficacy of NRTs with alcohol.

There is also the potential for pharmaceutical companies to improve current smoking cessation products by isolating the relevant tobacco factors within snus and

experimentally administering them alone or in combination with nicotine. Experimentation with isolated chemicals in tobacco can be done with or without alcohol to determine which of the various psychoactive chemicals found in snus lead to the reductions in cigarette consumption seen in this dissertation. This line of research could bolster the claim that other tobacco factors beyond nicotine play a significant role in the development of tobacco use disorders. As well, isolation of the chemicals within tobacco could create a pharmacologically superior, less addictive, and safer smoking cessation product that is effective when smokers drink and tolerated better than nicotine-only replacement products.

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APPENDIX A: STUDIES 1 & 2 INFORMED CONSENT FORMS

Capital Health

Psychiatry Clinical Trials Program
QEII Centre for Clinical Research
5790 University Avenue, Room #999
Halifax, Nova Scotia
B3H 1V7

CONSENT TO TAKE PART IN A RESEARCH STUDY

Participant Information

STUDY TITLE: The effects of alcohol on the reinforcing and subjective effects of tobacco and nicotine in smokers that drink.

PRINCIPAL INVESTIGATOR: Dr. Sean Barrett
Department of Psychology
Life Science Center
Dalhousie University
1355 Oxford Street
Halifax, Nova Scotia
CANADA (B3H 4H6)
Telephone: (902) 494-2956

CO-INVESTIGATOR: Dr. Sherry Stewart
Department of Psychiatry
5909 Veteran's
Memorial Lane, 8th Floor

Abbey J. Lane Memorial Building

QEII Health Sciences Centre

Halifax, N.S., Canada

B3H 2E2

Telephone: (902) 494-4546

FUNDING AGENCY: Natural Sciences and Engineering Research Council of Canada (NSERC)

PART A.

RESEARCH STUDIES – GENERAL INFORMATION

1. INTRODUCTION

You have been invited to take part in a research study. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study.

Please read this carefully. Take as much time as you like. If you like, take it home to think about for a while. Mark anything you don't understand or want explained better. After you have read it, please ask questions about anything that is not clear.

The researchers will:

Discuss the study with you

Answer your questions

Keep confidential any information which could identify you personally

Be available during the study to deal with problems and answer questions

We do not know if taking part in this study will help you. You may feel better. On the other hand it might not help you at all. It might even make you feel worse. We cannot

always predict these things. We will always give you the best possible care no matter what happens.

If you decide not to take part or if you leave the study early, your usual health care will not be affected.

PART B.

EXPLAINING THIS STUDY

2. WHY IS THIS STUDY BEING DONE?

We would like to find out whether different types of tobacco products affect how you perform on a computerized task and in response to questionnaires after drinking alcohol. The results of this study may help clarify the relative importance of different cigarette ingredients for understanding the link between alcohol consumption and smoking behaviour. We hope to gain knowledge from the study that may be used to develop better treatments to help people who want to quit smoking.

3. WHY AM I BEING ASKED TO JOIN THE STUDY?

At present you have indicated that you are 19 years of age (or older), are a moderate consumer of alcohol (e.g. consume at least four (4) alcoholic drinks on at least one occasion per week) and smoke at least five (5) cigarettes per week.

4. HOW LONG WILL I BE ON THE STUDY?

The study involves 2 sessions at the Dalhousie Tobacco and Addictions Laboratory. Each session will take approximately four (4) hours to complete. The sessions will be scheduled approximately one (1) week apart.

5. HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

This study will be done in Halifax, Nova Scotia. We expect that approximately forty-eight (48) participants will be recruited from the community. It is expected that the current study will take about twelve (12) months to complete.

6. HOW IS THE STUDY BEING DONE?

You will be required to attend two (2) experimental sessions at the Dalhousie Tobacco and Addictions Laboratory spaced approximately one week apart. During these sessions you will receive an alcoholic beverage and will be required to consume this beverage steadily for 15 minutes. The concentration of alcohol in the beverages you will be required to consume throughout this study may vary between sessions. Afterwards, you may receive substances that differ from one another according to ingredients that are normally found in regular cigarettes (e.g. tar, ammonia, menthol, nicotine, sucrose etc.). This study is being done, in part, to examine the effects of alcohol on subjective (e.g. satisfaction, sedation, stimulation, craving) and behavioural responses (self-administration) to different types of subtances.

7. WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

Telephone Screening:

In order to be in this study and sign this consent form, you must have consented to and successfully completed a telephone interview. The telephone screening was done to ensure that you have met all the eligibility criteria to participate. More specifically, you indicated that you are nineteen (19) years of age or older, you are a regular moderate consumer of alcohol and you smoke at least five (5) cigarettes per week. You have also indicated that you are not currently trying to quit smoking or planning to do so in the next thirty (30) days and are not currently using nicotine-replacement therapy (NRT) for any reason. Also, if you are a female, you have indicated you are not currently pregnant, are not currently planning to conceive and are not nursing.

Sessions 1-2

You will not be able to smoke tobacco or marijuana cigarettes or drink alcohol twelve (12) hours prior to the remaining four (4) sessions. During each of these sessions your tobacco abstinence will be verified by collecting a breath and saliva sample (if you choose to do so; saliva samples are not mandatory) at the beginning of each session; your alcohol abstinence will also be verified at the beginning of each session using a breath sample. All saliva samples will then be sent to a lab, with only a study code assigned to them. No information that could possibly identify you will be kept with the sample; however, the research staff will have access to a file that indicates which code is matched with your name. These records will be kept for seven (7) years in a secure area such as a locked file cabinet. Therefore, only the research staff will have access to them, and know your name. You can also contact the Principal Investigator at any time to make arrangements to have your sample destroyed. Following this, you will complete several questionnaires that indicate your level of tobacco craving, any symptoms of withdrawal, and your mood.

Will be scheduled during an afternoon following typical smoking behaviour. During the first session, after having the experiment explained to you, we will collect a breath sample from you in order to get your exhaled carbon monoxide reading during an afternoon following your normal smoking behaviour. In addition, women who are pregnant, currently trying to get pregnant, or are breastfeeding are not eligible to participate in this study. Women participants who have engaged in sexual activity that could lead to pregnancy and are not using effective means of birth control are strongly encouraged to privately take a pregnancy test at the beginning of the study. Afterwards, you will be asked to smoke a cigarette, and asked about your recent history of tobacco use with the help of a calendar during the first session, and then asked to complete a series of self-report questionnaires that look at various aspects of your lifestyle and personality during the second session.

You will then consume the assigned beverage steadily for fifteen (15) minutes, followed by a thirty minute period for absorption. During this absorption period, you will then sample your assigned product for the day over thirty (30) minutes. Afterwards, you will complete the same questionnaires you completed at the beginning of the session regarding your level of tobacco craving, symptoms of withdrawal, and mood and will provide another breath sample. will be followed by two (2) breath samples, and another saliva sample. Afterwards, you will complete another round of the questionnaires.

You will then be invited to earn as many cigarette puffs as you like by completing a computerized task. During the computerized task you will be required to repeatedly press a keyboard spacebar a predetermined number of times in order to obtain each additional puff. The amount of spacebar presses may change/increase each time you wish to obtain an extra puff. You are not required to earn any puffs if you do not wish to do so, and you are free to stop the computer task at any time. You will be able to earn cigarette puffs for up to one (1) hour, during which you will remain seated. After this period, you will be asked to provide another saliva sample and two (2) breath samples. You will then complete a final round of the questionnaires.

The researchers will then take you to another room where you will watch videos for up to two (2) hours. This will be done to ensure that your blood alcohol concentration is 0.04% or lower before you leave the laboratory. After this time you will be sent home safely via taxi or researcher escort. In total, each of the two sessions should take about four (4) hours to complete. You will be free to leave at any time to take bathroom breaks, or completely withdraw from the study.

You will not be asked to re-indicate your tobacco use history for any of these sessions. Your eligibility to continue with the study will be evaluated by re-examining the inclusion criteria to ensure that no applicable changes have occurred between sessions.

8. ARE THERE RISKS TO THE STUDY?

There are risks with this, as with any study. To give you the most complete information available, we have listed some *possible* risks. We want to make sure that if you decide to try the study, you have had a chance to think about the risks carefully. Please be aware that there may be risks that we do not yet know about.

STUDY RISKS

Ingredients normally found in cigarettes have some side effects associated with them. There is a small risk (less than 10%) of headache, coughing, hiccups, nausea, vomiting, and irritation in the mouth and throat and nasal congestion.

In addition, as you will be asked not to smoke the night prior (after midnight) to your first session, you may experience withdrawal symptoms. These symptoms may be physical (i.e. dizziness) and/or mental (i.e. feelings of frustration and/or anger).

Symptoms can include any of the following:

- dizziness
- feelings of frustration and/or anger
- irritability
- cravings
- trouble concentrating
- restlessness
- headache
- tiredness

You will also be required to consume alcohol throughout the course of the study. You may experience intoxication drunkenness, dizziness, stomach upset, tiredness and/or headaches. Please note that you will be consuming the alcoholic beverages over a short amount of time and that this may influence the effect you feel from the alcohol if you normally drink at a slower rate. You may stop consuming alcohol at any time. You may also experience physical and/or mental impairment for one (1) or two (2) hours after you have consumed the alcoholic beverages, similar to what you would experience if you were consuming this quantity of alcohol outside of the lab. If in feeling the effects of the alcohol you feel ill or otherwise uneasy you may end your participation at any time and ask to be released or accompanied to a medical facility. Additionally, if at any time you wish to leave the study for any reason, you are free to do so. However, if you have consumed alcohol at that time, you must agree not to leave the lab until your blood alcohol concentration falls below 0.04%.

SALIVA SAMPLES

The saliva samples that are being collected during the experimental sessions will be used to examine the concentration of certain tobacco ingredients (e.g. tar, ammonia, menthol, nicotine, sucrose) in your saliva. They will not be used for any other reason, including genetic analyses. To protect your identity/information, we will not keep your name or

other information that may identify you with the sample; only a code number. Files that link your name to the code number will be kept in a locked cabinet and only the study staff will be allowed to look at them. Although no one can absolutely guarantee confidentiality, using a code number greatly reduces the chance that someone other than the research staff or other authorized groups or persons (discussed later in the consent form) will ever be able to link your name to your sample or to any test results.

You may find that providing saliva samples throughout the study is uncomfortable and/or embarrassing. You do not have to provide the saliva samples if they make you feel uncomfortable.

QUESTIONNAIRES

You may find the questionnaires you receive during the course of the study upsetting or distressing. You may not like all the questions that you will be asked. You do not have to answer those questions you find distressing.

COMPUTERIZED TASKS

You may find the computerized task frustrating or boring. You do not have to complete the task if it makes you uncomfortable.

9. WHAT HAPPENS AT THE END OF THE STUDY?

Once the study is complete, you will be contacted by phone and told about the conduct and results of the study. At this time you can ask that your study data be removed if you wish.

10. WHAT ARE MY RESPONSIBILITIES?

As a study participant you will be expected to:

- Follow the directions of the Principal Investigator;
- Report all medications being taken or planned on taking to your family doctor;
- Report any changes in your health status;
- Report any serious adverse events that have occurred as soon as possible.

11. CAN I BE TAKEN OFF THE STUDY WITHOUT MY CONSENT?

Yes. You may taken out of the study at any time, if;

- You can't tolerate the side effects.

- There is new information that shows that being on this study is not in your best interests.
- Dalhousie University, NSERC, the Capital Health Research Ethics Board, or the Principal Investigator decides to stop the study.

You will be told about the reasons why you might need to be taken out of the study.

12. WHAT ABOUT NEW INFORMATION?

It is possible (but unlikely) that new information may become available while you are in the study that might affect your health, welfare, or willingness to stay in the study. If this happens, you will be informed in a timely manner and will be asked whether you wish to continue taking part in the study or not.

13. WILL IT COST ME ANYTHING?

Compensation

You will not be paid to be in the study. You will receive a small amount of money (**i.e. ten (10) dollars per hour or part thereof**) to cover your time, gas mileage, and parking for each of the two (2) sessions at the Dalhousie Tobacco and Addition Laboratory. Additionally, during both you will receive an additional **ten (10) dollars per session if you were successful at remaining abstinent for twelve (12) hours prior to arrival at the laboratory**. This will be awarded in order to compensate you for the time that your normal activities were disrupted.

If you decide to provide a saliva sample, please note: The aim of our research is to improve the public health. Your saliva sample will never be used to develop a process or invention that will be sold or patented.

14. WHAT ABOUT MY RIGHT TO PRIVACY?

Protecting your privacy is an important part of this study. A copy of this consent form will be put in your health record.

When you sign this consent form you give us permission to:

- Collect information from you
- Share information with the people conducting the study
- Share information with the people responsible for protecting your safety

Access to records

The Principal Investigator and members of the research team will see health and study records that identify you by name.

Other people may need to look at the health and study records that identify you by name. These might include:

- Dalhousie University and the Principal Investigator
- NSERC
- The CDHA Research Ethics Board and Research Quality Associate

Use of records

The research team will collect and use only the information they need to complete the study. This information will only be used for the purposes of this study.

This information will include your:

- date of birth
- sex
- medical conditions
- medications
- information from study interviews and questionnaires
- saliva samples

Your name and contact information will be kept secure by the research team in a locked cabinet at Dalhousie University in Halifax, Nova Scotia. It will not be shared with others without your permission. Your name will not appear in any report or article published as a result of this study. Information collected for this study will kept as long as required by law. This could be 7 years or more.

If you decide to withdraw from the study, the information collected up to that time will continue to be used by the research team. It may not be removed.

After your part in this study ends, we may continue to review your study records. We may want to follow your progress and to check that the information we collected is correct.

Information collected and used by the research team will be stored at the Dalhousie Tobacco and Addictions Laboratory. The Principal Investigator is the person responsible for keeping it secure.

You may also be contacted personally by Research Auditors for quality assurance purposes.

Your access to records

You may ask the Principal Investigator to see the information that has been collected about you.

Once we take your saliva samples (for non-genetic purposes), we will assign them a code number. We will separate your name and any other information that points to you from your samples. We will keep files that link your name to the code number in a locked file cabinet and office, away from your samples.

15. WHAT IF I WANT TO QUIT THE STUDY?

If you chose to participate and later change your mind, you can say no and stop the research at any time. If you wish to withdraw your consent, please inform the Principal Investigator. All data collected up to the date you withdraw your consent will remain in the study records, to be included in study related analyses.

16. WHAT WILL HAPPEN TO MY SAMPLES AFTER THE STUDY IS OVER?

After this study is over, we will dispose of all the saliva samples we collected by burning them.

17. DECLARATION OF FINANCIAL INTERESTS

The funding agency is paying the Principal Investigator and/or the Principal Investigator's institution to conduct this study. The amount of this payment is sufficient to cover the costs of conducting the study. The Principal Investigator has no financial interests in conducting this research study.

18. WHAT ABOUT QUESTIONS OR PROBLEMS?

For further information about the study call **Dr. Sean Barrett**. Dr. Barrett is in charge of this study at this institution (Principal Investigator). Dr. Sean Barrett is at (902) 494-2956.

If you experience any symptoms or possible side effects or other medical problems, please let the Principal Investigator know immediately.

The Principal Investigator is Dr. Sean Barrett
Telephone: 494-2956

19. WHAT ARE MY RIGHTS?

After you have signed this consent form you will be given a copy.

If you have any questions about your rights as a research subject, contact the **Patient Representative** at **(902) 473-2133**.

In the next part you will be asked if you agree (consent) to join this study. If the answer is yes, you will need to sign the form.

PART C.

20. CONSENT FORM SIGNATURE PAGE

I have reviewed all of the information in this consent form related to the study called:

THE EFFECTS OF ALCOHOL ON THE REINFORCING AND SUBJECTIVE EFFECTS OF TOBACCO AND NICOTINE IN SMOKERS THAT DRINK

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.

I agree to allow the people described in this consent form to have access to my health records.

This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time.

☐ **I agree** to provide a sample of my saliva (*chewing on a cotton swab*).

☐ **I do not agree** to provide a sample of my saliva.

_____	_____	___ / ____ / ___
Signature of Participant	Name (Printed)	Year Month Day*
_____	_____	___ / ____ / ___
Witness to Participant's Signature	Name (Printed)	Year Month Day*
_____	_____	___ / ____ / ___
Signature of Investigator	Name (Printed)	Year Month Day*
_____	_____	___ / ____ / ___
Signature of Person Conducting Consent Discussion	Name (Printed)	Year Month Day*

Note: Please fill in the dates personally

I WILL BE GIVEN A SIGNED COPY OF THIS CONSENT FORM.

Thank you for your time and patience!

APPENDIX B: STUDIES 1 & 2 TELEPHONE SCREEN AND FTND

Telephone Screen (+ Fagerström Test for Nicotine Dependence + Michigan Alcohol Screening Test)

ID #_____

Interviewer to read to potential participant: Hello, this is _____ calling from the Dalhousie Tobacco and Addictions Laboratory with regards to a study that you recently inquired about. First, I will tell you a little about the study and then I will ask you a few questions regarding your smoking and drinking habits.

The study will take place during 2 sessions at Dalhousie University and will be spaced about 2 to 7 days apart. In the first session you will be asked to come in during an afternoon following your typical smoking behaviour. You will complete a series of questionnaires that look at various personality variables and trait characteristics and will also be required to provide a breath sample so that we can see what your typical expired air carbon monoxide reading is (this will be used later to confirm your tobacco abstinence).

You will be required to abstain from smoking and drinking alcohol 12 hours before you arrive at the lab and this will be verified by two breath samples. We also ask that you eat your typical meals throughout the day but refrain from eating anything or drinking any caffeinated beverages 2 hours before your arrival at the lab. At the start of each session, you will be asked to smoke a cigarette. If you are unable to bring a cigarette of your own, then one will be provided. During the sessions, you will be asked to consume a beverage that may vary according to alcohol concentration. Afterwards, you may receive substances that differ from one another according to ingredients that are normally found in regular cigarettes (e.g. tar, ammonia, menthol, nicotine, sucrose etc.) You will also complete a series of questionnaires about your mood and tobacco craving, a basic computerized task, and will be asked to provide two additional saliva samples. These sessions are expected to take about 3.5 - 4 hours. You will be compensated $10 per hour, or part thereof, for each session. In addition to the hourly compensation, you will be awarded an extra 10$ per session for each session that you arrive tobacco abstinent after the first meeting.

Are you interested in participating in the study? If yes, I will need to ask you several questions to make sure that you are eligible to participate in this study. This will take about 10 minutes to complete. Is this okay? (If yes, proceed)

Question	Response	Interviewer Response
1. How old are you?		Reject if under 19
2. What is your birthday?		
3. How many days in the past 30 days have you smoked?		**Reject if under 28**
4a. Are you a daily smoker?	☐Y ☐N	Reject if N Move to question #5
4b. How long have you ever been a daily smoker	☐Y Length____	Reject if Y **and** less than one year
5. How many cigarettes do you smoke per week?		Reject if under 5 cigarettes per week
6. Are you currently trying to quit smoking, or do you intend to do so within the next 30 days?	☐Y ☐N	Reject if Y
7. Are you currently using Nicotine Replacement Therapy (i.e. patch, gum, inhalers)?	☐Y ☐N	Reject if Y
8. Are you a regular moderate consumer of alcohol? We define this as having had consumed a minimum of 5 drinks for males and 4 for females on at least one occasion per week over the past month.	☐Y ☐N	Reject if N
9. Have you ever experienced any unexpected negative reactions to alcohol? For example, fainting or a seizure, unusual flushing of your skin, problems with your liver or severe or unusual psychological reactions to alcohol?	☐Y ☐N	Reject if Y
10. As part of the study you will have to drink cranberry juice. Are you comfortable drinking cranberry juice (i.e. no allergies to cranberry juice)?	☐Y ☐N	Reject if N
11. As part of the study you will have to drink vodka. Are you comfortable drinking vodka (i.e. no allergies to vodka)?	☐Y ☐N	Reject if N
12. Are you currently under the regular care of a physician? (NOT your General Practitioner)	☐Y Specify_____ ☐N	Y go to Q#13 N go to Q#14
13. Has your doctor, nurse, or other health care provider suggested that you limit your drinking or do not drink because of this condition?	☐Y ☐N	Reject if Y
14. Are you currently taking any medications on a regular basis	☐Y Specify_____ ☐N	Y go to Q#15
15. Has your doctor, nurse, or other health care provider suggested that you limit your drinking or do not drink because of this medication?	☐Y ☐N	Reject if Y

Question	Response	Interviewer Response
Are you taking, going to start taking, or take for emergency purposes any of the following medications: • Insulin or other drugs used to control diabetes (e.g. chlorpropamide [Diabinese], metformin [Glucophage], phenformin, or tolbutamide [Orinase]) • MAO Inhibitors (e.g. isocarboxazid [Marplab] or phenelzine [Nardil]) • Antabuse • Anti-fungals (e.g. ketoconazole) • Antibiotics (e.g. flagyl) • Drugs used to control blood pressure (e.g. nifedipine or verapamil) • Drugs used for autoimmune disorders (e.g. methotrexate or procarbazine [Matulane]) • Benzodiazepines (e.g. Valium or Libruim) • Prescription pain medications	☐Y Specify_____ ☐N	Reject if Y
Are you taking any other prescription medication at this time?	☐Y ☐N	Reject if Y
Have you EVER suffered from any of the following medical conditions? • Asthma or any other ailments that affect your breathing • Diabetes • Liver Disease • Epilepsy or other neurological disorders that would impair your ability to carry out the necessary tasks • Ulcers or other gastrointestinal problems • Pancreatitis • High blood pressure, artery disease or heart disease • Lung Disease	☐Y Specify_____ ☐N	Reject if Y

Pregnancy **FEMALES:** *"We know that alcohol consumption during pregnancy can be unhealthy for babies before they are born. If you are pregnant, planning to get pregnant, or are nursing, you should not be in the study. If you have engaged in sexual activity that could lead to pregnancy and are not using effective birth control we recommend that you take a pregnancy test at the start of the study. This would be a urine screen test where you would need to urinate into onto a test strip in a private washroom and then allow the experimenter to test your urine for possible pregnancy. The pregnancy test would not involve a blood test".*		
	☐Y ☐N	Reject if Y N go to b
a) Are you currently pregnant, planning to get pregnant, or nursing a baby at this time?"	☐Y ☐N	Y go to c N go to FTND
b) Are you currently engaging in sexual activity that could lead to pregnancy?	☐Y ☐N	Y go to FTND N go to d
c) Are you using effective means of birth control? d) "*Given our concerns about the safety of developing babies before they are born, we recommend that you allow us to do a urine screen pregnancy test before the testing session. We will provide you with immediate feedback with the results. Would you like us to have a pregnancy test available for you to take?*"	☐Y ☐N	

Fagerström Test for Nicotine Dependence (FTND)

The following questions assess your dependence on nicotine. Please answer each question; each answer gets a set amount of points. Add up the points and check out the score indicator below:

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette	Within 5 minutes 6 to 30 minutes 31-60 minutes After 60 minutes	3 2 1 0
2. Do you find it difficult to refrain from smoking in places where it is forbidden such as church, the library, or movie theatres?	Yes No	1 0
3. Which cigarette would you hate most to give up?	The first one in the morning Any others	1 0
4. How many cigarettes do you smoke each day? (20 cigarettes are in a pack)	10 or less 11-20 21-30 31 or more	0 1 2 3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes No	1 0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes No	1 0

Total (Add items 1 to 6) =

_____

Reject if under 3

Short Form of the Michigan Alcohol Screening Test (SMAST)

1	Do you feel you are a normal drinker? (By normal we mean you drink less than or as much as most other people)	Y **N**	0 **1**
2	Does your wife, husband, a parent, other near relative, or close friend ever worry or complain about your drinking?	**Y** N	**1** 0
3	Do you ever feel guilty about your drinking?	**Y** N	**1** 0
4	Do friends or relatives think you are a normal drinker?	Y **N**	0 **1**
5	Are you able to stop drinking when you want to?	Y **N**	0 **1**
6	Have you ever attended a meeting of Alcoholics Anonymous (AA)?	**Y** N	**1** 0
7	Has drinking ever created problems between you and your wife, husband, a parent, other near relative, or close friend?	**Y** N	**1** 0
8	Have you ever gotten into trouble at work because of drinking?	**Y** N	**1** 0
9	Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?	**Y** N	**1** 0
10	Have you ever gone to anyone for help about your drinking?	**Y** N	**1** 0
11	Have you ever been in a hospital because of drinking?	**Y** N	**1** 0
12	Have you ever been arrested for drunken driving, driving while intoxicated, or driving under the influence of alcoholic beverages?	**Y** N	**1** 0
13	Have you ever been arrested, even for a few hours, because of other drunken behavior?	**Y** N	**1** 0

TOTAL (Reject if 3 or higher):

IF MEET REQUIREMENTS:

Because you will be receiving alcohol it is important that you arrange for someone to pick you up or that you are able to walk home. Is this possible?

__ Arrange to be picked up __Walk home __ Public Transit

IF DO NOT MEET REQUIREMENTS:

Currently you are not eligible to participate in the study, however because the requirements may change it is possible that you may be eligible at a later time. Is it okay if I keep you name in a database to be contacted regarding this study in the future?

APPENDIX C: STUDIES 1-3 MEASURES ADMINISTERED

Capital Health

Demographics and Smoking/Drinking History Questionnaire

SUBJECT ID:_____

1. How old are you? _____

2. Please indicate your sex: (Male) (Female)

3. Please indicate your marital status:

   (Single) (Common-Law) (Married) (Separated) (Divorced) (Widowed)

4. Please indicate your highest level of education completed:

   (Some High School) (High School Diploma) (Some College/University) (College/University Degree) (Other (Please specify): _____)

5. Are you currently enrolled in a post-secondary institution? (Yes/No)

6. Are you currently employed? (Yes/No)

7. At what age did you first try smoking? _____

8. How many days in the last thirty (30) days have you smoked? _____

9. How many cigarettes did you smoke, on average, on each of these days? _____

10. Are you a daily smoker? (Yes/No)
    If yes, please proceed to question #12

11. Have you ever been a daily smoker? (Yes/No)
    If no, please proceed to question #13

12. How many years and/or months were you / have you been a daily smoker? _____

13. What type (brand) of cigarettes do you normally smoke? _____

14. How long has it been since you had your last cigarette? _____

15. Have you ever made a serious attempt to quit smoking? (Yes/No)

    If yes, how many times have you made a serious attempt to quit smoking? _____

    The last time you tried, how long were you able to give up smoking?

    ___Years ___Weeks ___Days ___Hours

16. At what age did you first try drinking alcohol? _____

17. In the past month, on average, how many occasions per week did you typically consume alcohol? _____

18. How many months and/or years have you been a regular user of alcohol? [Note: regular use refers to consuming alcohol on *at least* one occasion per week]
    _____

19. In the past month, how many alcoholic beverages did you typically consume per drinking occasion? [Note: one alcoholic beverage = one bottle or beer, or one small glass of wine, or one shot/mixed drink containing an once of hard liquor]
    _____

20. In the past month, how many occasions per week did you consume at least 4 alcoholic beverages? _____

21. Which type of alcoholic beverage do you prefer? (circle one)

beer wine mixed drinks

(After last experimental session)

1. Have you ever tried any other tobacco products? (Yes/No)
   If yes, proceed to question # 2

2. What products can you remember? _____

3. Have you tried any Nicotine Replacement Therapy products? (Yes/No)
   If yes, proceed to question # 4

4. What products can you remember? _____

5. Ask if the participant has any final comments, record them:

(After paying) Ask if participant is interested in allowing us to contact them for future research studies Circle one **Y** **N**

Brief Biphasic Alcohol Effect Scales

Capital Health

SUBJECT ID: _____ **SESSION** 1 2 **ADMIN**: 1 2 3

For each of the following, please choose the number that best describes how you are feeling **RIGHT NOW.**

Energized	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Excited	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Sedated	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Slow thoughts	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Sluggish	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Up	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely

Questionnaire of Smoking Urges – Brief

Capital Health

SUBJECT ID: _____ **SESSION** 1 2 **ADMIN**: 1 2 3

For each of the following, please choose the number that best describes how you are feeling **RIGHT NOW.**

	Strongly disagree			**Neutral**			**Strongly agree**
1. I have a desire for a cigarette right now.	1	2	3	4	5	6	7
2. Nothing would be better than smoking a cigarette right now.	1	2	3	4	5	6	7
3. If it were possible, I probably would smoke right now.	1	2	3	4	5	6	7
4. I could control things better right now if I could smoke.	1	2	3	4	5	6	7
5. All I want right now is a cigarette.	1	2	3	4	5	6	7
6. I have an urge for a cigarette.	1	2	3	4	5	6	7
7. A cigarette would taste good right now.	1	2	3	4	5	6	7
8. I would do almost anything for a cigarette right now.	1	2	3	4	5	6	7
9. Smoking would make me less depressed.	1	2	3	4	5	6	7
10. I am going to smoke as soon as possible.	1	2	3	4	5	6	7

Subjective Rating Scales – Studies 1 and 3

Capital Health

SUBJECT ID: _____ **SESSION** ~~1~~ 2 3 4 5 **ADMIN**: 1 2 3

For each of the following, please choose the number that best describes how you are feeling **RIGHT NOW.**

Relaxed	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Pleasant	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Head Rush	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Stimulated	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Jittery	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Dizzy	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Irritable	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Trouble Concentrating	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Anxious	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Satisfied	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
High	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Alert	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Frustrated	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Sedated	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Intoxicated	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Crave Cigarette	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Enjoy Taste	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely

Subjective Rating Scales – Study 2

Capital Health

SUBJECT ID: _____ **SESSION** 1 2 **ADMIN**: 1 2 3 4

For each of the following, please choose the number that best describes how you are feeling **RIGHT NOW.**

Relaxed	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Pleasant	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Head Rush	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Stimulated	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Jittery	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Dizzy	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Irritable	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Trouble Concentrating	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Anxious	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Satisfied	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
High	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Alert	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Frustrated	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Sedated	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Intoxicated	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Crave Cigarette	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Enjoy Taste	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Want Alcohol	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely
Like Drink	Not at all	1	2	3	4	5	6	7	8	9	10	Extremely

APPENDIX D: STUDY 3 INFORMED CONSENT

Capital Health

Psychiatry Clinical Trials Program

QEII Centre for Clinical Research

5790 University Avenue, Room #999

Halifax, Nova Scotia

B3H 1V7

CONSENT TO TAKE PART IN A RESEARCH STUDY

Participant Information

STUDY TITLE: **The effects of alcohol on the reinforcing and subjective effects of tobacco and nicotine in smokers that drink.**

PRINCIPAL INVESTIGATOR: Dr. Sean Barrett

Department of Psychology

Life Science Center

Dalhousie University

1355 Oxford Street

Halifax, Nova Scotia

CANADA (B3H 4H6)

Telephone: (902) 494-2956

CO-INVESTIGATOR: Dr. Sherry Stewart

Department of Psychiatry

5909 Veteran's

Memorial Lane, 8th Floor

Abbey J. Lane Memorial Building

QEII Health Sciences Centre

Halifax, N.S., Canada

B3H 2E2

Telephone: (902) 494-4546

FUNDING AGENCY: Natural Sciences and Engineering Research Council of Canada (NSERC)

PART A.

RESEARCH STUDIES – GENERAL INFORMATION

1. INTRODUCTION

You have been invited to take part in a research study. Taking part in this study is voluntary. It is up to you to decide whether to be in the study or not. Before you decide, you need to understand what the study is for, what risks you might take and what benefits you might receive. This consent form explains the study.

Please read this carefully. Take as much time as you like. If you like, take it home to think about for a while. Mark anything you don't understand, or want explained better. After you have read it, please ask questions about anything that is not clear.

The researchers will:

- Discuss the study with you
- Answer your questions
- Keep confidential any information which could identify you personally
- Be available during the study to deal with problems and answer questions

We do not know if taking part in this study will help you. You may feel better. On the other hand it might not help you at all. It might even make you feel worse. We cannot

always predict these things. We will always give you the best possible care no matter what happens.

If you decide not to take part or if you leave the study early, your usual health care will not be affected.

PART B.

EXPLAINING THIS STUDY

2. WHY IS THIS STUDY BEING DONE?

We would like to find out whether different types of tobacco products affect how you perform on a computerized task and in response to questionnaires after drinking alcohol. The results of this study may help clarify the relative importance of different cigarette ingredients for understanding the link between alcohol consumption and smoking behavior. We hope to gain knowledge from the study that may be used to develop better treatments to help people who want to quit smoking.

3. WHY AM I BEING ASKED TO JOIN THE STUDY?

At present you have indicated that you are 19 years of age (or older), are a moderate consumer of alcohol (e.g. consume at least four (4) alcoholic drinks on at least one occasion per week) and smoke at least five (5) cigarettes per week.

4. HOW LONG WILL I BE ON THE STUDY?

The study involves five (5) sessions at the Dalhousie Tobacco and Addictions Laboratory. The first session will take approximately one-and-a-half (1.5) hours to complete, while the remaining four (4) sessions will take approximately four (4) hours to complete. The sessions will be scheduled approximately one (1) week apart.

5. HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

This study will be done in Halifax, Nova Scotia. We expect that approximately twenty-four (24) participants will be recruited from the community. It is expected that the current study will take about twelve (12) months to complete.

6. HOW IS THE STUDY BEING DONE?

You will be required to attend five (5) sessions at the Dalhousie Tobacco and Addictions Laboratory. Following the first session you will be required to attend four (4) experimental sessions spaced approximately one week apart. During these sessions you will receive an alcoholic beverage and will be required to consume this beverage steadily for 15 minutes. The concentration of alcohol in the beverages you will be required to consume throughout this study may vary between sessions. Afterwards, you may receive substances that differ from one another according to ingredients that are normally found in regular cigarettes (e.g. tar, ammonia, menthol, nicotine, sucrose etc.). This study is being done, in part, to examine the effects of alcohol on subjective (e.g. satisfaction, sedation, stimulation, craving) and behavioural responses (self-administration) to different types of subtances.

7. WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

Telephone Screening:

In order to be in this study and sign this consent form, you must have consented to and successfully completed a telephone interview. The telephone screening was done to ensure that you have met all the eligibility criteria to participate. More specifically, you indicated that you are nineteen (19) years of age or older, you are a regular moderate consumer of alcohol and you smoke at least five (5) cigarettes per week. You have also indicated that you are not currently trying to quit smoking or planning to do so in the next thirty (30) days and are not currently using nicotine-replacement therapy (NRT) for any reason. Also, if you are a female, you have indicated you are not currently pregnant, are not currently planning to conceive and are not nursing.

First Session:

Will be scheduled during an afternoon following typical smoking behavior. During the first session, after having the experiment explained to you, we will collect a breath sample from you in order to get your exhaled carbon monoxide reading during an afternoon following your normal smoking behavior. In addition, women who are pregnant, currently trying to get pregnant, or are breastfeeding are not eligible to participate in this study. Women participants who have engaged in sexual activity that could lead to pregnancy and are not using effective means of birth control are strongly encouraged to privately take a pregnancy test at the beginning of the study. You will then complete a series of self-report questionnaires that look at various aspects of your lifestyle and personality and will be asked about your recent history of tobacco use with the help of a calendar.

Sessions 2-5:

The four (4) remaining sessions at Dalhousie will be scheduled approximately one (1) week apart and should take approximately four (4) hours to complete. You will not be asked to re-indicate your tobacco use history for any of these sessions. Your eligibility to continue with the study will be evaluated by re-examining the inclusion criteria to ensure that no applicable changes have occurred between sessions.

You will not be able to smoke tobacco or marijuana cigarettes or drink alcohol twelve (12) hours prior to the remaining four (4) sessions. During each of these sessions your tobacco abstinence will be verified by collecting a breath and saliva sample (if you choose to do so; saliva samples are not mandatory) at the beginning of each session; your alcohol abstinence will also be verified at the beginning of each session using a breath sample. All saliva samples will then be sent to a lab, with only a study code assigned to them. No information that could possibly identify you will be kept with the sample; however, the research staff will have access to a file that indicates which code is matched with your name. These records will be kept for seven (7) years in a secure area such as a locked file cabinet. Therefore, only the research staff will have access to them, and know your name. You can also contact the Principal Investigator at any time to make arrangements to have your sample destroyed. Following this, you will complete several questionnaires that indicate your level of tobacco craving, any symptoms of withdrawal, and your mood.

You will then consume the assigned beverage steadily for fifteen (15) minutes, followed by a twenty (20) minute period for absorption. Afterwards, you will complete the same

questionnaires you completed at the beginning of the session regarding your level of tobacco craving, symptoms of withdrawal, and mood and will provide another breath sample. You will then sample your assigned product for the day over thirty (30) minutes. This will be followed by two (2) breath samples, and another saliva sample. Afterwards, you will complete another round of the questionnaires.

You will then be invited to earn as many cigarette puffs as you like by completing a computerized task. During the computerized task you will be required to repeatedly press a keyboard spacebar a predetermined number of times in order to obtain each additional puff. The amount of spacebar presses may change/increase each time you wish to obtain an extra puff. You are not required to earn any puffs if you do not wish to do so, and you are free to stop the computer task at any time. You will be able to earn cigarette puffs for up to one (1) hour, during which you will remain seated. After this period, you will be asked to provide another saliva sample and two (2) breath samples. You will then complete a final round of the questionnaires.

The researchers will then take you to another room where you will watch videos for up to two (2) hours. This will be done to ensure that your blood alcohol concentration is 0.04% or lower before you leave the laboratory. After this time you will be sent home safely via taxi or researcher escort. In total, each of the four sessions should take about four (4) hours to complete. You will be free to leave at any time to take bathroom breaks, or completely withdraw from the study.

8. ARE THERE RISKS TO THE STUDY?

There are risks with this, as with any study. To give you the most complete information available, we have listed some *possible* risks. We want to make sure that if you decide to try the study, you have had a chance to think about the risks carefully. Please be aware that there may be risks that we do not yet know about.

STUDY RISKS

Ingredients normally found in cigarettes have some side effects associated with them. There is a small risk (less than 10%) of headache, coughing, hiccups, nausea, vomiting, and irritation in the mouth and throat and nasal congestion.

In addition, as you will be asked not to smoke the night prior (after midnight) to your first session, you may experience withdrawal symptoms. These symptoms may be physical (i.e. dizziness) and/or mental (i.e. feelings of frustration and/or anger).

Symptoms can include any of the following:

- dizziness
- feelings of frustration and/or anger
- irritability
- cravings
- trouble concentrating
- restlessness
- headache
- tiredness

You will also be required to consume alcohol throughout the course of the study. You may experience intoxication drunkenness, dizziness, stomach upset, tiredness and/or headaches. Please note that you will be consuming the alcoholic beverages over a short amount of time and that this may influence the effect you feel from the alcohol if you normally drink at a slower rate. You may stop consuming alcohol at any time. You may also experience physical and/or mental impairment for one (1) or two (2) hours after you have consumed the alcoholic beverages, similar to what you would experience if you were consuming this quantity of alcohol outside of the lab. If in feeling the effects of the alcohol you feel ill or otherwise uneasy you may end your participation at any time and ask to be released or accompanied to a medical facility. Additionally, if at any time you wish to leave the study for any reason, you are free to do so. However, if you have consumed alcohol at that time, you must agree not to leave the lab until your blood alcohol concentration falls below 0.04%.

SALIVA SAMPLES

The saliva samples that are being collected during the experimental sessions will be used to examine the concentration of certain tobacco ingredients (e.g. tar, ammonia, menthol, nicotine, sucrose) in your saliva. They will not be used for any other reason, including genetic analyses. To protect your identity/information, we will not keep your name or other information that may identify you with the sample; only a code number. Files that link your name to the code number will be kept in a locked cabinet and only the study staff will be allowed to look at them. Although no one can absolutely guarantee confidentiality, using a code number greatly reduces the chance that someone other than the research staff or other authorized groups or persons (discussed later in the consent form) will ever be able to link your name to your sample or to any test results.

You may find that providing saliva samples throughout the study is uncomfortable and/or embarrassing. You do not have to provide the saliva samples if they make you feel uncomfortable.

QUESTIONNAIRES

You may find the questionnaires you receive during the course of the study upsetting or distressing. You may not like all the questions that you will be asked. You do not have to answer those questions you find distressing.

COMPUTERIZED TASKS

You may find the computerized task frustrating or boring. You do not have to complete the task if it makes you uncomfortable.

9. WHAT HAPPENS AT THE END OF THE STUDY?

Once the study is complete, you will be contacted by phone and told about the results of the study.

10. WHAT ARE MY RESPONSIBILITIES?

As a study participant you will be expected to:

- Follow the directions of the Principal Investigator;
- Report all medications being taken or planned on taking to your family doctor;
- Report any changes in your health status;
- Report any serious adverse events that have occurred as soon as possible.

11. CAN I BE TAKEN OFF THE STUDY WITHOUT MY CONSENT?

Yes. You may be taken out of the study at any time, if;

- You can't tolerate the side effects.
- There is new information that shows that being on this study is not in your best interests.

- Dalhousie University, NSERC, the Capital Health Research Ethics Board, or the Principal Investigator decides to stop the study.

You will be told about the reasons why you might need to be taken out of the study.

12. WHAT ABOUT NEW INFORMATION?

It is possible (but unlikely) that new information may become available while you are in the study that might affect your health, welfare, or willingness to stay in the study. If this happens, you will be informed in a timely manner and will be asked whether you wish to continue taking part in the study or not.

13. WILL IT COST ME ANYTHING?

Compensation

You will not be paid to be in the study. You will receive a small amount of money (**i.e. ten (10) dollars per hour or part thereof**) to cover your time, gas mileage, and parking for each of the five (5) sessions at the Dalhousie Tobacco and Addition Laboratory. Additionally, during sessions two (2) through five (5), you will receive an additional **ten (10) dollars per session if you were successful at remaining abstinent for twelve (12) hours prior to arrival at the laboratory**. This will be awarded in order to compensate you for the time that your normal activities were disrupted.

If you decide to provide a saliva sample, please note: The aim of our research is to improve the public health. Your saliva sample will never be used to develop a process or invention that will be sold or patented.

14. WHAT ABOUT MY RIGHT TO PRIVACY?

Protecting your privacy is an important part of this study. A copy of this consent form will be put in your health record.

When you sign this consent form you give us permission to:

- Collect information from you
- Share information with the people conducting the study
- Share information with the people responsible for protecting your safety

Access to records

The Principal Investigator and members of the research team will see health and study records that identify you by name.

Other people may need to look at the health and study records that identify you by name. These might include:

- Dalhousie University and the Principal Investigator
- NSERC
- The CDHA Research Ethics Board and Research Quality Associate

Use of records

The research team will collect and use only the information they need to complete the study. This information will only be used for the purposes of this study.

This information will include your:

- date of birth
- sex
- medical conditions
- medications
- information from study interviews and questionnaires
- saliva samples

Your name and contact information will be kept secure by the research team in a locked cabinet at Dalhousie University in Halifax, Nova Scotia. It will not be shared with others without your permission. Your name will not appear in any report or article published as a result of this study. Information collected for this study will kept as long as required by law. This could be 7 years or more.

If you decide to withdraw from the study, the information collected up to that time will continue to be used by the research team. It may not be removed.

After your part in this study ends, we may continue to review your study records. We may want to follow your progress and to check that the information we collected is correct.

Information collected and used by the research team will be stored at the Dalhousie

Tobacco and Addictions Laboratory. The Principal Investigator is the person responsible for keeping it secure.

You may also be contacted personally by Research Auditors for quality assurance purposes.

Your access to records

You may ask the Principal Investigator to see the information that has been collected about you.

Once we take your saliva samples (for non-genetic purposes), we will assign them a code number. We will separate your name and any other information that points to you from your samples. We will keep files that link your name to the code number in a locked file cabinet and office, away from your samples.

15. WHAT IF I WANT TO QUIT THE STUDY?

If you chose to participate and later change your mind, you can say no and stop the research at any time. If you wish to withdraw your consent, please inform the Principal Investigator. All data collected up to the date you withdraw your consent will remain in the study records, to be included in study related analyses.

16. WHAT WILL HAPPEN TO MY SAMPLES AFTER THE STUDY IS OVER?

After this study is over, we will dispose of all the saliva samples we collected by burning them.

17. DECLARATION OF FINANCIAL INTERESTS

The funding agency is paying the Principal Investigator and/or the Principal Investigator's institution to conduct this study. The amount of this payment is sufficient to cover the costs of conducting the study. The Principal Investigator has no financial interests in conducting this research study.

18. WHAT ABOUT QUESTIONS OR PROBLEMS?

For further information about the study call **Dr. Sean Barrett**. Dr. Barrett is in charge of this study at this institution (Principal Investigator). Dr. Sean Barrett is at (902) 494-2956.

If you experience any symptoms or possible side effects or other medical problems, please let the Principal Investigator know immediately.

The Principal Investigator is Dr. Sean Barrett

Telephone: 494-2956

19. WHAT ARE MY RIGHTS?

After you have signed this consent form you will be given a copy.

If you have any questions about your rights as a research subject, contact the **Patient Representative** at **(902) 473-2133**.

In the next part you will be asked if you agree (consent) to join this study. If the answer is yes, you will need to sign the form.

PART C.

20. CONSENT FORM SIGNATURE PAGE

I have reviewed all of the information in this consent form related to the study called:

THE EFFECTS OF ALCOHOL ON THE REINFORCING AND SUBJECTIVE EFFECTS OF TOBACCO AND NICOTINE IN SMOKERS THAT DRINK

I have been given the opportunity to discuss this study. All of my questions have been answered to my satisfaction.

I agree to allow the people described in this consent form to have access to my health records.

This signature on this consent form means that I agree to take part in this study. I understand that I am free to withdraw at any time.

☐ **I agree** to provide a sample of my saliva (*chewing on a cotton swab*).

☐ **I do not agree** to provide a sample of my saliva.

_____	_____	___ / ____ / ___
Signature of Participant	Name (Printed)	Year Month Day*
_____	_____	___ / ____ / ___
Witness Name (Printed)		Year Month Day*
_____	_____	___ / ____ / ___
Signature of Investigator	Name (Printed)	Year Month Day*
_____	_____	___ / ____ / ___
Signature of Person Conducting Consent Discussion	Name (Printed)	Year Month Day*

Note: Please fill in the dates personally

I WILL BE GIVEN A SIGNED COPY OF THIS CONSENT FORM.

Thank you for your time and patience!

APPENDIX E: STUDY 3 TELEPHONE SCREEN AND FTND

Telephone Screen (+ Fagerström Test for Nicotine Dependence + Michigan Alcohol Screening Test)

ID #_____

Interviewer to read to potential participant: Hello, this is _____ calling from the Dalhousie Tobacco and Addictions Laboratory with regards to a study that you recently inquired about. First I will tell you a little about the study and then I will ask you a few questions regarding your smoking and drinking habits.

The study will take place during 5 sessions at Dalhousie University and will be spaced about 2 to 7 days apart. In the first session you will be asked to come in during an afternoon following your typical smoking behavior. You will complete a series of questionnaires that look at various personality variables and trait characteristics and will also be required to provide a breath sample so that we can see what your typical expired air carbon monoxide reading is (this will be used later to confirm your tobacco abstinence). The first session will take between approximately 1-1.5 hours.

For the remaining sessions, you will be required to abstain from smoking and drinking alcohol 12 hours before you arrive at the lab and this will be verified by two breath samples. We also ask that you eat your typical meals throughout the day but refrain from eating anything or drinking any caffeinated beverages 2 hours before your arrival at the lab. During the sessions, you will be asked to consume a beverage that may vary according to alcohol concentration. Afterwards, you may receive substances that differ from one another according to ingredients that are normally found in regular cigarettes (e.g. tar, ammonia, menthol, nicotine, sucrose etc.) You will also complete a series of questionnaires about your mood and tobacco craving, a basic computerized task, and will be asked to provide two additional saliva samples. These sessions are expected to take about 3.5 - 4 hours. You will be compensated $10 per hour, or part thereof, for each session. In addition to the hourly compensation, you will be awarded an extra 10$ per session for each session that you arrive tobacco abstinent after the first meeting.

Are you interested in participating in the study? If yes, I will need to ask you several questions to make sure that you are eligible to participate in this study. This will take about 10 minutes to complete. Is this okay? (If yes, proceed)

Question	Response	Interviewer Response
1. How old are you?		Reject if under 19
2. What is your birthday?		
3. How many days in the past 30 days have you smoked?		Question #4a if 28-30 Questions #4b, #4c if 1-28 **Reject if 0**
4a. Are you a daily smoker?	☐Y ☐N	Reject if N Move to question #5
4b. Have you ever been a daily smoker? How long ago?	☐Y Length____ ☐N	Reject if Y **and** less than one year
4c. Have you been an occasional smoker for a least the past year?	☐Y ☐N	Reject if N
5. How many cigarettes do you smoke per week?		Reject if under 5 cigarettes per week
6. Are you currently trying to quit smoking, or do you intend to do so within the next 30 days?	☐Y ☐N	Reject if Y
7. Are you currently using Nicotine Replacement Therapy (i.e. patch, gum, inhalers)?	☐Y ☐N	Reject if Y
8. Are you a regular moderate consumer of alcohol? We define this as having had consumed a minimum of 5 drinks for males and 4 for females on at least one occasion per week over the past month.	☐Y ☐N	Reject if N
9. Have you ever experienced any unexpected negative reactions to alcohol? For example, fainting or a seizure, unusual flushing of your skin, problems with your liver or severe or unusual psychological reactions to alcohol?	☐Y ☐N	Reject if Y
10. As part of the study you will have to drink cranberry juice. Are you comfortable drinking cranberry juice (i.e. no allergies to cranberry juice)?	☐Y ☐N	Reject if N
11. As part of the study you will have to drink vodka. Are you comfortable drinking vodka (i.e. no allergies to vodka)?	☐Y ☐N	Reject if N
12. Are you currently under the regular care of a physician? (NOT your General Practitioner)	☐Y Specify_____ ☐N	Y go to Q#13 N go to Q#14
13. Has your doctor, nurse, or other health care provider suggested that you limit your drinking or do not drink because of this condition?	☐Y ☐N	Reject if Y
14. Are you currently taking any medications on a regular basis	☐Y Specify_____ ☐N	Y go to Q#15

15. Has your doctor, nurse, or other health care provider suggested that you limit your drinking or do not drink because of this medication?	☐Y ☐N	Reject if Y

Question	Response	Interviewer Response
Are you taking, going to start taking, or take for emergency purposes any of the following medications: • Insulin or other drugs used to control diabetes (e.g. chlorpropamide [Diabinese], metformin [Glucophage], phenformin, or tolbutamide [Orinase]) • MAO Inhibitors (e.g. isocarboxazid [Marplab] or phenelzine [Nardil]) • Antabuse • Anti-fungals (e.g. ketoconazole) • Antibiotics (e.g. flagyl) • Drugs used to control blood pressure (e.g. nifedipine or verapamil) • Drugs used for autoimmune disorders (e.g. methotrexate or procarbazine [Matulane]) • Benzodiazepines (e.g. Valium or Libruim) • Prescription pain medications	☐Y Specify_____ ☐N	Reject if Y
Are you taking any other prescription medication at this time?	☐Y ☐N	Reject if Y
Have you EVER suffered from any of the following medical conditions? • Asthma or any other ailments that affect your breathing • Diabetes • Liver Disease • Epilepsy or other neurological disorders that would impair your ability to carry out the necessary tasks • Ulcers or other gastrointestinal problems • Pancreatitis • High blood pressure, artery disease or heart disease • Lung Disease	☐Y Specify_____ ☐N	Reject if Y

Pregnancy **FEMALES:** *"We know that alcohol consumption during pregnancy can be unhealthy for babies before they are born. If you are pregnant, planning to get pregnant, or are nursing, you should not be in the study. If you have engaged in sexual activity that could lead to pregnancy and are not using effective birth control we recommend that you take a pregnancy test at the start of the study. This would be a urine screen test where you would need to urinate into onto a test strip in a private washroom and then allow the experimenter to test your urine for possible pregnancy. The pregnancy test would not involve a blood test".*		
	☐Y ☐N	Reject if Y N go to b
a) Are you currently pregnant, planning to get pregnant, or nursing a baby at this time?"	☐Y ☐N	Y go to c N go to FTND
b) Are you currently engaging in sexual activity that could lead to pregnancy?	☐Y ☐N	Y go to FTND N go to d
c) Are you using effective means of birth control? d) "*Given our concerns about the safety of developing babies before they are born, we recommend that you allow us to do a urine screen pregnancy test before the testing session. We will provide you with immediate feedback with the results. Would you like us to have a pregnancy test available for you to take?*"	☐Y ☐N	

Fagerström Test for Nicotine Dependence (FTND)

The following questions assess your dependence on nicotine. Please answer each question; each answer gets a set amount of points. Add up the points and check out the score indicator below:

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette	Within 5 minutes 6 to 30 minutes 31-60 minutes After 60 minutes	3 2 1 0
2. Do you find it difficult to refrain from smoking in places where it is forbidden such as church, the library, or movie theatres?	Yes No	1 0
3. Which cigarette would you hate most to give up?	The first one in the morning Any others	1 0
4. How many cigarettes do you smoke each day? (20 cigarettes are in a pack)	10 or less 11-20 21-30 31 or more	0 1 2 3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes No	1 0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes No	1 0

Total (Add items 1 to 6) =

_____

Check category:

0 and non-daily	3+ and daily

Short Form of the Michigan Alcohol Screening Test (SMAST)

1	Do you feel you are a normal drinker? (By normal we mean you drink less than or as much as most other people)	Y **N**	0 **1**
2	Does your wife, husband, a parent, other near relative, or close friend ever worry or complain about your drinking?	**Y** N	**1** 0
3	Do you ever feel guilty about your drinking?	**Y** N	**1** 0
4	Do friends or relatives think you are a normal drinker?	Y **N**	0 **1**
5	Are you able to stop drinking when you want to?	Y **N**	0 **1**
6	Have you ever attended a meeting of Alcoholics Anonymous (AA)?	**Y** N	**1** 0
7	Has drinking ever created problems between you and your wife, husband, a parent, other near relative, or close friend?	**Y** N	**1** 0
8	Have you ever gotten into trouble at work because of drinking?	**Y** N	**1** 0
9	Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?	**Y** N	**1** 0
10	Have you ever gone to anyone for help about your drinking?	**Y** N	**1** 0
11	Have you ever been in a hospital because of drinking?	**Y** N	**1** 0
12	Have you ever been arrested for drunken driving, driving while intoxicated, or driving under the influence of alcoholic beverages?	**Y** N	**1** 0
13	Have you ever been arrested, even for a few hours, because of other drunken behavior?	**Y** N	**1** 0

TOTAL (Reject if 3 or higher):

IF MEET REQUIREMENTS:

Because you will be receiving alcohol it is important that you arrange for someone to pick you up or that you are able to walk home. Is this possible?

__ Arrange to be picked up __Walk home __ Public Transit

IF DO NOT MEET REQUIREMENTS:

Currently you are not eligible to participate in the study, however because the requirements may change it is possible that you may be eligible at a later time. Is it okay if I keep you name in a database to be contacted regarding this study in the future?

APPENDIX F: COPYRIGHT RELEASE REQUEST

August 28, 2018

Pharmacology, Biochemistry, and Behavior
Radarweg 29, 1043 NX Amsterdam, The Netherlands

I am preparing my PhD in Clinical Psychology thesis for submission to the Faculty of Graduate Studies at Dalhousie University, Halifax, Nova Scotia, Canada. I am seeking your permission to include a manuscript version of the following paper(s) as a chapter in the thesis:

THE BEHAVIOURAL PHARMACOLOGY OF SNUS AND ETHANOL ABSORPTION ON CIGARETTE CRAVING AND CONSUMPTION

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Marcel PJ Peloquin

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APPENDIX G: PUBLISHED STUDY 3

Pharmacology, Biochemistry and Behavior 114–115 (2013) 97–102

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

The effect of snus on alcohol-related cigarette administration in dependent a non-dependent smokers

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ARTICLE INFO

Article history:
Received 15 July 2013
Received in revised form 19 August 2013
Accepted 26 August 2013
Available online 3 September 2013

Keywords:
Snus
Alcohol
Smoking
Craving
Self-administration
Nicotine

ABSTRACT

Introduction: Alcohol has been found to increase tobacco smoking in both dependent daily smokers (DDS) and nondependent nondaily smokers (NNS), yet little attention has been directed toward examining how different treatments/products modify drinking-related smoking behavior.
Methods: This study examined the acute effects of snus (4 mg of nicotine) on alcohol-related smoking responses in 18 DDS and 17 NNS. During each double-blind session, participants were randomly assigned to receive one of the following combinations: alcohol and snus, alcohol and placebo snus, placebo alcohol and snus, or placebo alcohol and placebo snus. Participants consumed their assigned beverage before absorbing their session's product, and after 30 min participants could self-administer puffs of their preferred brand of cigarette over a 60-minute period using a progressive ratio task.
Results: Alcohol significantly increased tobacco craving ($p < .001$) and tended to decrease latency to start smoking ($p = .021$) but only among NNS. In contrast, snus tended to decrease the number of puffs earned and how hard DDS worked for puffs in both beverage conditions ($ps \leq .019$) but it did not alter the smoking behavior of NNS. Craving was not significantly impacted by snus in either type of smoker.
Discussion: These findings raise the possibility that different processes mediate alcohol and cigarette co-use in NNS and DDS and suggest that snus may be effective in reducing alcohol-related cigarette use in DDS specifically.

1. Introduction

It is well established that alcohol consumption is linked with increased cigarette use among those who smoke (e.g. Falk et al., 2006). This increased use is seen in both dependent and non-dependent smokers (e.g. Shiffman and Paty, 2006). Alcohol also plays a major role in smoking initiation (e.g. O'Loughlin et al., 2009), smoking maintenance (Glautier et al., 1996; Kahler et al., 2010), and relapse to cigarette use among smokers trying to quit (Shiffman, 1986). Few – if any – treatments are known to affect alcohol-related smoking. Kouri et al. (2004) found that a nicotine patch decreased smokers' subjective tobacco craving; however, this effect diminished when smokers consumed alcohol. Alcohol consumption is typically not restricted in smoking cessation trials and most smokers intending to quit smoking do not simultaneously abstain from alcohol (e.g. Bobo et al., 1998). It is possible that drinking may affect individuals' efforts to quit smoking either by altering smokers' motivation to quit (Burton and Tiffany, 1997) or by reducing the effectiveness of nicotine replacement therapy (NRT) (Kouri et al., 2004).

One product that may hold promise for reducing alcohol-related smoking is snus. Snus is a moist pasteurized oral tobacco product that has been proposed as a smoking cessation aid (Gilljam and Galanti, 2003b; Lindström, 2007; Lund et al., 2010; Fagerstrom et al., 2012). Although the use of snus is not risk-free and it has been associated with the development of dependence, it has a higher margin of safety relative to cigarettes (Rodu and Cole 2002; Boffetta and Straif 2009), and it may be an appropriate smoking cessation option, for those that do not respond favorably to NRT (e.g. Fagerström and Schildt 2003; Gilljam and Galanti, 2003; Caldwell et al. 2010). In Norway, snus use has been reported to be a common self-selected smoking cessation strategy (Lund et al., 2010) and it has been argued that the relatively low rates of smoking in Sweden may be in part attributable to snus use (Norberg et al., 2011). Rates of alcohol use among snus users are high (Lund et al., 2008; Engström et al., 2010; Loukas et al., 2012; Larsen et al., 2013) suggesting that snus may be well tolerated when co-administered with alcohol. In addition, unlike NRT, snus contains several

Abbreviations: BAC, Blood alcohol content; B-BAES, Brief Biphasic Alcohol Effects Scale; CO, Carbon monoxide; DDS, dependent daily smokers; FTCD, Fagerström test for Cigarette Dependence; NNS, nondependent nondaily smokers; NRT, nicotine replacement therapy; QSU-Brief, Questionnaire of Smoking Urges-Brief; SMAST, Short version of the Michigan Alcoholism Screening Test; SRS, Subjective Rating Scales; PR, Progressive Ratio; USP, United States Pharmacopeia.

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0091-3057/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pbb.2013.08.011

tobacco constituents beyond nicotine such as anatabine, nornicotine, and acetaldehyde (ENVIRON International Corporation, 2010) and there is evidence that the replacement of non-nicotine tobacco constituents may help reduce alcohol-related cigarette craving (Barrett et al., 2013; King et al., 2009). Snus has been demonstrated to acutely reduce cigarette craving in laboratory settings (Barrett et al., 2011; Barrett and Wagner, 2011), although the extent to which such findings extend to alcohol-related smoking remains unknown.

The purpose of the present study is to examine the effects of snus on alcohol-related cigarette craving and smoking behavior in both nondependent nondaily smokers (NNS) and dependent daily smokers (DDS).

2. Methods

2.1. Participants

Non-treatment seeking DDS (i.e., daily tobacco use for a minimum of one year; score ≥ 3 on the Fagerström test for Cigarette Dependence (FTCD); Fagerström, 2012) and NNS (i.e., tobacco use on fewer than 25 days in the previous month; FTCD = 0) were recruited from the Halifax, Nova Scotia community. All were regular consumers of alcohol, having consumed a minimum of 4 drinks for women (5 drinks for men) at least once/week during the previous month, and non-problem drinkers, scoring 2 or less on the short version of the Michigan Alcoholism Screening Test (SMAST; Selzer et al., 1975). Potential participants were told that the study would consist of an initial session to complete screening measures and collect a non-abstinent breath carbon monoxide (CO) sample, and four experimental sessions that would involve the administration of beverages that may vary in alcohol content, followed by the administration of substances that may vary according to ingredients normally found in cigarettes (e.g., tar, ammonia, menthol, nicotine, sucrose). Women who reported pregnancy, nursing, intention to become pregnant, or who screened positive on an elective urine pregnancy test were not permitted to participate. All participants reported that they were medically healthy, all had reached the minimum age to legally consume alcohol and tobacco in Nova Scotia, and none intended to quit smoking over the subsequent 30 days or were using NRT products. All were naïve to snus. Participants were compensated CDN$10 per hour. The study was conducted in accordance with the Declaration of Helsinki and was approved by a local research ethics board.

2.2. Design

The protocol consisted of four double-blind, randomized sessions with a 2(beverage condition: alcohol or placebo) × 2(product condition: snus or placebo) within-subject design. All sessions were identical in procedure except that participants received a different beverage–product combination during each session.

2.3. Beverages

In the alcohol conditions, participants received 2.28 ml 50% USP units of alcohol per kilogram of body weight for women and 2.73 ml 50% USP units of alcohol per kilogram of body weight for men (MacDonald et al., 2000) to target a peak blood alcohol concentration (BAC) of 0.06%. Drinks were mixed 1:4 parts vodka to cranberry juice. The placebo beverage was made up of 5 parts cranberry juice with a small amount of alcohol applied to the rim of the glasses and on the drink tray to ensure the odor and taste of alcohol (Kushner et al., 1996).

2.4. Products

In the snus condition, participants received a Phantom brand Swedish-style snus mini portion containing 4 mg of nicotine and a manufacturer reported pH of 8.5 (V2 Tobacco; Silkeborg, Denmark). Snus has a nicotine loading time peaking at 30 min (Foulds et al., 2003; Lunell and Lunell, 2005). In the placebo condition, participants received a BaccOff brand nontobacco placebo portion (V2 Tobacco; Silkeborg, Denmark), which mimics the sensory properties of portion snus (Coffey and Lombardo, 1998).

2.5. Blinding

Participants were blind to the contents of the beverages and products received during each session. Participants were informed that the products might vary between sessions in their content of ingredients, but not in their nicotine content specifically. Similarly, participants were informed that the alcohol content of the beverages might vary, but not that the doses were selected to produce either mild or no intoxication. To maintain integrity of the blind, research personnel not otherwise involved with data collection prepared all beverages, administered the oral product, and recorded all breath alcohol measurements.

2.6. Subjective assessment

2.6.1. Subjective Rating Scales

An author-compiled Subjective Rating Scale (SRS) were used to assess subjective state (i.e., relaxed, pleasant, head rush, stimulated, jittery, dizzy, irritable, trouble concentrating, anxious, frustrated, intoxicated, and crave cigarette). Each item was rated on a 10-cm horizontal line labeled with integers 1–10 and anchored with the endpoints "Not at all" and "Extremely." Similar scales have been widely used to assess subjective drug effects, and this method of assessment has been shown to be both reliable (e.g. Wewers and Lowe, 1990) and sensitive to the acute effects of alcohol and tobacco (e.g. Barrett et al., 2006, 2013).

2.6.2. Questionnaire of Smoking Urges-Brief

The Questionnaire of Smoking Urges-Brief (QSU-Brief; Cox et al., 2001) is a 10-item self-report measure used to assess tobacco craving across 2 dimensions (factor 1: intention to smoke; factor 2: withdrawal/negative affect relief).

2.6.3. Brief Biphasic Alcohol Effects Scale

The Brief Biphasic Alcohol Effects Scale (B-BAES; Martin, Earleywine, and Musty, 1993) is a 6-item self-report measure used to assess the subjective stimulant effects of alcohol associated with a rising BAC (factor 1), as well as the subjective depressant effects associated with a descending BAC (factor 2) (Rueger et al., 2009).

2.7. Behavioral measures

2.7.1. Progressive ratio task

Participants were allowed to earn puffs of their preferred brand of cigarette (supplied by the lab) using a computerized progressive ratio (PR) task over 60 min. Ten key presses were required to earn the initial puff, and the requirement increased at a ratio of 1.3 for each subsequent puff. Participants were not required to earn any puffs but were required to remain seated in front of the cigarette until the end of the session. The latency to start smoking, the total number of puffs earned, and the breakpoint – the number of key presses completed to earn their last puff – were recorded for each session. The PR task has been demonstrated to be sensitive to pharmacological manipulations in human tobacco self-administration studies (e.g., Barrett and Darredeau, 2012).

2.8. Procedure

Participants arrived for each testing session having abstained from smoking and alcohol for a minimum of 12 h and from food and caffeine for a minimum of 2 h. Abstinence from smoking was confirmed with a breath CO reading of 15 ppm or less or a 50% reduction in CO from the non-abstinent baseline (Vitalograph; Lenexa, KS), and abstinence

from alcohol was confirmed using an Alcomate Premium breath alcohol analyzer (AK Solutions; Lansdale, PA) with a cutoff of 0.00%. A timeline outlining the sequence of procedures is presented in Table A.1.

After completing a baseline subjective assessment (SRS, QSU-Brief, B-BAES) and heart rate recording (RS-100 Polar Heart Rate Monitor; Polar Electro Canada; Lachine, Canada), participants consumed their assigned beverage (alcohol or active placebo) over 15 min. Afterwards, participants were given their product and instructed to place it between their upper gum and upper lip for 30 min while they waited alone in the testing room. A post-product subjective assessment, BAC, and heart rate recording were conducted. Participants could then earn cigarette puffs over the following 60 min. Following the PR task, the session concluded with a "sobering period" of at least 1 h during which participants were provided with a light snack and rested until their BAC was below 0.04 g/dl. All participants completed this sobering period in each session to maintain the blind of the experiment.

2.9. Statistical analysis

Data were analyzed using linear mixed models in SPSS version 20.0 for Windows (SPSS Inc.; Chicago, IL). An appropriate covariance structure was selected for each variable on the basis of model simplicity and of the likelihood ratio test. The behavioral measures were the latency (time in seconds) to start smoking on the PR task, the breakpoint, and the total number of puffs self-administered. Behavioral data were analyzed using Beverage (alcohol vs. placebo beverage) and Product (snus vs. placebo snus) conditions as fixed and repeated factors, Sex and Dependence level as fixed factors, and Subject as a random factor. The residuals were screened for normality and Shapiro–Wilk and Kolmogorov–Smirnov tests indicated that normality assumptions were best met following a logarithmic (log) transformation for latency and a square root (sr) transformation for breakpoint. The effects of interest were the main effects of Beverage, Product, Dependence, and Sex, as well as interactions of Beverage and/or Product with Sex and/or Dependence. Subjective, BAC and heart rate data were analyzed using Beverage and Product as fixed and repeated factors, Sex and Dependence level as fixed factors, and Subject as a random factor. Baseline scores [T1] were used as a time-varying covariate for post-beverage and product absorption scores [T2]. The effects of interest were the main effects of Beverage, Product, Dependence, and Sex, as well as interactions of Beverage and/or Product with Sex and/or Dependence. For interactions, the simple effects of variables within each level combination of the other variable(s) were tested. To account for multiple testing, an experimental alpha of .01 was selected for all analyses.

3. Results

3.1. Participants

Eighteen (9 female) DDS and 17 (7 female) NNS enrolled in the study. Sixteen (8 female) DDS and 13 (6 female) NNS completed all four experimental sessions, while the remaining two DDS and four NNS each completed three sessions. All sessions were retained for analysis. DDS had higher FTCD levels, $t(33) = 12.20$, $p < .001$ ($M = 5.4$, $SE = 0.43$ vs. zero for NNS) and smoked more cigarettes in the previous week, $t(33) = 7.98$, $p < .001$ (M = 122.3, $SE = 13.35$ vs. $M = 11.3$, $SE = 2.22$). No dependence group differences were detected in participants' age, age of initial tobacco use, age of initial alcohol use, or total alcoholic drinks in the previous week.

3.2. Self-administration

Analyses revealed a main effect of Dependence for total number of puffs, $F(1, 29.0) = 13.69$, $p < .001$, and for sr breakpoint, $F(1, 29.0) = 21.71$, $p < .001$. DDS earned more puffs ($M = 19.4$, $SE = 1.28$ vs. $M = 12.3$ $SE = 1.26$), and worked harder for puffs ($M = 38.5$, $SE = 2.91$ vs. $M = 19.5$, $SE = 2.85$), than NNS.

A marginal interaction of Dependence × Beverage was detected for log latency, $F(1, 81.4) = 6.16$, $p = .015$. NNS were marginally quicker to start smoking in the alcohol versus the placebo beverage condition ($M = 1.4$, $SE = 0.18$ vs. $M = 1.7$, $SE = 0.18$; p = .021), but beverage type made no difference in latency to start smoking for DDS ($M = 1.1$, $SE = 0.19$ for alcohol vs. $M = 0.9$, $SE = 0.19$ for placebo; $p = .248$).

Finally, a Dependence × Product interaction was found for both puffs, $F(1, 81.2) = 7.54$, $p = .007$, and sr breakpoint, $F(1, 81.4) = 7.17$, $p = .009$. DDS tended to smoke fewer puffs ($p = .019$) and worked less hard to earn puffs ($p = .004$) in the snus versus the placebo snus condition, whereas this effect was not seen for NNS (p values > .1) (Fig. 1).

3.3. Heart rate

Alcohol increased average heart rate relative to the placebo beverage, $F(1, 106.7) = 7.22$, $p = .008$ ($M = 79.8$, SE = 1.00 vs. $M = 76.3$, $SE = 1.01$ beats per minute), as did snus relative to placebo snus, $F(1, 64.4) = 35.28$, $p < .001$ ($M = 81.3$, $SE = 0.95$ vs. $M = 74.8$, $SE = 0.92$), but these effects did not interact ($p = .38$).

3.4. Alcohol administration verification

All BAC readings were 0.00% at baseline. Alcohol increased BACs 30 min post ingestion relative to the placebo beverage $F(1, 54.5) = 903.5$; $p < 0.001$ (M = 0.045, SE 0.001 for alcohol; M = 0.00, SE =

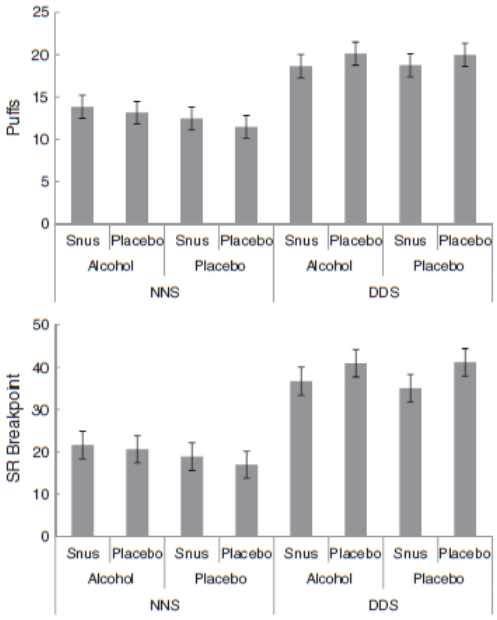

Fig. 1. Estimated marginal mean puffs (above) and square root breakpoints (below) with standard errors of non-daily non-dependent smokers (NNS) and daily dependent smokers (DDS) during each combination of alcohol or placebo beverage condition by snus or placebo snus product condition. The estimated marginal means and standard error were selected from the model which best fit the data. DDS earned more puffs and worked harder (sr breakpoint) for puffs than NNS ($p < .001$), and DDS tended to smoke fewer puffs ($p = .019$) and worked less hard to earn puffs ($p = .004$) in the snus condition versus the placebo snus condition, whereas these effects were not seen for NNS (ps = .140 and .402, respectively).

0.00 for placebo). BAC readings did not significantly vary by Sex, Dependence or Product condition (p values > 0.1).

3.5. Subjective responses

3.5.1. Cigarette craving

Cigarette craving was assessed using the two factors of the QSU-Brief (factor 1: intention to smoke; factor 2: withdrawal/negative affect relief) and the SRS item "crave cigarette".

Main effects of Dependence showed that DDS had higher QSU-Brief factor 1, $F(1, 45.6) = 9.97$, $p = .003$ ($M = 27.5$, $SE = 0.99$ vs. $M = 22.6$, $SE = 1.01$), and factor 2, $F(1, 45.4) = 16.91$, $p < .001$ ($M = 29.8$, $SE = 1.41$ vs. $M = 20.5$, $SE = 1.45$), craving scores as well as marginally higher SRS "crave cigarette" ratings, $F(1, 51.3) = 5.84$, $p = .019$, ($M = 6.9$, $SE = 0.31$ vs. $M = 5.6$, $SE = 0.32$) than NNS. A main effect of Beverage showed that alcohol also increased QSU-Brief factor 1, $F(1, 28.9) = 16.39$, $p = .002$ ($M = 26.0$, $SE = 0.78$ vs. $M = 24.0$, $SE = 0.78$), and factor 2, $F(1, 82.1) = 7.97$, $p = .006$ ($M = 26.1$, $SE = 0.94$ vs. $M = 24.2$, $SE = 0.94$), craving relative to placebo beverage in both types of smokers.

Dependence × Beverage interactions were also detected for QSU-B factor 1 and factor 2 cravings along with a marginal interaction of Dependence × Beverage for SRS "crave cigarette". For factor 1 craving, $F(1, 29.1) = 16.39$, $p < .001$, when NNS received alcohol they reported greater craving than when they received a placebo beverage (M =24.8, $SE = 1.19$ vs. $M = 20.4$, $SE = 0.98$; $p < .001$); however, this effect was not seen for DDS ($p = .653$). Additionally, DDS reported greater factor 1 craving than NNS in the placebo beverage condition ($p < .001$), but not in the alcohol condition ($p = .168$). For factor 2 craving, $F(1, 82.7) = 14.48$, $p < .001$, NNS reported higher craving in the alcohol versus placebo beverage condition ($M = 22.8$, $SE = 1.52$ vs. $M = 18.2$, $SE = 1.55$; $p < .001$) and this effect was again not evident for DDS ($p = .483$). For SRS "crave cigarette", $F(1, 51.0) = 6.91$, $p = .011$, NNS rated their craving higher in the alcohol than the placebo condition ($M = 6.2$, $SE = 0.37$ vs. $M = 5.1$, $SE = 0.35$; $p = .004$); however, this effect was not found with DDS ($p = .504$). Additionally, DDS showed higher SRS "crave cigarette" ratings than NNS in the placebo beverage condition ($p = .002$), but not in the alcohol condition ($p = .300$). Product condition was not found to affect subjective cigarette craving.

3.5.2. Subjective mood effects

Subjective mood effects were assessed using the remaining 11 SRS items and two B-BAES factors. A main effect of Beverage was detected for "intoxicated", $F(1, 37.1) = 52.01$, $p < .001$, with participants rating their subjective intoxication higher in the alcohol condition than in the placebo beverage condition ($M = 4.7$, $SE = 0.37$ vs. $M = 2.1$, $SE = 0.22$). A main effect of Beverage was also detected for B-BAES factor 1, $F(1, 82.4) = 9.35$, $p = .003$, where greater stimulating effects were detected post-alcohol beverage absorption than post-placebo beverage absorption ($M = 15.1$, $SE = 0.61$ vs. $M = 13.6$, $SE = 0.61$). No effects of Beverage for B-BAES factor 2 (sedative effects) were detected.

A main effect of Beverage for "pleasant" was detected, $F(1, 66.6) = 10.16$, $p = .002$, with individuals rating pleasantness higher in the alcohol than the placebo condition ($M = 6.3$, $SE = 0.21$ vs. $M = 5.6$, $SE = 0.21$). A main effect of Beverage for "stimulated", $F(1, 84.7) = 6.77$, $p = 0.01$, showed that participants experienced more subjective stimulation when consuming alcohol versus placebo beverage ($M = 4.5$, $SE = 0.30$ vs. $M = 3.7$, $SE = 0.29$). A main effect of Beverage was detected for "irritable", $F(1, 34.0) = 8.31$, $p = .007$, with alcohol condition ratings of irritability lower than those in the placebo beverage condition ($M = 2.6$, $SE = 0.18$ vs. $M = 3.4$, $SE = 0.18$), as well as a Dependence by Sex interaction, $F(1, 27.4) = 7.76$, $p = .01$, with male DDS rating their irritability higher than female DDS ($M = 3.9$, $SE = 0.40$ vs. $M = 2.3$, $SE = 0.37$; $p = .004$). There was no Sex effect in the NNS group ($p = .398$). Product condition did not appear to influence subjective mood states.

4. Discussion

The results of this study suggest that snus can acutely reduce smoking behavior regardless of alcohol consumption in DDS but not in NNS. While these findings suggest that snus may have therapeutic potential in DDS even when alcohol is consumed, its potential appears limited for NNS. Such findings are consistent with evidence that pharmacological factors may regulate the smoking behavior of DDS to a greater extent than that of NNS (Heatherton et al., 1991), including following alcohol consumption (Barrett et al., 2013) and suggest that different smoking cessation approaches may be necessary for DDS and NNS.

A somewhat unexpected outcome was that snus reduced DDS smoking behavior without reducing subjective cigarette craving before the PR task. While the craving measures used were sensitive enough to detect snus related effects in past studies (Barrett et al., 2011; Barrett and Wagner, 2011), in the present study snus was administered following the consumption of a beverage, which may have affected its absorption. However, snus' cardiac and behavioral effects suggest that a pharmacologically active dose was administered. It is also possible that snus' effects on craving may have been diminished by the anticipation of smoking during the PR task. Participants were aware that they would have an opportunity to smoke their preferred brand of cigarettes following the snus administration and evidence suggests that cigarette cravings are related to the anticipation of an opportunity to smoke (e.g. Dar et al., 2010; Dar et al., 2005; McBride et al., 2006). Alternatively, it is possible that these findings may relate to the timing and/or dose of snus administration. Snus is known to have a similar nicotine loading profile as a cigarette (Benowitz, 1997) and nicotine has a half-life of 2 h (Benowitz, 2009); therefore the nicotine absorbed from the snus can be assumed to have influenced smoking behavior throughout the PR task but may not have been sufficient to have an immediate impact on cigarette craving for DDS.

Alcohol consumption increased craving and decreased the latency to start smoking in NNS, but not in DDS. This finding is consistent with prior evidence suggesting that NNS may be more susceptible than DDS to the effect of alcohol on smoking behavior (Barrett et al., 2013; Sayette et al., 2005). However, NNS did not earn more puffs in response to alcohol. This is inconsistent with previous studies where NNS increased smoking following alcohol consumption (Barrett et al., 2013; McKee et al., 2010). The most notable difference between these prior studies and our own is that the alcohol dose given to our participants was designed to produce a peak BAC of 0.06 g/dL whereas the alcohol dose in these other studies was designed to produce a higher BAC of 0.08 g/dL. Dose-dependent alcohol effects have been found for cigarette smoking in dependent smokers (Mitchell et al., 1995), and cigarette craving for non-dependent smokers (Epstein et al., 2007; King and Epstein, 2005), but no other study to our knowledge has examined alcohol dose-dependent effects on smoking behavior in NNS. Additionally, in Barrett et al. (2013), King et al. (2009), and McKee et al. (2010) studies, non-dependent smokers were allowed to smoke a cigarette after consuming alcohol but before they could earn additional puffs, which may prime increased cigarette consumption (e.g Piasecki et al., 2011).

The current findings should be interpreted in light of the following methodological considerations. First, participants ingested their beverage over 15 min and then immediately absorbed their product over the following 30 min. This was intended to maximize concurrent alcohol (Holt et al., 1980) and nicotine absorption (Benowitz, 1997) during the PR task. However it is not clear the extent to which the present results can generalize to other administration patterns. Second, participants were expected to arrive at the lab having abstained from tobacco for at least 12 h, something atypical for DDS (Heatherton et al., 1991) but not for NNS. This timeframe was selected to increase the sensitivity of both groups of smokers to the effect snus may have on both smoking behavior and craving. It is possible that as a result of the abstinence requirement many DDS may have been experiencing severe withdrawal during the experiment; however no participants discontinued the study because they were unable to abstain from tobacco for the required period. It is

also possible that some heavily dependent smokers may have decided against participating in the study due to the abstinence requirement. Third, portion snus comes in different sizes ranging from 0.5 g to > 1.0 g with different levels of bioavailable nicotine, other psychoactive alkaloids, and acetaldehyde (Rutqvist et al., 2011). The 4 mg nicotine portion snus was selected because many oral NRTs contain 4 mg of nicotine and reach similar plasma nicotine levels (e.g. Lunell and Curvall, 2011). However, the bioavailability of nicotine in snus is dependent upon the pH of snus remaining alkaline (ENVIRON International Corporation, 2010). It is possible that participants' mucosal pH levels may have decreased after consuming their experimental beverage, potentially decreasing snus absorption rates. Finally, although the sample size was within the field's norms for a mixed design, it is possible that there was inadequate power to detect sex differences or other between-group effects.

5. Conclusions

Our findings suggest that snus reduces smoking behavior in DDS, including following alcohol consumption. To our knowledge, only one RCT has examined the efficacy of snus as a smoking cessation product. Fagerstrom and colleagues (2012) found snus more than doubled smokers' odds of achieving point prevalent cigarette cessation 6 and 16 weeks later. However, because participants with active alcohol use disorders were screened out and alcohol use data were not collected, it is unknown whether snus reduced alcohol-related smoking in this study. Our findings suggests that snus shows promise for reducing smoking among DDS even following alcohol ingestion and that this product warrants further exploration as a smoking cessation aid. As well, since no effect of snus was detected for NNS, our findings suggest that snus may be of limited utility for reducing smoking in this population.

Funding

This work was supported by a Discovery Grant awarded to Dr. Sean P. Barrett by the Natural Sciences and Engineering Research Council of Canada and a Scotia Support Grant awarded to Dr. Sean P. Barrett and Dr. Sherry H. Stewart from the Nova Scotia Health Research Foundation. Mr. Marcel P.J. Peloquin was supported by a Scotia Scholar Award from the Nova Scotia Health Research Foundation.

Acknowledgments

The authors would like to thank Annie Haider and Cayla Bayne for their assistance with blinding procedures.

Appendix A

Table A.1
Timeline of experimental procedures.

Procedure	Time (minutes)	Total time (minutes)
Confirmation of alcohol and smoking abstinence	5	5
Heart rate recording and subjective assessment	7	12
Administration of beverage	15	27
Administration of product	30	57
Disposal of product, heart rate recording, breath alcohol and subjective assessment	10	67
PR task	60	127
Sobering period	60	187

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