Effects of Varenicline on Cue-reactivity in Individuals with Concurrent Tobacco Dependence and Heavy Alcohol Use:
A Randomized, Double-blind, Placebo-controlled Trial

by
Shan Wang

A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Pharmaceutical Sciences
University of Toronto

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ABSTRACT

BACKGROUND: Alcohol and tobacco misuse and dependence are highly comorbid disorders. Varenicline alleviates symptoms of cigarette craving while preventing nicotine from binding to nicotinic acetylcholine receptors, thereby reducing nicotine’s reinforcing effects. Recent studies have shown that varenicline decreased alcohol self-administration in animal models and in one human study of heavy-drinking smokers. AIMS: To assess the effect of two-week varenicline (0.5-2mg) vs. placebo administration on cue-induced craving for tobacco and alcohol in smokers with heavy alcohol use (n = 24). METHODS: Subjects participated in two study visits where nicotine and alcohol craving and withdrawal were assessed with self-report questionnaires under four conditions (abstinence/one cigarette/neutral cues/tobacco-alcohol cues). RESULTS: Two-week administration of varenicline reduced tobacco-alcohol cue-induced cigarette cravings and reduced emotionality aspects of alcohol craving after smoking a cigarette compared to abstinence in heavy-drinking smokers. CONCLUSION: It is possible that varenicline may have particular advantages as a smoking cessation aid in heavy drinkers.
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<td>5HT</td>
<td>5-hydroxytryptamine</td>
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<td>ACQ</td>
<td>Alcohol Craving Questionnaire</td>
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<td>Alkaline phosphatase</td>
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1. Introduction

1.1 Statement of problem

Tobacco and alcohol are commonly used together and there is evidence that nicotinic acetylcholine receptors (nAChRs) are involved in the neuropharmacology of both alcohol and nicotine (Cardoso, Brozowski et al. 1999; Ait-Daoud, Wiesbeck et al. 2005; Meyerhoff, Tizabi et al. 2006). Varenicline is a partial nAChR agonist approved for smoking cessation. Recent evidence suggests that varenicline alters alcohol-associated behaviours in animal models (Steensland, Simms et al. 2007; Gulick and Gould 2008; Ericson, Lof et al. 2009) and in human volunteers (McKee, Harrison et al. 2009). Smokers who are heavy drinkers often consume both drugs concurrently and thus experience mixed tobacco and alcohol cues in their environment. Understanding the interrelationship amongst the concurrent use of tobacco and alcohol, cue reactivity, and varenicline may lead to improvements in smoking cessation strategies, particularly in smokers who also drink alcohol.

1.2 Purpose of the Study and Objectives

The primary objective of this study was to examine the effects of two-week administration of varenicline (0.5-2mg/day) on cigarette and alcohol cue-induced cravings and nicotine withdrawal in daily smokers who are heavy alcohol drinkers. The secondary objective was to assess the influence of varenicline on alcohol and tobacco consumption.
1.3 Study Rationale

There is limited information on how varenicline affects cue-induced craving and cigarette consumption in heavy alcohol drinkers. Cue-induced craving is intense and episodic craving that stimulates urges to smoke or drink by previous conditioned use. Clinically, a smoker’s cue-induced craving over the first days of quitting predict relapse rates (Shiffman, Paty et al. 1996; Killen and Fortmann 1997; Ferguson, Shiffman et al. 2006). Cue-induced craving paradigms have been used to examine the influence of smoking cessation medications (Durcan, Deener et al. 2002; Hussain, Zawertailo et al. 2009) and nicotine replacement therapy (Teneggi, Tiffany et al. 2002; Henningfield, Fant et al. 2005; Ferguson and Shiffman 2009) on smoking-related outcomes. Also, exposures to cigarette and alcohol associated visual, olfactory and tactile stimuli have reliably increased self-reported cigarette cravings in smokers who drink alcohol (Burton and Tiffany 1997; Niaura, Shadel et al. 1998; Carter and Tiffany 1999; Field, Mogg et al. 2005; Hutchison, Ray et al. 2006). Cue-induced craving paradigms have also been used to assess alcohol craving (Noel, Van der Linden et al. 2007) and the influences of tobacco on alcohol (Cooney, Cooney et al. 2003; Colby, Rohsenow et al. 2004; Field, Mogg et al. 2005; Donny, Griffin et al. 2008; Erblich, Montgomery et al. 2009). The influence of varenicline on alcohol and tobacco craving is not well established despite the availability of useful cue-reactivity paradigms.
1.4 Statement of Research Hypotheses

Cue-induced craving for cigarettes and alcohol will decrease in smokers who are heavy drinkers following two weeks of varenicline administration compared to placebo. Cigarettes and alcohol consumption will decrease in smokers who are heavy drinkers following two weeks of varenicline administration compared to placebo.

1.5 Rationale for Hypotheses

Alcohol consumption and the exposure to alcohol cues increases a smoker’s urge and motivation to smoke cigarettes (Burton and Tiffany 1997; Drobes 2002; Cooney, Cooney et al. 2003; Sayette, Martin et al. 2005). Preclinical findings suggest that varenicline modulates alcohol consumption (Steensland, Simms et al. 2007). Varenicline, a partial agonist at the α4β2 nAChRs has potential to attenuate the salient cues and positive reinforcement associated with cigarette smoking (Rollema, Coe et al. 2007). Also, acute administration of varenicline in doses reported to reduce nicotine reward decreased alcohol seeking in preclinical studies using three different animal models (Steensland, Simms et al. 2007; Ericson, Lof et al. 2009). Furthermore, in one human behavioural study, one week of varenicline administration significantly decreased alcohol consumption in 20 smokers who are heavy drinkers (McKee, Harrison et al. 2009). Since both nicotine and alcohol activate the α4β2 nAChRs, varenicline may have potential therapeutically benefits for smokers who drink alcohol heavily.
1.6 Review of the Literature

1.6.1 Tobacco and Alcohol

Tobacco smoking is the leading cause of preventable death worldwide, and it has been estimated that in 2015 it will account for 6.4 million deaths worldwide per annum (Taylor and Bettcher 2000; Mathers and Loncar 2006). Nicotine is the main addictive compound in tobacco and thus is the key component in continued and compulsive tobacco use (Benowitz 1996). Inhalation of tobacco smoke delivers nicotine to the brain and it induces a rapid dopamine release in the nucleus accumbens (Henningfield and Jasinski 1983; Pomerleau 1992; Rose 2006), the area of the brain associated with reward and drug addiction (Goldstein and Volkow 2002). Thus, nicotine-induced dopamine release is thought to sustain compulsive tobacco seeking and dependence (Koob 1992; Benowitz 1996; Leshner and Koob 1999). The reinforcing effects of nicotine combined with strong behavioural and environmental cues are the major reasons for relapse when smokers are attempting to quit (Stolerman and Shoaib 1991; Rose, Brauer et al. 2004; Le Foll and Goldberg 2005).

Alcohol is linked with 1 in every 25 deaths world wide (Rehm, Mathers et al. 2009). Chronic alcohol use alters the mesolimbic dopaminergic system and these changes may increase alcohol craving, seeking and vulnerability to relapse (Katner and Weiss 1999; Weiss and Porrino 2002; Breese, Chu et al. 2005). Alcohol craving is composed of positive (e.g. expectancies, compulsiveness), and a negative reinforcement components (e.g. withdrawal related distress) (Bohn, Krahn et al. 1995; Tiffany 1999;
Anton 2000; Sayette, Shiffman et al. 2000). The reinforcing effect of alcohol is also mediated through the mesolimbic dopamine pathway (Hemby, Johnson et al. 1997).

**Summary Point:**

- Both tobacco and alcohol use are associated with alarming death rates.
- The reinforcing effects of tobacco and alcohol are both mediated by the mesolimbic dopamine system.

### 1.6.1.1 Comorbid Tobacco and Alcohol Use

Nicotine, in the form of cigarette smoking, and alcohol are commonly co-administered by humans. Chronic alcohol use increases the reinforcing effects of nicotine (Dani and Harris, 2005) and may promote smoking behaviours such that heavy drinkers also commonly smoke heavily (Zacny 1990; Daeppen, Smith et al. 2000). The negative consequences of smoking combined with heavy drinking are significant. For example, neurocognitive abnormalities in alcohol-dependent smokers are partially modulated by tobacco use (Meyerhoff, Tizabi et al. 2006). Heavy drinkers who smoke have smaller frontal and temporal neocortical gray matter volumes compared to non-smoking heavy drinkers (Durazzo, Cardenas et al. 2007). Compared to smoking alone or drinking alone, the effect of concurrent smoking and heavy alcohol use further increases the risk for oral, pharyngeal, laryngeal and esophageal cancer (Kuper, Tzonou et al. 2000; Pelucchi, Gallus et al. 2006). As well, smokers with heavy alcohol use often have more severe alcohol dependence compared to nonsmoking drinkers (Gazdzinski, Durazzo et al. 2006).
Many studies have shown a consistent positive association between levels of smoking and alcohol drinking (Istvan and Matarazzo 1984; Friedman, Tekawa et al. 1991; Dawson 2000; Cooney, Cooney et al. 2003; Chiolero, Wietlisbach et al. 2006; Falk, Yi et al. 2006). In fact, alcohol consumption has been linked with increases in cigarette craving (Gulliver, Rohsenow et al. 1995; Burton and Tiffany 1997; Dawson 2000; Field, Mogg et al. 2005; Falk, Yi et al. 2006; Erblich, Montgomery et al. 2009). However, there is mixed evidence regarding smoking cessation and its impact on alcohol consumption in smokers who drink (Madden, Heath et al. 1995; Cooney, Cooney et al. 2003; Prochaska, Delucchi et al. 2004; Acheson, Mahler et al. 2006). One study found smokers abstaining or reducing their alcohol consumption during smoking cessation may be more vulnerable to relapse (Joseph, Lexau et al. 2004; Joseph, Willenbring et al. 2004). On the other hand, smokers are also likely to relapse after consuming alcohol (Garvey, Bliss et al. 1992; Shiffman and Balabanis 1995; Ockene, Emmons et al. 2000). Studies have shown that alcohol use (Sherman, Wang et al. 1996; Humfleet, Munoz et al. 1999; Smith, Kraemer et al. 1999) and binge drinking (Murray, Istvan et al. 1995) are negatively associated with abstinence from smoking. In particular, large longitudinal and population-based studies found that cigarette smokers in North American communities reported that heavy alcohol consumption adversely influenced success of smoking cessation (Zimmerman, Warheit et al. 1990; Hymowitz, Cummings et al. 1997; Osler, Prescott et al. 1999);(Sorlie and Kannel 1990).
There are mixed findings regarding whether smoking cessation itself results in reductions in alcohol consumption. One longitudinal study, involving six communities as a part of a 10-year project in the Minnesota Heart Health Program, found no differences between those who quit smoking and those who continued to smoke with respect to alcohol consumption (Nothwehr, Lando et al. 1995). In another study, a large cohort of 5510 male twins was monitored over a 16-year period (Carmelli, Swan et al. 1993). Carmelli and colleagues found an increase in alcohol consumption in those who continued to smoke (Carmelli, Swan et al. 1993). Another recent longitudinal study showed in 14,127 subjects aged from 25 to 74 years of age, a decrease in heavy drinking during smoking cessation (Karlamangla, Zhou et al. 2006). Moreover, a 35-year prospective study of 483 men found that alcohol consumption increased in smokers trying to quit (Krall, Garvey et al. 2002). As well, Krall et al. found that the use of alcohol increased risk of relapse to smoking after 10 years of abstinence from smoking (Krall, Garvey et al. 2002).

Alcohol consumption and history of use are often overlooked in those who are attempting to quit smoking. A recent review of 212 published clinical trials in smokers with alcohol use disorders found that alcohol related characteristics are often ignored (Leeman, Huffman et al. 2007). A recent double-blind, placebo-controlled study investigated the efficacy of bupropion in smokers with and without an alcohol use disorder (Grant, Kelley et al. 2007). Grant and colleagues reported individuals with and without alcohol use disorders have similar 7-day point prevalence cigarette abstinence rates over 6 months with bupropion (Grant, Kelley et al. 2007). Grant et al. also reported
that alcohol outcomes, such as number of drinks per day and 30-day continuous alcohol abstinence, were improved in individuals who discontinued smoking (Grant, Kelley et al. 2007). Another trial examined the efficacy of an integrated approach to treatment by providing alcohol interventions concurrently with NRT for heavy-drinking smokers (Kahler, Metrik et al. 2008). They found a 20% reduction of alcoholic beverages consumed per week and greater smoking abstinence compared to individuals who received standard treatment (Kahler, Metrik et al. 2008). The number of participants who maintained National Institute on Alcohol Abuse and Alcoholism criteria for heavy drinking (>14 drinks/week or >5 drinks/occasion for 12 months in men; >7 drinks/week or >4 drinks/occasion for 12 months in women; NIAAA and Alcoholism 1995) decreased (60% in standard treatment and 68% in the alcohol intervention group) at the 26-week follow-up (Kahler, Metrik et al. 2008). The abstinence rates of smoking had dropped from 1-week to the 26-week follow-up (45.4% to 17.7% in the standard treatment group, 57.3% to 19.1% in the alcohol intervention group; Kahler, Metrik et al. 2008).

**Summary Points:**

- Many studies found strong linkage between tobacco and alcohol use.
- There is a need to clarify the role of alcohol in relation to tobacco consumption.
1.6.1.2. Nicotine and Alcohol Reward and Dependence: α4β2 nAChRs

The neuronal nAChRs are well-characterized ligand-gated ion channels and they are members of a superfamily that also includes glycine, gamma-aminobutyric acid (GABA) and 5-HT3 receptors (Betz 1990). The nAChRs are either homomeric or heteromeric pentameric ion channels consisting of different combinations of α and β subunits (Flores, Rogers et al. 1992; Zoli, Lena et al. 1998). Although there are a total of nine alpha subunits (α2-α10) and three beta subunits (β2-4) that have been identified in the central nervous system to date (Hogg, Raggenbass et al. 2003), the majority of functional nAChRs are of the α4β2 subtype (Mann and Mody 2008). Overall, nAChRs respond to local conditions and to bindings of agonists and modulators in a dynamic process.

Both nicotine and alcohol can activate the mesocorticolimbic dopaminergic system through the nAChRs, by either direct or indirect routes (Narahashi, Aistrup et al. 1999; Dani and Harris 2005; Davis and de Fiebre 2006). Alcohol was found to also influence GABA_A (gamma-aminobutyric acid) (Harris and Allan 1985; Suzdak, Schwartz et al. 1986), NMDA (N-methyl-D-aspartate) (Lovinger, White et al. 1989), and 5-HT3 (5-hydroxytryptamine3) (Lovinger and White 1991) receptors in addition to its activities at the nAChRs. Preclinical experiments have found that both nicotine and alcohol administration elevate dopamine release in the nucleus accumbens (Soderpalm, Ericson et al. 2000; Tizabi, Copeland et al. 2002; Ericson, Molander et al. 2003), which is the area of the brain associated with reward and drug addiction (Goldstein and Volkow 2002).
Nicotine’s addictive properties are thought to be mediated via several nAChR subtypes (Grady, Moretti et al. 2009; Livingstone, Srinivasan et al. 2009), with the mesolimbic α4β2 and α7 nAChRs playing the most crucial role (Picciotto, Zoli et al. 1998; Mansvelder and McGehee 2002; Marubio, Gardier et al. 2003; Laviolette and van der Kooy 2004). For example, the α4β2 nAChR subtype has the highest sensitivity to nicotine (Benowitz, Porchet et al. 1988; Fenster, Rains et al. 1997). Additionally, the removal of either the α4 or β2 subunits in the α4β2 nAChRs by genetic knockout in a mouse model attenuates the pharmacological and behavioural effects of nicotine (Picciotto, Zoli et al. 1998; Marubio, Gardier et al. 2003). Maskos et al. demonstrated that nicotine-seeking behaviour and nicotine-induced dopamine release could be reinstated by re-expressing β2-subunits of the α4β2 nAChRs via a lentiviral vector injected into the ventral tegmental area of β2 knock-out mice (Maskos, Molles et al. 2005). Nicotine activates the α4β2 nAChRs in the ventral tegmental area to cause rapid and transitory increases in dopamine release from the ventral tegmental area to the nucleus accumbens (Mansvelder and McGehee 2002; Laviolette and van der Kooy 2004; Dani and Harris 2005; Everitt and Robbins 2005; Rollema, Chambers et al. 2007). Since nAChRs normally respond to acetylcholine to modulate neuronal excitability and synaptic communications, nicotine binding alters normal cholinergic functions and synaptic plasticity (McGehee and Role 1995; Albuquerque, Pereira et al. 1997; Jones, Sudweeks et al. 1999). In addition to the α4β2 and α7 subtypes, the α6 nAChR subtype has also been found to be involved in nicotine reward and dependence. However, very little is known about its distribution, physiological functions and pharmacological
properties (Yang, Jin et al. 2009). Nicotine-induced dopamine release serves as reinforcement in rewarding behaviours and it is the key element in addiction to nicotine (Robinson and Berridge, 1993).

The involvement of nAChRs in alcohol behaviour in animal models is consistent across electrophysiological, pharmacological, genetic and neurochemical methods (Soderpalm, Ericson et al. 2000; Larsson and Engel 2004; Dani and Harris 2005; Davis and de Fiebre 2006; Li, Volkow et al. 2007). Also, acute alcohol treatment on human nAChRs subunits expressed in Xenopus oocytes suggests that low concentrations of alcohol produced an inhibitory effect on the α7 subunit of the receptor (Cardoso, Brozowski et al. 1999). Some transgenic animal studies have suggested the possible involvement of α4β2, α3β2, and/or α7 subunits in moderating alcohol’s rewarding effects (Kuzmin, Jerlhag et al. 2009). Because nicotine and alcohol reward are both modulated through the nAChRs, they provide an interesting target in treating those with alcohol and tobacco dependence (Blomqvist, Engel et al. 1993; Rose, Behm et al. 1994; Arneric, Holladay et al. 2007; Hogg and Bertrand 2007; Levin and Rezvani 2007; Picciotto, Addy et al. 2008).

**Summary Points:**

- Nicotine and alcohol both activate α4β2 nAChRs
- Pharmacological targeting of nAChRs may provide therapeutic benefits for smokers who drink alcohol heavily
1.6.2. Craving & Cue Reactivity

Drug craving can be explained as the urge to consume drugs, while addiction is defined as a pattern of compulsive drug-seeking and drug-taking behaviour from strong cravings experienced by an individual (Edwards, Arif et al. 1981; Kozlowski and Wilkinson 1987). Craving can be categorized as background and cue-induced craving. Background craving is characterized as relatively steady, tonic states over the course of a few days (Edwards, Arif et al. 1981; Kozlowski and Wilkinson 1987). Cue-elicited cravings are episodic spikes of craving triggered by the presence of specific objects and environments and may vary from one individual to another (Isbell 1955). The incentive-sensitization theory for drug abuse states that continued drug use is determined by the incentive-motivational properties of drugs and their corresponding stimuli (Stewart, de Wit et al. 1984). As a result, environmental stimuli become positive motivational properties associated with the drug. And thus, cue-specific reactions trigger motivational processes responsible for continued drug use and relapse in persons attempting to remain abstinent (Carter and Tiffany 1999).

The key question behind cue-reactivity research is: what happens when someone is exposed to stimuli that have been paired with drug consumption over a history of drug use? The three leading models of cue-reactivity are: (1) unconditioned drug withdrawal (Wikler 1948) (2) unconditioned drug effects (Stewart, de Wit et al. 1984); and (3) cue-reactivity that oppose unconditioned drug effect (Siegel 1975). The unconditioned drug withdrawal model can be described as the development of a state similar to unconditioned drug withdrawal as cues become associated with withdrawal (Wikler
The unconditioned drug effects model states that drug-related cues can be associated with the pleasurable unconditioned effects of drugs (Stewart, de Wit et al. 1984). The cue-reactivity opposed unconditioned drug effect model states, the conditioned responses to drug-related cues are homeostatic responses which lead to drug tolerance (Siegel 1975).

Cue reactivity paradigms monitor the reactions of a person with drug use disorders to various drug-related stimuli, and they have been used regularly over the past several decades (Drummond 2000) to test cue-to-reactivity to heroin, cocaine, alcohol and cigarette use disorders (Childress, Hole et al. 1993; Dawe, Powell et al. 1993; Glautier and Drummond 1994; Burton and Tiffany 1997). Cues and cue paradigms can be classified into the following four categories: “exteroceptive”, “interoceptive”, “temporal” and “cue relationships” (Drummond 2000). Exteroceptive cues are related to sight, smell, and taste. Interoceptive cues involve moods and cognitions such as dreams about drugs (Christo and Franey 1996). Temporal relationship cues involve aspects such as time of day and seasonal habits (Drummond 2000). Cue relationships are when cues that are often presented together may influence reactivity to each other (Staiger and White 1988). When testing cue-reactivity, contextual stimuli are often used in comparison to drug-associated stimuli. In other words, drug related cues are often paired with a neutral condition, regarded as the control. Control stimuli used in laboratory cue-induced studies typically involve comparing a neutral object (e.g. a pencil) to a smoking-associated object (e.g. a cigarette) (Sayette, Martin et al. 2001; Baumann and Sayette 2006; LaRowe, Saladin et al. 2007; Erblich, Montgomery et al. 2009).
Cue exposure is not only evident in subjective craving, it also impacts objective measures of emotional states measured by facial expressions (Sayette, Martin et al. 2001), physiological measures of heart rate, mean arterial pressure (Carter and Tiffany 1999; Sayette, Shiffman et al. 2000; Miranda, Rohsenow et al. 2008) and brain activation (Brody, Mandelkern et al. 2004; Wilson and Bigelow 2004; Wilson, Sayette et al. 2005). In some studies, cue reactivity to drug cues has been compared to pre-stimulus baseline conditions instead of comparisons against neutral cue conditions (Robbins, Ehrman et al. 1992; Powell 1995). However, this makes it impossible to assess cue specificity (i.e. the response related to cues presented) (Tiffany 1999). The most commonly collected data from cue-reactivity paradigms are self-reported cravings and desires for a substance. Physiological responses such as heart rate and skin temperature are also commonly measured.

Many factors can influence cue-reactivity. Personal and individual variability such as degree of drug dependence can influence the salience of cues (Kaplan, Meyer et al. 1983; Glautier and Drummond 1994). Cue characteristics can also influence reactivity, since in vivo cues tend to be more salient compared to visual cues. Also, contextual factors are likely to influence cue reactivity. For example, exposure to drug cues will influence craving differently in those who are abstaining compared to those who are continued users (Drummond, Cooper et al. 1990).

**Summary Points:**
- Drug craving is the urge that leads to drug taking.
Drug cues are associations that can induce drug craving (e.g. objects, places, smells, events).

Cue paradigms measure the reactivity of the individuals to drug-associated stimuli.

1.6.2.1. Tobacco Cues and Cue-induced Craving

The motivation to smoke is hypothesized to be comprised of several elements: subjective craving, cognitive attentional bias to smoking associated cues, behavioural approach bias, and alleviating or preventing withdrawal (Stolerman and Shoaib 1991; Robinson and Berridge 1993; Baker, Piper et al. 2004; Field, Mogg et al. 2005). All of these elements can manifest clinically as craving for cigarettes. Craving is a common symptom smokers seek to diminish in the process of quitting.

Background cigarette craving often increases slowly after quitting and then decreases slowly as the abstinence period is prolonged after smoking cessation (Hughes 1992; Piasecki, Niaura et al. 2000). In addition to background craving, smokers also experience episodic intense cravings (Ferguson and Shiffman 2009); these acute craving states are usually triggered when smokers are exposed to situational or environmental stimuli associated with smoking such as emotional distress or alcohol consumption (Curry and Marlatt 1985; O’Connell and Martin 1987; Niaura, Rohsenow et al. 1988; Bliss, Garvey et al. 1989). Former smokers who are exposed to smoking-related cues may experience intense acute cravings that may lead to relapse (Shiffman, Paty et al. 1996). The intensity of craving experienced by smokers during attempts at quitting
significantly influences whether they will succeed (Killen and Fortmann 1997; Ferguson, Shiffman et al. 2006).

Cue reactivity of nicotine is based on the classical conditioning model of learning where nicotine is the unconditioned stimulus and situations and objects related to nicotine become the conditioned stimuli. The conditioned stimuli can induce craving by a learned association over a history of numerous previous pairings with smoking (Niaura, Rohsenow et al. 1988). Social learning theory indicates that the conditioning factors of such cues are risk factors in relapse (Niaura, Rohsenow et al. 1988). Motivation for actions that are evoked by conditioned stimuli will lead to cigarette seeking. For example, the sight or smell of an alcoholic drink can prompt a strong urge to smoke in former smokers who paired cigarettes with alcohol drinking.

A multi-center, randomized, placebo-controlled study was conducted in 296 smokers to evaluate the effectiveness of nicotine gum in relieving acute craving (Shiffman, Shadel et al. 2003). Participants received 3 days of either active or inactive nicotine gum (Shiffman, Shadel et al. 2003). On the third day, participants were exposed to smoking cues and rated their cravings (Shiffman, Shadel et al. 2003). Shiffman and colleagues found that active nicotine gum significantly reduced acute cravings following smoking cues compared to inactive gum in smokers (Shiffman, Shadel et al. 2003). In another study with nicotine gum, 319 smokers were randomized to chew either a rapid-release nicotine gum or regular nicotine gum (Niaura, Sayette et al. 2005).
found that rapid-release formulation gum lowered cue-induced subjective ratings of tobacco craving more than a slower-release nicotine gum (Niaura, Sayette et al. 2005).

**Summary Point:**

- Cue-induced cravings are associated with smoking relapse in those who are attempting to quit.
- Nicotine gum reduces acute tobacco cue-induced cravings

### 1.6.2.2 Theories of Tobacco and Alcohol Craving

The Conditioned Theory posulates that alcohol consumption intensifies cigarette craving as a classically conditioned response to stimuli that were previously paired with drug use (Wikler 1948; Ludwig and Wikler 1974; Poulos, Hinson et al. 1981; Melchior and Tabakoff 1984; Robinson and Berridge 1993). This theory posits that individuals who drink alcohol heavily may frequently pair alcohol with cigarettes during their history of smoking. In other words, alcohol consumption becomes the conditioned stimulus responsible for evoking the response of smoking. Thus, alcohol and smoking related environmental cues paired together can cause an additive effect to further evoke craving (Wikler 1948; Ludwig and Wikler 1974; Poulos, Hinson et al. 1981; Melchior and Tabakoff 1984; Robinson and Berridge 1993).

A second theory, the Cognitive Processing Model explains the comorbidity of alcohol and tobacco as behaviours that became automatized through numerous administrations (Tiffany and Drobès 1990). According to this model, smokers with a
history of pairing smoking with alcohol drinking may attribute alcohol consumption as a part of the stimulus complex controlling automated cigarette use. In other words, alcohol consumption activates an automatized smoking sequence and thus triggers cigarette craving. Specifically, alcohol may increase background craving with no change to smoking cues induced craving (Burton and Tiffany 1997).

**Summary Point:**

- Both the Conditioned Theory and the Cognitive Model predict that cigarette craving will increase with alcohol administration.

### 1.6.2.3 Clinical Studies of Tobacco and Alcohol Cue-induced Craving

There is strong evidence suggesting alcohol consumption and the exposure of alcohol cues increases smokers’ urge and motivation to smoke cigarettes (Burton and Tiffany 1997; Drobes 2002; Cooney, Cooney et al. 2003; Sayette, Martin et al. 2005). The rate of smoking and the volume of puffs taken are increased in the presence of alcohol (Nil, Buzzi et al. 1984; Mintz, Boyd et al. 1985). Additionally, the subjective satisfaction from smoking (Rose and Behm 2004) as well as cigarette craving (Glautier and Drummond 1994; Burton and Tiffany 1997) also increases after alcohol consumption. One study utilized a visual probe task that recorded eye movement in order to investigate biases in visual response to smoking-related cues in daily cigarette smokers (Field, Mogg et al. 2005). Participants consumed an alcoholic drink (0.4g/kg alcohol) in one session and a non-alcoholic drink in another session (Field, Mogg et al. 2005). Field
and colleagues found that administration of moderate doses of alcohol caused increased attention, perceived pleasantness of smoking cues, and cigarette craving in smokers who drink alcohol (Field, Mogg et al. 2005). Another study examined the effects of alcohol consumption on cigarette craving in 138 heavy smokers and tobacco chippers (Sayette, Martin et al. 2005). Participants were assigned to receive a moderate dose of alcohol or a placebo drink before they were exposed to both smoking cues and control cues (Sayette, Martin et al. 2005). Sayette and colleagues found alcohol consumption increased smoking urges and the likelihood of displaying positive affect in facial expressions (Sayette, Martin et al. 2005).

It is hypothesized that alcohol consumption increases dopamine release in the nucleus accumbens by either directly inducing excitatory effects or indirectly reducing inhibition from interneurons (Harris, Brodie et al. 1992). In turn, elevated dopamine levels increase the attractiveness or salience of smoking-related cues, which over time results in the cues increasing the motivation to smoke (Robinson and Berridge 1993; Robinson and Berridge 2003). Robinson and Berridge’s incentive-sensitization theory suggests that the increased dopaminergic transmission would produce an automatic increase in the incentive salience of smoking associated cues. In addition, alcohol often serves as a conditioned stimulus for smoking and it may potentiate the incentive properties of any tobacco-associated cues. Moreover, other evidence has demonstrated that giving smokers a moderate dose of alcohol increased their sensitivity for smoking-associated cues (Cooney, Cooney et al. 2003; Field, Mogg et al. 2005; Sayette, Martin et
al. 2005), and thus alcohol consumption has been suggested to increase the likelihood of future smoking behaviour (Field, Mogg et al. 2005).

**Summary Point:**

- Alcohol consumption increases cigarette-related cravings in smokers.

### 1.6.3. Varenicline Review

#### 1.6.3.1. Pharmacokinetics of Varenicline

The pharmacokinetics of varenicline have been well characterized by Faessel and colleagues. They compared single and multiple dosing of varenicline in a double-blind, placebo-controlled, dose-escalation study in 44 daily smokers (Faessel, Smith et al. 2006). They found varenicline was well absorbed following oral administration with linear pharmacokinetics (Faess, Smith et al. 2006). Varenicline is not hepatically metabolized, and is almost completely excreted renally as the parent compound (Faessel, Smith et al. 2006). Maximum plasma concentration of varenicline is typically reached within 4 hours for both single and multiple doses (1-2mg) in daily smokers (Faessel, Smith et al. 2006). Furthermore, the mean elimination half-life of varenicline is approximately 21.4 (±3.3) hours following single dose and 26.1 (±5.5) hours after repeated dose administrations (Faessel, Smith et al. 2006). Steady-state conditions in smokers were reached within 4 days of repeated varenicline administration (Faessel, Smith et al. 2006). These findings have been confirmed by others (Burstein, Fullerton et al. 2006; Zhao, Schwam et al. 2010; Ravva, Gastonguay et al. 2009; Xiao, Lv et al. 2009; Kikkawa, Maruyama et al. 2010).
Summary Points:

- Varenicline produces steady state conditions within 4 days of repeated administration, elimination half-life of 21 hours.

1.6.3.2. Pharmacodynamics of Varenicline

Varenicline is a derivative of a plant alkaloid cytisine, which has been used for smoking cessation in Eastern Europe (Etter, Lukas et al. 2008). Varenicline is a nicotine receptor partial agonist for the α4β2 nAChR and a full agonist at the α7 nAChRs (Mihalak, Carroll et al. 2006). In vitro receptor binding studies showed that varenicline has high affinity and selectivity for the α4β2 nAChRs (Coe, Brooks et al. 2005; Rollema, Chambers et al. 2007). The agonist effect of varenicline is hypothesized to decrease nicotine craving and alleviate withdrawal symptoms by binding at the α4β2 nAChR to increase dopaminergic tone in the brain. The antagonist effect of varenicline binding at the α4β2 nAChR is hypothesized to decrease the rewarding and reinforcing effects of nicotine-induced dopamine release (Coe, Brooks et al. 2005; Rollema, Chambers et al. 2007). When co-administered with agonists of lower affinity, partial agonists with high binding affinity can suppress the agonist effects by acting as antagonists (Rollema, Chambers et al. 2007). During smoking, the presence of a partial agonist will reduce nicotine-induced mesolimbic dopamine release and thus minimize reinforcement (Rollema, Chambers et al. 2007). Partial agonists have lower intrinsic functional activity compared to a full agonist such that they cause a smaller maximal effect at full receptor occupancy (Rollema, Chambers et al. 2007). For example, α4β2 nAChR partial agonists
can partially stimulate the nAChRs in the absence of nicotine (Rollema, Coe et al. 2007). In other words, partial agonists reduce cigarette craving and withdrawal by inducing a partial dopamine release, and preventing nicotine from binding (Faessel, Smith et al. 2006; Rollema, Coe et al. 2007; Cahill, Stead et al. 2008). Over the short term, a partial agonist at the α4β2 nAChRs can reduce smoking, and over a period of a few months it can attenuate the salient cues and positive reinforcement associated with cigarette smoking, and thus assist in long-term abstinence.

In preclinical studies using rat models, varenicline and nicotine’s dopamine effects were compared. Varenicline induced a later onset but longer duration of dopamine release (Rollema, Chambers et al. 2007). Further, varenicline lead to 60% of the maximum dopamine release associated with intravenous nicotine administration (Coe, Brooks et al. 2005; Rollema, Chambers et al. 2007). When varenicline is administered with nicotine, varenicline’s partial agonist activities attenuated nicotine-induced dopamine release to the level of varenicline alone (Rollema, Chambers et al. 2007). Thus, varenicline creates a ceiling effect on dopamine release in the mesolimbic pathway when administered alone or concurrently with nicotine (Rollema, Chambers et al. 2007).

In one human study, Faessel et al. found a 50-90% decrease in mean plasma nicotine and cotinine levels following administration of varenicline (2-3mg once daily, 1mg twice daily) compared to baseline. The mean number of cigarettes smoked per day also decreased approximately 60-80% within 2-4 days of varenicline dosing (Faessel, Smith et al. 2006). Tonstad et al. studied the efficacy of 12 weeks of varenicline
treatment (1mg twice per day) in a multi-center randomized, placebo-controlled trial in 7 countries with a sample of 1927 cigarette smokers (Tonstad, Tonnesen et al. 2006). Tonstad and colleagues found that the 52-week abstinence rate was significantly higher in participants who received varenicline compared to placebo (43.6% vs 36.9%; OR 1.34; 95% CI: 1.06-1.69; p=0.02) (Tonstad, Tonnesen et al. 2006).

**Summary Point:**

- Varenicline decreases the number of cigarettes smoked per day, plasma nicotine/cotinine levels, and cigarette cravings.

**1.6.3.3. Safety of Varenicline**

In clinical placebo-controlled settings, adverse effects of varenicline compared to placebo were as follows: nausea (30% vs. 10%), insomnia (19% vs. 13%), headache (19% vs. 13%), abnormal dreams (13% vs. 5%), constipation (8% vs. 3%), and abdominal pain (7% vs. 5%) (Pfizer 2006). In Phase 2 and 3 clinical trials, the percentage of participants who discontinued medication due to adverse symptoms ranged from 9-28% for active treatment compared to 7-17% in the placebo group (Jorenby, Hays et al. 2006; Nides, Oncken et al. 2006; Oncken, Gonzales et al. 2006).

In one large community study, 1,018 smokers were evaluated with varenicline in a randomized trial comparing the effectiveness of three types of behavioural support (web-based, telephone-based, or both) for smoking cessation. (Halperin, McAfee et al. 2009). The major side effect from varenicline was nausea, experienced in 57% of
participants (Halperin, McAfee et al. 2009). Overall, most of the participants who experienced adverse symptoms reported a very mild to moderate level of severity (67-96%) (Halperin, McAfee et al. 2009). Other studies also demonstrated tolerable adverse events profile of varenicline various populations (Burstein, Fullerton et al. 2006; Zhao, Schwam et al. 2010; Ravva, Gastonguay et al. 2009; Xiao, Lv et al. 2009; Kikkawa, Maruyama et al. 2010).

Varenicline has acquired a series of warnings since its approval related to potential adverse psychiatric effects. In 2007, the U.S. Food and Drug Administration announced that patients using varenicline for smoking cessation had experienced serious symptoms, including drowsiness, erratic behaviour, suicidal ideation and occasional suicidal behaviour (FDA, 2009). In 2009, the FDA required varenicline to carry a black box warning to address these potential side effects (FDA, 2009). However, it is unknown whether the reported psychiatric symptoms are related to varenicline or to nicotine withdrawal symptoms since most of these patients have stopped smoking (FDA, 2009). Despite these warnings, recent research showed promising results for varenicline in mentally ill and psychiatric populations (Ebbert, Wyatt et al. 2009; Philip, Carpenter et al. 2009; Smith, Lindenmayer et al. 2009). Philip and colleagues administered open-label varenicline (0.5mg daily titrated to 1mg twice daily) in 18 patients with DSM-IV-TR Axis I depressive disorders for 8 weeks while being stabilized on antidepressants or mood-stabilizers (Philip, Carpenter et al. 2009). Philip et al. found these patients had significantly improved depressive symptoms at the end of the study (Philip, Carpenter et al. 2009). Mild adverse events were reported and four subjects discontinued due to
gastrointestinal effects (n=3) and worsened mood/irritability (n=1) (Philip, Carpenter et al. 2009). Similarly, Smith and colleagues administered open-label varenicline in 14 smokers with schizophrenia for nine weeks while taking antipsychotics and psychotropic medications (Smith, Lindenmayer et al. 2009). Smith et al. found varenicline significantly decreased smoking indices and improved scores in cognitive tests associated with verbal learning and memory (Smith, Lindenmayer et al. 2009). Smith also found mild adverse events in the form of nausea, vomiting, dry mouth, and cramps (Smith, Lindenmayer et al. 2009). Regardless, it is prudent to monitor psychiatric symptoms when administering varenicline.

**Summary Point:**

- Varenicline is well tolerated in clinical usage for smoking cessation.
- Because some patients reported adverse effects and there have been FDA warnings, it is prudent to monitor psychiatric symptoms while administering varenicline.
1.6.3.4 Varenicline vs. Other Smoking Cessation Pharmacotherapy

Current available treatments for tobacco dependence other than varenicline (Champix©) include nicotine replacement therapies (NRT) and bupropion (Zyban©). Nicotine replacement therapy (e.g. gum, lozenge) delivers nicotine as an agonist in a safe form, eliminating other elements of smoking that are associated with tobacco-related diseases. NRT was found to be effective in reducing nicotine craving and withdrawal during quit attempts (Silagy, Lancaster et al. 2004). However, those attempting to quit may still find themselves smoking cigarettes in addition to the NRT to gain higher levels of nicotine reinforcement (Benowitz, Porchet et al. 1988). In a randomized open-label trial, subjects who received varenicline had a 26.1% continuous abstinence rate from weeks 9 to 52 compared to 20.3% in those who received NRT (Aubin, Bobak et al. 2008). Additionally, varenicline also more effective compared to NRT in the reduction of cigarette craving, nicotine withdrawal symptoms and smoking satisfaction (Aubin, Bobak et al. 2008).

Bupropion is another medication used for smoking cessation. Bupropion primarily acts as a dopamine reuptake inhibitor, as well as the α3β4-nicotinic receptor antagonist (Fryer and Lukas 1999; Slemmer, Martin et al. 2000). Jorenby and colleagues conducted a double-blind, placebo-controlled trial where 1027 smokers were randomized to bupropion (titrated to 150mg twice daily), varenicline (titrated to 1mg twice daily) or placebo for 12 weeks (Jorenby, Hays et al. 2006). Results showed that varenicline was more efficacious than bupropion and placebo with 52 week continuous abstinence rates of 23.0%, 14.6% and 10.3% respectively (Jorenby, Hays et al. 2006). Similarly,
Gonzales and colleagues conducted a randomized, double-blind, placebo-controlled clinical trial at 19 centers in 1025 daily smokers (Gonzales, Rennard et al. 2006). Participants were randomly assigned in a 1:1:1 ratio to receive varenicline (1mg twice per day), bupropion (150mg twice per day), or placebo for 12 weeks in addition to counseling (Gonzales, Rennard et al. 2006). Results showed that varenicline was more efficacious than bupropion and placebo with 52-week abstinence rates of 21.9%, 16.1%, and 8.4% respectively (Gonzales, Rennard et al. 2006). These findings have been confirmed in other similarly designed studies (Gonzales, Rennard et al. 2006; Nides, Oncken et al. 2006; Oncken, Gonzales et al. 2006; Tonstad, Tonnesen et al. 2006).

West and colleagues examined the effect of varenicline on cigarette craving in two 52-week double-blind, randomized trials that compared varenicline (1mg BID), bupropion (150mg BID) and placebo (West, Baker et al. 2008). Participants took study medication for 1 week while still smoking and then attempted to quit (West, Baker et al. 2008). West et al. found in abstinent and non-abstinent participants combined, varenicline significantly reduced cigarette craving and ratings of satisfaction and psychological reward after the first cigarette smoked more than bupropion and placebo (West, Baker et al. 2008).

**Summary Point:**
- Varenicline produces increased abstinence rates compared to bupropion or NRT.
- Varenicline reduces cigarette craving more than bupropion
1.6.3.5. Varenicline’s Effects on Alcohol Use

Varenicline is hypothesized to reduce alcohol consumption through its partial agonist activity at $\alpha 4\beta 2$ nAChRs by preventing alcohol-induced dopamine release in the nucleus accumbens (Steensland, Simms et al. 2007; Gulick and Gould 2008; Ericson, Lof et al. 2009). In Steensland and colleagues’ rat self-administration model, alcohol (10%) or sucrose (5%) reward was given contingent on a light and a 3 second tone cue (Steensland, Simms et al. 2007). After the rats had maintained a stable level of responding over 5 months of alcohol exposure, varenicline (0.3, 1, or 2mg/kg) was administered 30 minutes before test sessions. Acute administration of varenicline selectively reduced alcohol seeking, but not sucrose seeking (Steensland, Simms et al. 2007). Chronic varenicline administration decreased alcohol consumption while no increase was found when varenicline was no longer administered (Steensland, Simms et al. 2007). Thus, Steensland and colleagues’ results showed varenicline, in doses reported to reduce nicotine reward (Rollema, Chambers et al. 2007) selectively reduced alcohol seeking and consumption in rats (Steensland, Simms et al. 2007). This finding supports the claim that nAChRs play a role in changing alcohol consumption.

Gulick and Gould found that low varenicline doses in mice can improve ethanol-induced disruptions in cognitive processes such as learning (Gulick and Gould 2008). Specifically, this group investigated hippocampus-dependent contextual learning with an unconditioned foot-shock stimulus, and hippocampus-independent cued learning in the form of an auditory conditioned stimulus (Gulick and Gould 2008). They found that
varenicline dose-dependently improved ethanol-induced conditioning deficits across three doses of alcohol (1.0, 1.5, 2.0g/kg) administration (Gulick and Gould 2008).

Recently, Ericson et al showed that not only did varenicline inhibit alcohol-induced dopamine release, it also inhibited the dopamine release produced by a co-administration of alcohol and nicotine in the rat nucleus accumbens (Ericson, Lof et al. 2009). This suggests that varenicline can modulate the effects of ethanol and nicotine in the mesocortical dopamine system (Ericson, Lof et al. 2009). Evidence suggests that the α4β2 and α7 nAChR subtypes are associated with ethanol reduction in rats (Rollema, Hajos et al. 2009). It is possible that other nAChR subtypes such as the α3β2, β3, and α6 can also be involved (Kuzmin, Jerlhag et al. 2009). Varenicline has some binding affinity for the α3β2, β3, and α6 nAChR subtypes (Rollema, Coe et al. 2007).

There is limited evidence on the impact of varenicline on alcohol consumption or craving in humans. A recent double-blind, placebo-controlled investigation examined the effect of a 2mg/day varenicline dosage versus placebo on alcohol self-administration in 20 heavy drinkers who also smoke (McKee, Harrison et al. 2009). Following one week of varenicline or placebo pretreatment, participants would either choose to drink an alcoholic beverage or receive monetary reinforcement (McKee, Harrison et al. 2009). Also, participants completed a 14-hour session where a priming dose of alcoholic drink (0.3g/kg) was administered prior to two occasions of 1-hour ad libitum drinking periods (McKee, Harrison et al. 2009). During the study session, McKee and colleagues measured blood alcohol levels, alcohol and tobacco self-reported cravings, and
physiological measures (blood pressure, heart rate and skin temperature). Varenicline significantly reduced alcohol self-administration and increased the likelihood of abstaining from drinking during the study day (McKee, Harrison et al. 2009). Varenicline was also found to reduce subjective reinforcing effects of alcohol (McKee, Harrison et al. 2009). In a similarly designed study with the opioid antagonist naltrexone comparable results were reported (O'Malley, Krishnan-Sarin et al. 2002). Since naltrexone is indicated for the treatment of alcohol use disorders, McKee and colleagues concluded that the observed effects of varenicline have therapeutic potential. Thus, more research is still needed to clarify the effect of varenicline on alcohol craving and consumption in smokers who consume alcohol.

**Summary Points:**

- Preclinical studies suggested that varenicline may impact alcohol related behaviours and reactivity.
- Human evidence for the effect of varenicline on alcohol craving and consumption is scarce.

**1.7 Restatement of Research Hypothesis**

Cue-induced craving for cigarettes and alcohol will decrease in smokers who are heavy drinkers following two weeks of varenicline administration compared to placebo. Cigarettes and alcohol consumption will decrease in smokers who are heavy drinkers following two weeks of varenicline administration compared to placebo.
2. Methodology

2.1 Study Design

This was a double-blind, randomized placebo-controlled trial evaluating the effect of varenicline administration (0.5-2mg/day) on tobacco and alcohol cue-induced craving in daily dependent smokers who are also heavy drinkers. All participants were instructed to take their study medication for two weeks and participated in two laboratory sessions at the Centre for Addiction and Mental Health (CAMH). Each laboratory session involved testing at four time-points, which are composed of (1) 12-hour abstinence from alcohol and cigarettes; (2) after 1 cigarette; (3) neutral cue presentation; and (4) tobacco-alcohol cue presentation. The Research Ethics Board at CAMH approved the study protocol.

Participants were eligible if they were (a) treatment-seeking smokers; (b) between 18-65 years of age; (c) currently smoking at least 10 cigarettes a day; (d) scored at least a 3 on the Fagerström Test of Nicotine Dependence (FTND) (Heatherton, Kozlowski et al. 1991); (e) currently drinking at least 20 standard alcoholic beverages per week (females) or 25 per week (males), and; (f) scored at least an 8 on the Alcohol Use Disorder Identification Test (AUDIT) (Saunders, Aasland et al. 1993) to be considered as a heavy drinker. Participants were excluded if they; (a) had any medical condition requiring immediate attention; (b) scored more than 16 on the Beck Depression Inventory (BDI) (Beck, Ward et al. 1961); (c) had insulin-dependent diabetes; (d) currently drank more than 70 standard alcoholic drinks per week (males) or more than 52 per week (females); (e) were currently pregnant or lactating (females); (f) currently met criteria of DSM-IV
Axis I psychiatric disorder in the Mini International Neuropsychiatric Interview (MINI) (Sheehan, Lecrubier et al. 1998); (g) had any substance use disorder except tobacco and alcohol, confirmed by urine toxicology screening.

Each participant attended four study sessions: (1) Assessment; (2) Study Day 1; (3) Mid-Study Visit; and (4) Study Day 2. After assessment, eligible subjects were given a diary to record their daily cigarette and alcohol consumption for one week. They then participated in three subsequent study visits as outlined in the overall study design (Table 2.1). The first week’s study medication was given to participants on Study Day 1 and the second week’s medication on the Mid-Study Visit. Additionally, a total of 3 diaries were collected tracking alcohol and cigarette consumption from the subject covering the whole study length of 21-days. Participants were informed that although they may reduce cigarette smoking during the study, the main objective was to assess their cue reactivity. They were also informed that further smoking-cessation aid and counseling could be provided for the participants after study completion.

**Table 2.1: Overall Study Design**

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<td>Daily Diary: week 1</td>
<td>No medication</td>
<td><strong>Study Day 1</strong></td>
<td>Diary: week 2</td>
<td>Medication: varenicline/placebo</td>
<td>Daily Diary: Week 2</td>
<td><strong>Mid-study visit</strong></td>
<td>Diary: week 3</td>
<td>Medication: varenicline/placebo</td>
<td>Daily diary: Week 3</td>
<td><strong>Study Day 2</strong></td>
<td>(end of study craving)</td>
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2.2 Subject Recruitment

Participants were recruited from advertisements placed in local newspapers, word-of-mouth, online classified websites, and postings in CAMH. All subjects provided voluntary written informed consent prior to any assessment procedures but following telephone screening for initial eligibility. Figure 2.1 shows the flow chart of subject recruitment. Out of the 581 people who responded to advertisements, 429 could be contacted for telephone screening. Of these, 110 were eligible according to the smoking criteria and of these, 57 met criteria for heavy drinking. These 57 individuals were booked for an initial assessment at our clinic in CAMH. However, 25 participants did not show up for this appointment. Therefore, 32 participants completed their initial assessment but 2 were excluded due to signs of suicide risk and signs of depression. These 2 excluded volunteers were referred to the CAMH emergency clinic on the same day where they were able to speak with a clinician. Thirty subjects were enrolled into the study but 6 dropped out due to scheduling (4 people) or medical reasons (2 people). One medical reason was an advised dropout from the subject’s neurologist since she has a history of severe migraines. The second medical reason was a concern of adverse events and a sudden change of mind, although he had not been given any study medications yet. As a result, 24 participants completed the full study.
Figure 2.1 Subject Recruitment Chart

Calls Received (n = 581)

Callers Screened (n = 429)

Eligible Smokers (n = 110)

Eligible Smoker-heavy-drinker Group (n = 57)

Subjects Assessed (n = 32)

Subjects Enrolled (n = 30)

Randomized to Varenicline (n = 13)

Randomized to Placebo (n = 12)

Subjects Completed (n = 24)

Exclusion (n = 152)
• Unable to contact

Exclusion (n = 319)
• Not interested (69)
• Depression screen positive (50)
• Failed alcohol criteria (48)
• Smokes < 10 cig/day (44)
• Other (e.g. incoherent) (27)
• No phone (e.g. shelter) (25)
• Taking other medication (21)
• Drug dependence (20)
• Does not drink alcohol (15)

Exclusion (n = 25)
• no show, unreachable (18)
• drop-out (7)

Exclusion (n = 53)
• Light/social drinkers

Exclusion (n = 2)
• depressed, BDI > 16 (1)
• suicide risk (1)

Drop-out (n = 5)
• medical reasons (2)
• scheduling reasons (3)

Drop-out (n = 1)
• scheduling reasons (1)
2.3 Sample Size

The \textit{a priori} sample size calculation for this study was based on a previous study which investigated the effect of bupropion on tobacco cue-induced craving (Brody, Mandelkern et al. 2004) with G* Power analysis program (Erdfelder, Faul et al. 1996). We assumed the differences in cue-reactivity between subjects receiving placebo and subjects receiving varenicline was similar to those comparing bupropion to an untreated group in the study by Brody et al (Brody, Mandelkern et al. 2004). This assumption was made because when the current study was designed, there were no published reports on the effect of varenicline on laboratory cue-induced craving. Since this study is novel in investigating cue-reactivity with varenicline, we assumed varenicline would induce similar effect with bupropion towards tobacco related cues compared to placebo. The effect size of the current study was calculated by taking the difference of the means of Brody’s bupropion group (1.4±1.4) and the untreated group (4.1±1.6) after cigarette cue presentations, and then divided by the standard deviation (Brody, Mandelkern et al. 2004). Hence, with an effect size of 1.8, alpha of 0.05, and the standard power of 0.95, the total sample size is 16 with an actual power of 0.96. Thus the present study should be able to detect a significant difference between varenicline vs. placebo groups with a total sample size of 16 (8 in each group). The stringent power of 0.95 was chosen to minimize the probability of a false negative. The current study recruited 24 subjects in total in order to be more conservative in terms of power since the sample size calculation was based on a different medication.
2.4 Assessment Procedures (Day 0)

Responders from the study advertisement were initially contacted by telephone to
determine their basic eligibility, which included age, alcohol and cigarette consumption,
FTND score, symptoms of depression, diabetes, pregnancy and substance use. Interested
participants then attended an assessment visit to our clinic at CAMH in Toronto for a
comprehensive screening session. After the informed consent process, the assessment
screening session involved: demographics, self-reported AUDIT, BDI, Drug Use History,
the MINI psychiatric interview, blood collection for basic hematology, biochemistry,
urine collection for toxicology, and ended with a medical examination completed by a
physician at the Nicotine Dependence Clinic at CAMH. Individuals who were healthy
and who met the inclusion and exclusion criteria were enrolled in the study.

2.5 Study Days Procedures (Day: 7, 14, 21)

Each subject completed a total of three additional sessions following the initial
assessment (Day 0). Prior to Study Day 1, subjects completed the daily diaries that were
distributed after the assessment, thereby providing baseline data of their smoking and
drinking patterns. On Study Day 1 (Day 7) overnight (12-hour) abstinence from both
tobacco and alcohol was confirmed by breath CO (<10ppm) and alcohol (0 mg/dl)
measurements and a blood sample was taken for baseline analysis of plasma nicotine and
cotinine concentrations. The BDI was then administered along with the Questionnaire of
Smoking Urges (Tiffany and Drobes 1991) and the 47 item version of the Alcohol
Craving Questionnaire (ACQ; (Singleton, Tiffany et al. 1995) respectively. The QSU
provides craving scores on two scales. Factor 1 scale in the QSU represents intention and desire to smoke where smoking is anticipated to be pleasurable. The Factor 2 scale represents desire to smoke where smoking is expected to relieve nicotine withdrawal. The ACQ also provides two methods of ratings. Method 1 of the ACQ rates emotionality aspects while Method 2 evaluates alcohol craving. Additionally, subjects were requested to complete the Obsessive Compulsive Drinking Scale (Anton, Moak et al. 1995) to assess the compulsive behaviours and obsessive thoughts about alcohol use and drinking. The Visual Analogue Scale (Folstein and Luria 1973) was used to rate nicotine and alcohol cravings at four time-points during the study days. Finally, the Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami, 1986) was administered to measure nicotine withdrawal. Subjects were then allowed to smoke a single cigarette and answer another battery of questionnaires before resting for 1 hour. Subjects were then shown the study cue paradigm described in Section 2.7 and questionnaires are administered as per Figure 2.2. Subjective craving was again measured in addition to a Nicotine/Alcohol Stroop test (Stroop 1935) and Digit Symbol Substitution Test (Wechsler 1958) to assess attentional bias, attention and memory. Individuals were then provided with a 1-week supply of study medication and a daily diary to complete.

During the Mid-Study Visit (Day 14), subjects returned to the lab to receive their second week of study medication. At this time, subjects could verbalize any adverse events experienced. A 90-item Symptoms Checklist (SCL-90) (Derogatis, Lipman et al. 1974) and the BDI were also administered. On Study Day Two (Day 21), the procedure
from the first study day was repeated (Figure 2.2). Blood samples were drawn for analysis of plasma nicotine and cotinine concentrations.

**Figure 2.2 Study Day Outline (Day 7, 21)**

![Study Day Outline Diagram]

**BDI: Beck Depression Inventory**  
**QSU: Questionnaire of Smoking Urges**  
**ACQ: Alcohol Craving Questionnaire**  
**OCDS: Obsessive Compulsive Drinking Scale**  
**MNWS: Minnesota Nicotine Withdrawal Scale**  
**DSST: Digital Symbol Substitution Task**  
**Stroop: Alcohol and tobacco stroop**

### 2.6 Materials: Study Medication

The Nicotine Dependence Clinic at CAMH supplied the varenicline. Pharmacy.ca (PurePharm Inc.) encapsulated both the placebo and varenicline for the present study. After the encapsulation, the study medication was randomized by the CAMH pharmacy in a double-blind manner and the randomization code was kept by the pharmacy until study completion. Participants received either placebo or varenicline at the first study visit. The supplied varenicline tablets were encapsulated in a plain generic
capsule identical to the placebo capsules. Subjects were instructed to take their study medication in the same manner. Varenicline was titrated according to the product label’s recommended dosing from Pfizer’s Champix© product monograph (0.5mg once daily for days 1-3, 0.5mg twice daily for days 4-7 followed by 1mg twice daily for days 8-14). Medication compliance was monitored with pill counts and self-reports in a daily diary. If at any point a subject reported that he/she wanted to discontinue their study medication due to any reason, they could withdraw from the study. At the end of the study, all subjects are asked to guess whether they had received varenicline or placebo. After the study completion, subjects were offered the option to receive a free 12-week supply of varenicline or other smoking cessation medication as well as behavioural counseling and support through the Nicotine Dependence Clinic of CAMH.

2.7 Cue Paradigm

The cue-paradigm in the present study consisted of two sets of slide-show format pictures on a computer: neutral picture cues and tobacco- and alcohol-related picture cues. These cues were presented to participants using a randomized block design (Refer to Appendix for a sample). In addition, subjects were also exposed to suitable olfactory, auditory and tactile components for each set of visual cues. The neutral cue was presented first in a regular interview room without music. Subjects were first shown a slideshow of 44 neutral images from the International Affective Picture System with 7 seconds per image (5 min 8 sec) (Lang, Bradley et al. 1999). Then, subjects were asked to hold a pencil in their hand while smelling a cup of water before they completed
questionnaires outlined in Figure 2. Subjects were then escorted to the CAMH simulated bar with jazz music playing in the background. A slideshow (5min 8 sec) of tobacco (22 pictures) (van Hanswijck de Jonge and Gormley 2005; Hussain, Zawertailo et al. 2009) and alcohol (22 pictures) (Wrase, Grusser et al. 2002; Wrase, Schlagenhauf et al. 2007) related images was also shown to the individuals to evoke craving. Then, an ashtray with a cigarette in it was presented to the subject along with his/her alcoholic drink of choice. Subjects were then asked to hold the cigarette in their hand in a similar fashion as if they were smoking while smelling the alcoholic drink but not consume it. Finally, the subjects also completed a last set of questionnaires outlined in Figure 2.

2.8 Self-Reported Measures

The following list of self-reported measures was administered in this study. The Alcohol Use Disorders Identification Test, the Fagerström Test of Nicotine Dependence, and the Mini International Neuropsychiatric Interview were administered during study assessment. The Beck Depression Inventory was administered at all visits to detect changes in the symptoms of depression. Subjective feelings of tobacco and alcohol cravings and withdrawal were assessed by: the Questionnaire of Smoking Urges, the Alcohol Craving Questionnaire, the Obsessive Compulsive Drinking Scale, the Minnesota Nicotine Withdrawal Scale and the Visual Analogue Scales. The Digital Symbol Substitution Task assessed attention and memory, while the Modified Stroop was used to evaluate attentional bias. Any adverse events (see Section 2.9) experienced by
subjects were reported verbally during study visits, written in the daily diary, and recorded in the 90-item Hopkins Symptoms Checklist.

1. **Alcohol Use Disorders Identification Test (AUDIT)** (Saunders, Aasland et al. 1993): The AUDIT is a 10-question test developed by the World Health Organization to evaluate the harmfulness a person’s alcohol consumption. The content of this questionnaire include the assessments of alcohol consumption, dependence, and related problems. A total AUDIT score of 8 or more in men (7 or more in women) indicate hazardous alcohol consumption, while a score of 20 or more suggest alcohol dependence. Following the AUDIT guideline, subjects who scored 8 or more were regarded as heavy drinkers in this study.

2. **Fagerström Test of Nicotine Dependence (FTND)** (Heatherton, Kozlowski et al. 1991): The FTND is a 6-item questionnaire that is used to determine a subject’s level of nicotine dependence. The FTND score rates an individual as ‘very low dependence’ with a score of 1-2; ‘low to moderate dependence’ with a score of 3; ‘moderate dependence’ with a score of 4; and ‘high dependence’ with a score of 5 or more.

3. **Beck Depression Inventory (BDI)** (Beck, Ward et al. 1961; Beck, Steer et al. 1996): The BDI is composed of 21 self-reported multiple choice questions widely used for measuring depression via the subject’s feelings for the past two weeks. The content of these questions include evaluations of sleep, appetite, suicide, sex and so forth.
The original cutoffs for the total BDI score are: minimal depression (0-13); mild depression (14-19); moderate depression (20-28); and severe depression (29-63).

4. **Mini International Neuropsychiatric Interview** (MINI) (Sheehan, Lecrubier et al. 1998): The MINI is a short structured diagnostic interview jointly developed by psychiatrists and clinicians in the United States and Europe. It examines Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Thus, the MINI was used in the assessment of subjects in our study in order to rule out any undiagnosed past or current psychiatric conditions.

5. **Questionnaire of Smoking Urges** (QSU) (Tiffany and Drobes 1991): The QSU is a 32-item questionnaire that measures desire to smoke, anticipation of positive outcomes, relief of withdrawal or negative affect and intention to smoke. Furthermore, the QSU is commonly divided into factors one and two, accounting for positive and negative reinforcement respectively (Davies, Willner et al. 2000). Factor one covers the intention and desire to smoke, while factor two provides information on the relief of negative affect and withdrawal of smoking. Throughout the study, participants completed the QSU on each of the study days (days 7, 21) after each of the conditions of baseline, one cigarette, neutral cues and tobacco-alcohol cue presentations.

6. **Alcohol Craving Questionnaire** (ACQ) (Singleton, Tiffany et al. 2000): The ACQ is a 47-item test that provides a measure of four dimensions identified in the ACQ labeled as emotionality, purposefulness, compulsivity, and expectancy. These four
dimensions are summarized as ACQ Scoring Method 1. In addition, the ACQ can evaluate five domains relevant to alcohol craving: desire to drink, intention to drink, lack of control, anticipation of positive effects, and expectancy of relief from negative effects (withdrawal). Hence the ACQ Scoring Method 2 consists of such five domains. Each question is scored on a 7-point scale ranging from “strongly disagree” to “strongly agree”. Furthermore, the ACQ measures the index of acute craving as the questions prompt the subject to evaluate their present state.

7. **Obsessive Compulsive Drinking Scale** (OCDS) (Anton, Moak et al. 1996): The OCDS is a 14-item self-rating global measure that evaluates an individual’s alcohol craving and drinking over a period of 1 or 2 weeks. There are two subscale scores that delve into the cognitive obsessive and compulsive aspects of alcohol craving. In addition, the OCDS is sensitive to the severity of an individual’s alcoholism as well as the change during abstinence and relapse drinking (Anton, Moak et al. 1996). Therefore, the OCDS is important in this study in measuring overall and longer-term alcohol craving in comparison to the ACQ and the VAS.

8. **Minnesota Nicotine Withdrawal Scale** (MNWS) (Hughes and Hatsukami 1986): The MNWS is a brief 8-item scale that measures feelings of nicotine withdrawal based on withdrawal symptoms of the DSM-IV. The MNWS is sensitive to acute changes in smoking and it is included to rule out confounding effects of nicotine withdrawal.

9. **Visual Analogue Scale** (VAS) (Folstein and Luria 1973): The VAS is a measure widely used to assess acute changes in mood. In this study, we employed a VAS for
alcohol and another VAS for nicotine at various time-points during the study days. Subjects answered the questions “I have a craving for cigarettes” and “I have a craving for alcohol” with gliders on 100-point scales where 0 = “not at all” and 100 = “extremely”.

10. **Hopkins Symptom Checklist** (HSCL-90) (Derogatis, Lipman et al. 1974): The HSCL is a 90-item questionnaire that evaluates current psychological symptoms. The nine categories in the HSCL-90 are: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic-anxiety, psychoticism, paranoia, and sleep-difficulty. Each of the 90 items is presented in a 5-point scale ranging from “not at all” to “extremely”.

11. **Alcohol and Tobacco Stroop** (STROOP) (Stroop 1935): The STROOP task is an assessment of attentional bias via a modified Stroop test composed of tobacco, alcohol and neutral words presented to subjects in a random order. In this task, words are presented in four colours and subjects are asked to name the colour of the word as quickly as possible. Increases in the reaction time for smoking or alcohol related words would suggest an attentional bias towards these words.

12. **Digital Symbol Substitution Task** (DSST) (Wechsler 1958): The DSST is a task where subjects are asked to substitute symbols for a random assortment of numbers. It was administered to subjects to assess their speed of information processing, attention and memory.
13. **Daily Diary**: The diary was designed to track an individual’s daily cigarette and alcohol consumption and cravings, as well as any experience of adverse events throughout the study. The content of this diary included time of first cigarette from waking up, time of taking medication, and so on. The data from diaries of this study are used in the analysis of consumption. Refer to Appendix 4 for an example page from the daily diary.

**2.9 Blood Cotinine**

Blood samples were taken on Study Day 1 and Study Day 2 after 12-hour overnight abstinence from subject’s last cigarette. About 10 ml of blood was drawn and the serum separated for storage. At study completion, serum samples were batched and analyzed for nicotine, cotinine, and 3’hydroxycotinine (3HC)/cotinine ratios by Dr. Rachel Tyndale’s laboratory at the University of Toronto.

Nicotine is metabolized to cotinine, which is then metabolized to 3HC by the cytochrome P450 2A6 enzyme (Nakajima, Yamamoto et al. 1996; Messina, Tyndale et al. 1997). Cotinine level in the blood has a relatively long half-life (~16 hours) with minimal fluctuations after cigarette smoking, which makes it a suitable objective indicator of ad-lib smoking (Muranaka, Higashi et al. 1988; Perez-Stable, Benowitz et al. 1995; Benowitz 1996). Genetic variations in CYP2A6 alleles can lead to an altered functional state of the enzyme. In smokers this can manifest itself as fast or slow metabolism phenotypes (Malaiyandi, Lerman et al. 2006). Smokers with more rapid metabolism require higher levels of smoking to maintain the desired levels of nicotine in
the body (Lerman, et al. 2006). The ratio of 3HC/cotinine is a phenotypic measure of CYP2A6 activity and it also correlates with a smoker’s daily smoking rate (Dempsey, Tutka et al. 2004; Lea, Dickson et al. 2006; Mooney, Li et al. 2008).

2.10 Adverse Events

Subjects reported adverse events to the study coordinator on days 14 (Mid-Study Visit) and 21 (Study Day 2), and completed the HSCL-90 form. All subjects reported common adverse events in their daily diary according to the common adverse events summarized by the varenicline product monograph. These events are: nausea, vomiting, insomnia, gas and constipation. If at any time a subject felt uncomfortable or had severe side effects, would be advised to stop the medication and consult the study physician. Additionally, subjects could withdrawal from this study at any point and for any reason. At study completion, subjects were asked to guess whether they were taking varenicline or placebo.

2.11 Ethical Considerations

The CAMH Research Ethics Board approved the present study. Each participant provided written informed consent prior to his or her enrollment. A subject number identified each participant, and all data collected in the study were kept strictly confidential. For study completion, the first nine subjects were compensated $200.00 CAD, while the remaining 15 subjects were compensated $350.00 CAD. The increase in payment was adjusted in order to increase the rate of recruitment. Furthermore, participant payment was prorated for incomplete participation: $25.00 CAD for
assessment, $100.00 CAD for Study Day 1 and $50.00 for the Mid-Study Visit. Subject who were excluded after assessment were paid $25.00 for their time.

2.12 Data Analyses

All data in the present study was analyzed using SPSS software 15.0 (SPSS Inc, Chicago, Ill). Participant characteristics were reported with descriptive statistics and differences between the varenicline and the placebo group were compared using independent samples t-test for continuous variables and cross-tabs chi-squared analyses for categorical characteristics. Study data collected on Study Day 1 are referred to as baseline. Study data collected on Study Day 2 are referred to as end of study.

The varenicline and placebo groups were analyzed before any medication was given. Subjects were compared in differences in cigarette and alcohol craving, and all study scales. Analysis of the subjective craving ratings in response to the different cue conditions was performed for all subjects in order to verify that the cue-paradigm used throughout the study was able to induce a significant increase in craving. Subjective cravings and cigarette withdrawal were analyzed with repeated measures analysis of variance.

The primary outcome of this study was to monitor tobacco and alcohol cravings for the conditions of 12-hour abstinence, after one cigarette, neutral and tobacco-alcohol cues. Tobacco craving was assessed using the Visual Analogue Scale and the Questionnaire of Smoking Urges, while the Minnesota Nicotine Withdrawal Scale
measured withdrawal. Alcohol craving was assessed using the Alcohol Craving Questionnaire and the Visual Analogue Scale with the addition of the Obsessive Compulsive Drinking Scale that measured components of alcohol drinking.

The repeated measures ANOVA in the primary analysis consisted of one between-subject factor (2 Groups: varenicline/placebo) and two within-subject factors (2 Days: baseline/end of study; 4 Time-points: abstinence/after 1 cigarette/neutral cues/tobacco-alcohol cues). Because the primary outcomes of this study is focused on cue-induced cravings, a two-part subsequent confirmatory analysis was performed using the data collected at the abstinence and after one cigarette time-points, and the neutral and tobacco-alcohol cue time-points. The first part of the confirmatory ANOVAs was composed of one between-subject factor (2 Groups: varenicline/placebo) and two within-subject factors (2 Days: baseline/end of study; 2 Time-points: abstinence/after 1 cigarette). The second part of the confirmatory ANOVAs was composed of one between-subject factor (2 Groups: varenicline/placebo) and two within-subject factors (2 Days: baseline/end of study; 2 Time-points: neutral cues/tobacco-alcohol cues). Lastly, the OCDS is analyzed by repeated measures ANOVAs consisted of one between-subject factor (2 Groups: varenicline/placebo) and one within-subject factor (2 Days: baseline/end of study) for the obsessive and the compulsive subscales separately.

The secondary outcomes aimed to track subjects’ cigarette and alcohol consumption for the duration of the study using self-completed diaries. Week 1 constituted the participants’ baseline consumption, while week 2 and 3 measured
consumption while on the study medication. The diary consumption data was analyzed with the average weekly consumptions using repeated measures ANOVAs that consisted of one between-subject factor (2 Groups: varenicline/placebo) and one within-subject factor (3 Days: baseline/mid-study/end of study). The Digital Symbol Substitution Task was analyzed using repeated measures ANOVA that consisted of one between-subject factor (2 Groups: varenicline/placebo) and one within-subject factor (2 Days: baseline/end of study). The modified Stroop task was analyzed using repeated measures ANOVA that consisted of one between-subject factor (2 Groups: varenicline/placebo) and two within-subject factors (2 Days: baseline/end of study; 3 word-types: alcohol/tobacco/neutral). Adverse events from the HSCL-90 were analyzed using a one-way ANOVA with (2 Groups: varenicline/placebo) at the end of the study. In addition, common adverse events reported in the daily diary were analyzed using a chi-squared analysis for the events with expected cell counts larger than or equal to five. For events with expected cell counts less than five, Fisher’s Exact Tests were used. The Beck Depression Inventory scores were analyzed using repeated measures ANOVA that consisted of one between-subject factor (2 Groups: varenicline/placebo) and one within-subject factor (4 Days: assessment/baseline/mid-study/end of study). Finally, the blood nicotine and cotinine analysis was analyzed using repeated measures ANOVA that consisted of one between-subject factor (2 Groups: varenicline/placebo) and one within-subject factor (2 Days: baseline/end of study). The criteria for significance in the data analyses constituted two-tailed alpha of 0.05.
3.0 Results

3.1 Participants

A total of 24 participants (16 males, 6 females) completed the study. The sample ethnicity was 74.9% White, 16.7% Asian, 4.2% Hispanic, and 4.2% Canadian aboriginal. In the varenicline group, the mean age was 32.2 ± 9.9 years, 69% were males, the average number of cigarettes smoked per day was 19.2 ± 5.6 with FTND score of 5.6 ± 1.7; and the average number of standard alcoholic drinks per week was 23.9 ± 4.6 with an average AUDIT score of 14.9 ± 3.8. In the placebo group, the mean age was 40.7 ± 11.6 years, 64% were males, the average number of cigarettes smoked per day was 17.8 ± 5.5 with FTND score of 5.5 ± 2.0; and the average number of standard alcoholic drinks per week was 25.2 ± 7.5 with an average AUDIT score of 11.9 ± 3.7. See Table 3.1.

There were no significant differences between groups on demographics, smoking and alcohol use characteristics with the exception that the placebo group smoked for significantly longer than the varenicline group (26.7±11.1 vs. 15.7±9.5 years, p=0.02). There was a trend for the placebo group to be older than the varenicline group (40.7±11.6 vs. 32.2±9.9 years, p=0.06) and a trend for the placebo group to have been drinking (any amounts of alcohol) longer than the varenicline group (25.2±10.0 vs. 18.0±9.0, p=0.07). The mean GGT level in the placebo group was higher than the healthy range of 15-85 U/L, driven by one individual with a very high GGT level.
Table 3.1 Baseline demographic characteristics with tobacco and alcohol history

<table>
<thead>
<tr>
<th></th>
<th>Varenicline (N=13)</th>
<th>Placebo (N=11)</th>
<th>P</th>
<th>All subjects (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>32.2 (9.9)</td>
<td>40.7 (11.6)</td>
<td>0.06</td>
<td>36.1 (11.3)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>69%</td>
<td>64%</td>
<td>0.83</td>
<td>66.7%</td>
</tr>
<tr>
<td>Education (% College)</td>
<td>62%</td>
<td>73%</td>
<td>0.20</td>
<td>67.0%</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>76.9%</td>
<td>72.7%</td>
<td>0.81</td>
<td>74.9%</td>
</tr>
<tr>
<td>Asian</td>
<td>15.4%</td>
<td>18.2%</td>
<td>0.86</td>
<td>16.7%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.0%</td>
<td>9.1%</td>
<td>0.26</td>
<td>4.2%</td>
</tr>
<tr>
<td>Aboriginal Canadian</td>
<td>7.7%</td>
<td>0.0%</td>
<td>0.34</td>
<td>4.2%</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td>19.2 (5.6)</td>
<td>17.8 (5.5)</td>
<td>0.55</td>
<td>18.6 (5.5)</td>
</tr>
<tr>
<td>FTND scores</td>
<td>5.6 (1.7)</td>
<td>5.5 (2.0)</td>
<td>0.84</td>
<td>5.5 (1.8)</td>
</tr>
<tr>
<td>Years smoked *</td>
<td>15.7 (9.5)</td>
<td>26.7 (11.1)</td>
<td>*0.02</td>
<td>20.8 (11.5)</td>
</tr>
<tr>
<td>No. of quit attempts</td>
<td>4.1 (3.2)</td>
<td>5.4 (8.4)</td>
<td>0.61</td>
<td>4.7 (6.0)</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinks per week</td>
<td>23.9 (4.6)</td>
<td>25.2 (7.5)</td>
<td>0.51</td>
<td>24.5 (6.0)</td>
</tr>
<tr>
<td>AUDIT scores</td>
<td>14.9 (3.8)</td>
<td>11.9 (3.7)</td>
<td>0.06</td>
<td>13.5 (3.9)</td>
</tr>
<tr>
<td>Years drinking</td>
<td>18.0 (9.0)</td>
<td>25.2 (10.0)</td>
<td>0.07</td>
<td>21.3 (10.0)</td>
</tr>
<tr>
<td>Liver Enzyme</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>45.8 (27.3)</td>
<td>39.6 (15.3)</td>
<td>0.52</td>
<td>42.3 (22.1)</td>
</tr>
<tr>
<td>AST</td>
<td>23.3 (9.3)</td>
<td>24.6 (6.5)</td>
<td>0.72</td>
<td>23.9 (7.9)</td>
</tr>
<tr>
<td>ALP</td>
<td>85.3 (17.9)</td>
<td>104.1 (19.6)</td>
<td>0.08</td>
<td>94.3 (25.5)</td>
</tr>
<tr>
<td>GGT</td>
<td>38.4 (22.3)</td>
<td>**112.3 (167.6)</td>
<td>0.14</td>
<td>73.7 (120.2)</td>
</tr>
</tbody>
</table>

Table 3.1 Mean (SD) scores of baseline characteristics. ALT: alanine transaminase; AST: aspartate transaminase; ALP: alkaline phosphatase; GGT: gamma glutamyl transpeptidase. *The placebo group had smoked longer than the varenicline group (p=0.02). ** High variability in the GGT of the placebo group is driven by one subject whose GGT level was more than 2 standard deviations from the mean.
3.2 Baseline Comparisons (Study Day 1)

3.2.1 Baseline: Cigarette and Alcohol Craving

At baseline (Study Day 1), the varenicline group had significantly higher cigarette cravings following overnight (12h) abstinence compared to the placebo group using the VAS questionnaire \[t(22) = -2.643, p=0.015\]. Cigarette craving at all other time points was not significantly different \((p>0.1)\) between groups. Alcohol cravings at all time points were not significantly different \((p>0.3)\) between drug groups. This is shown in Figure 3.2.1. Other craving measures collected (QSU, ACQ, and VAS-alcohol) in cigarette and alcohol cravings demonstrated similar results.

Figure 3.2.1-A. Baseline Comparison Between Drug Groups for Cigarette and Alcohol Craving

Figure 3.2.1 Mean bars (±SD) for baseline pre-medication comparison between groups. Cig: cigarette craving; Alc: alcohol craving; Abs: 12-h abstinence; Cig: after 1 cigarette; Neu: neutral cues; tob-alc: tobacco-alcohol cues. Varenicline group had significantly * \((p=0.015)\) higher abstinence cigarette craving.
3.2.2 Cue-Paradigm

The study cue-paradigm elicited both cigarette and alcohol cravings on the first study day. There was increases in both cigarette \([t(23)=3.17, p=0.004]\) and alcohol \([t(23)=4.93, p<0.001]\) cravings from the neutral to tobacco-alcohol cue condition. For cigarette craving (max. 100), the mean score \(\pm SD\) for the neutral cue was 41.8 \(\pm 25.5\) and this increased to 50.8 \(\pm 27.9\) after the tobacco-alcohol cue condition. Similarly, the mean score for alcohol craving (max. 100) in the neutral condition was 13.5 \(\pm 17.0\) and 34.6 \(\pm 28.3\) for the tobacco-alcohol cues. This is shown in Figure 3.3.2.

![Figure 3.3.2 Comparison of Cue Conditions](image)

**Figure 3.3.2** Mean VAS craving score bars \((\pm SD)\) for all subjects measured at baseline. The cue-paradigm significantly increased cigarette * \((p=0.004)\) and alcohol ** \((p<0.001)\) craving.
3.3 Primary Outcomes

3.3.1 Tobacco Primary Outcomes

3.3.1.1 Visual Analogue Scale (VAS) – Cigarette Craving

The primary 2x2x4 ANOVA analysis showed a main effect of day associated with a decreased VAS-craving score at the end of study compared to baseline \([F(1,22)=8.26, p=0.009]\). There was also a main effect of time-point associated with different VAS craving scores amongst the conditions \([F(3,20)=32.13, p<0.001]\). The varenicline group had significantly more craving at the baseline abstinence condition \((p=0.015)\). There were significant day*drug \([F(1,22)=7.14, p=0.014]\) and day*time-point \([F(3,20)=4.99, p=0.010]\) interactions associated with decreased craving in subjects receiving varenicline compared to placebo at the end of the study compared to baseline. These interactions seem to be driven by the higher VAS score in the varenicline group at baseline \((p=0.015)\). This is shown in Figure 3.3.1.1.

The subsequent 2x2x2 ANOVA (with only the first two time points, Appendix 7) showed a main effect of time-point associated with decreased VAS craving following the administration of a cigarette compared to the 12-hour abstinence baseline \([F(1,22)=96.16, p<0.001]\). There were significant day*drug \([F(1,22)=6.61, p=0.017]\), time-point*drug \([F(1,22)=4.97, p=0.036]\) and day*time-point \([F(1,22)=4.71, p=0.041]\) interactions associated with decreased craving in patients receiving varenicline compared to placebo and at the end of study compared to baseline. These interactions seemed to be driven by the higher VAS craving score in the varenicline group at baseline \((p=0.015)\).
The 2x2x2 ANOVA (with only the two cue conditions, Appendix 7) showed a main effect of day associated with a decreased VAS-craving score at the end of the study compared to baseline \[F(1,22)=11.29, p=0.003\] and a main effect of time-point associated with increased VAS craving following the presentation of tobacco-alcohol cues compared to neutral cues \[F(1,22)=11.09, p=0.003\]. There was a significant day*drug \[F(1,22)=5.50, p=0.028\] interaction associated with decreased craving in patients receiving varenicline compared to placebo.

![Figure 3.3.1.1 Comparison of Cigarette Craving Between Drug Groups](image)

**Figure 3.3.1.1** (B: baseline, E: end of treatment) Mean Visual Analogue Scale craving score bars (±SD) in response to the single-item: “I am craving a cigarette”. 
3.3.1.2 Questionnaire of Smoking Urges (QSU)

*QSU Factor 1: Desire to smoke*

The primary 2x2x4 ANOVA analysis for the desire to smoke showed a main effect of day associated with a decreased QSU Factor 1 score at the end of study compared to baseline \[F(1,22)=16.08, \ p=0.001\]. There was also a main effect of time-point associated with different QSU (Factor 1: desire to smoke) craving scores amongst the conditions \[F(3,20)=28.38, \ p<0.001\]. This is shown in Figure 3.3.1.1-A.

The subsequent 2x2x2 ANOVA for the desire to smoke (with only the first two time points, Appendix 7) showed main effects of day associated with decreased desire to smoke at the end of the study compared to baseline \[F(1,22)=10.03, \ p=0.004\] and a main effect of time-point associated with decreased desire to smoke following a cigarette compared to abstinence baseline \[F(1,22)=66.87, \ p<0.001\]. The 2x2x2 ANOVA for the desire to smoke (with only the two cue conditions, Appendix 7) showed a main effect of day associated with a decreased desire to smoke at the end of the study compared to baseline \[F(1,22)=12.59, \ p=0.002\] and a main effect of time-point associated with increased desire to smoke following the presentation of tobacco-alcohol cues compared to neutral cues \[F(1,22)=13.11, \ p=0.002\].

*QSU Factor 2: Relief of negative affect or withdrawal by smoking*

The primary 2x2x4 ANOVA analysis showed a main effect of day associated with a decreased QSU Factor 2 score at the end of study compared to baseline \[F(1,22)=9.73, \ p=0.005\]. There was also a main effect of time-point associated with different QSU
Factor 2 scores amongst the conditions [F(3,20)=15.85, p<0.001]. This is shown in Figure 3.3.1.1-B.

The subsequent 2x2x2 ANOVA for the relief of negative affect (with only the first two time points, Appendix 7) showed main effects of day associated with decreased negative affect at the end of the study compared to baseline [F(1,22)=5.63, p=0.027] and a main effect of time-point associated with decreased negative affect following a cigarette compared to abstinence baseline [F(1,22)=48.96, p<0.001]. The 2x2x2 ANOVA for the relief of negative affect (with only the two cue conditions, Appendix 7) showed a main effect of day associated with a decreased in negative affect at the end of the study compared to baseline [F(1,22)=8.88, p=0.007].
Figure 3.3.1.2-A. Comparison of Intention & Desire to Smoke (QSU Factor 1) Between Drug Groups

2x2x4 ANOVA
day, p=0.001
time-point, p<0.001

Figure 3.3.1.2-B. Comparison of Relief of Negative Affect & Withdrawal of Smoking (QSU Factor 2) Between Drug Groups

2x2x4 ANOVA
day, p=0.005
time-point, p<0.001

Figure 3.3.1.2 Mean QSU scores (±SD). B: baseline, E: end of treatment. A) Questionnaire of Smoking Urges Factor 1: intention & desire to smoke scores B) Questionnaire of Smoking Urges Factor 1: relief of negative affect & withdrawal scores
3.3.1.3 Minnesota Nicotine Withdrawal Scale (MNWS)

The primary 2x2x4 ANOVA analysis for nicotine withdrawal showed a main effect of day associated with a decreased MNWS score at the end of study compared to baseline [F(1,22)=10.30, p=0.004]. There was also a main effect of time-point associated with different MNWS scores amongst the conditions [F(3,20)=7.08, p=0.002]. This is seen in Figure 3.3.1.3-A.

The subsequent 2x2x2 ANOVA for nicotine withdrawal (with only the first two time points, Appendix 7) showed main effects of day associated with decreased nicotine withdrawal at the end of the study compared to baseline [F(1,22)=7.12, p=0.014] and a main effect of time-point associated with decreased nicotine withdrawal following a cigarette compared to abstinence baseline [F(1,22)=22.05, p<0.001]. The 2x2x2 ANOVA for nicotine withdrawal (with only the two cue conditions, Appendix 7) showed a main effect of day associated with a decreased nicotine withdrawal at the end of the study compared to baseline [F(1,22)=11.01, p=0.003].

Nicotine withdrawal in all subjects across time-points was compared. There were significant reductions in withdrawal from abstinence compared to after one cigarette at the baseline # [t(23)=3.74, p=0.001] and end of treatment # # [t(23)=3.51, p=0.002] sessions. However, there were no significant changes in total group nicotine withdrawal between the neutral and tobacco-alcohol cue conditions at both the baseline day (p>0.5, NS) and the end of treatment day (p>0.4, NS). Thus nicotine withdrawal was consistent across presentation of neutral and tobacco-alcohol cues. This is shown in Figure 3.3.1.3-B.
Figure 3.3.1.3-A. Comparison of Minnesota Nicotine Withdrawal Scale Scores Between Drug Groups

2x2x4 ANOVA 2x2x2 Confirmatory
day, p=0.004 ANOVA time-point, p=0.002 day, p=0.003

Figure 3.3.1.3-B. Comparing Nicotine Withdrawal in All Subjects

Baseline End of Treatment

Figure 3.3.1.3 A) Mean MNWS (±SD) (B: baseline, E: end of treatment). B) Withdrawal comparison in all subjects across time-points on both study days. Significant reduction in withdrawal from baseline to after 1 cigarette at baseline # (p=0.001) and end of treatment ## (p=0.002)
3.3.2 Alcohol Primary Outcomes

3.3.2.1 Alcohol Craving Questionnaire (ACQ)

ACQ Method 1: Emotionality aspects of alcohol craving

The primary 2x2x4 ANOVA analysis for the emotionality of alcohol craving showed a main effect of time-point associated with a decreased ACQ Method 1 score amongst the conditions [F(3,20)=12.98, p<0.001]. This is seen in Figure 3.3.2.1-A.

The subsequent 2x2x2 ANOVA for the emotionality of alcohol craving (with only the first two time points, Appendix 7) showed a significant day*time-point*drug interaction [F(1,22)=4.42, p=0.047] associated with decreased emotionality of alcohol craving in patients receiving varenicline compared to placebo after smoking a cigarette compared to abstinence. The 2x2x2 ANOVA for the emotionality of alcohol craving (with only the two cue conditions, Appendix 7) showed a main effect of time-point associated with increased emotionality of alcohol craving following the presentation of tobacco-alcohol cues compared to neutral cues [F(1,22)=40.69, p<0.001].

ACQ Method 2: Desire to drink

The primary 2x2x4 ANOVA analysis for desire to drink showed a main effect of time-point associated with different craving scores amongst the conditions [F(3,20)=12.87, p<0.001]. This is shown in Figure 3.3.2.1-B.

The subsequent 2x2x2 ANOVA for desire to drink (with only the first two time points, Appendix 7) found no significant main effects or interactions. The 2x2x2
ANOVA for desire to drink (with only the two cue conditions, Appendix 7) showed a main effect of time-point associated with increased emotionality of alcohol craving following the presentation of tobacco-alcohol cues compared to neutral cues [F(1,22)=40.87, p<0.001]. There was a significant day*time-point interaction [F(1,22)=4.707, p=0.041] associated with a decreased desire to drink at the end of the study compared to baseline after the tobacco-alcohol cues.
Figure 3.3.2.1-A. Comparison of Emotionality Aspects of Alcohol Consumption (ACQ Method 1) Between Groups

![Figure 3.3.2.1-A. Comparison of Emotionality Aspects of Alcohol Consumption (ACQ Method 1) Between Groups](image)

2x2x4 ANOVA time-point, p<0.001

Figure 3.3.2.1-B. Comparison of Desire & Intention to Drink Aspects (ACQ Method 2) Between Groups

![Figure 3.3.2.1-B. Comparison of Desire & Intention to Drink Aspects (ACQ Method 2) Between Groups](image)

2x2x4 ANOVA time-point, p<0.001

**Figure 3.3.2.1** (B: baseline, E: end of treatment) Mean ACQ bars (±SD) for subjects in each group. **A)** Method 1 scores.  **B)** Method 2 scores
3.3.2.2 Visual Analogue Scale (VAS) – Alcohol Craving

The primary 2x2x4 ANOVA for single-item alcohol craving analysis showed a main effect of time-point associated with different VAS craving scores amongst the conditions [F(3,20)=7.08, p=0.002]. There was a significant day*time-point [F(3,20)=3.66, p=0.03] interaction associated with decreased craving at the end of the study compared to baseline. This is shown in Figure 3.3.2.2.

The subsequent 2x2x2 ANOVA for alcohol craving (with only the first two time points, Appendix 7) showed no significant main effects or interactions. The 2x2x2 ANOVA (with only the two cue conditions, Appendix 7) showed a main effect of time-point associated with increased VAS alcohol craving following the presentation of tobacco-alcohol cues compared to neutral cues [F(1,22)=22.88, p<0.001]. There was a significant day*time-point [F(1,22)=11.69, p=0.002] interaction associated with decreased craving in the tobacco-alcohol cue-induced craving at the end of the study compared to baseline.
Figure 3.3.2.2 (B: baseline, E: end of treatment) Mean VAS alcohol craving score bars (±SD) for subjects in each group in response to the single-item “I have a craving for alcohol”.

2x2x4 ANOVA

time-point, p=0.002
day x time-point, p=0.030
3.3.2.3 Obsessive Compulsive Drinking Scale (OCDS)

The 2x2 ANOVA for the obsessive subscale produced no significant main effects or interactions. Similarly, the 2x2 ANOVA for the compulsive subscale also produced no significant main effects or interactions. There were no significant differences between the drug groups for the total score or any of the subscales (p>0.2, NS). The OCDS for alcohol craving agreed with the ACQ and the VAS acute alcohol craving across the scales. Thus, the OCDS showed that the two-week administration of varenicline had no effect on the long-term alcohol craving. This can be seen in Figure 3.3.2.3.

Figure 3.3.2.3 Comparison of Obsessive Compulsive Drinking Scale (OCDS) Between Drug Groups

2x2 ANOVAs for each subscale: No main effects or interactions

Figure 3.3.23 Mean OCDS score bars (±SD) for subjects in each group.
3.4 Secondary Outcomes

3.4.1 Diary: Cigarettes & Alcohol Consumption

The baseline period (week 1) for the cigarette and alcohol consumption showed no significant changes between day 1 and day 7 in both cigarette (p= 0.781, NS) and alcohol (p=0.327, NS) consumptions for all participants. This is shown in Table 3.4.1.

<table>
<thead>
<tr>
<th></th>
<th>Mean (±SD)</th>
<th>Day 1</th>
<th>Day 7</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarettes</td>
<td>16.8 (±5.1)</td>
<td>16.3 (±9.3)</td>
<td>t(23)=0.28, p=0.781</td>
<td></td>
</tr>
<tr>
<td>Alcoholic drinks</td>
<td>5.0 (±3.7)</td>
<td>3.9 (±3.7)</td>
<td>t(23)=1.00, p=0.327</td>
<td></td>
</tr>
</tbody>
</table>

In addition, the mean ±SD number of cigarettes smoked per day for the placebo group decreased from 17.8 ±5.9 during the baseline week to 11.9 ±5.0 at the end of study. The mean number of cigarettes smoked per day for the varenicline group decreased from 16.1 ±5.8 to 10.6 ±5.8 at the end of study. Furthermore, the mean total of alcoholic drinks consumed per week for the placebo group was 27.6 ±10.0 at baseline and 24.6 ±12.7 at the end of study. Lastly, the mean total of alcoholic drinks consumed per week for the varenicline group decreased from 27.6 ±8.5 at baseline to 21.2 ±10.9 at the end of study.
**Figure 3.4-A. Comparison of Average Cigarette Smoked Per Day Between Drug Groups**

2x3 ANOVA
Day, p<0.001

**Figure 3.4-B. Comparison of Total Alcoholic Drinks Consumed Per Week Between Drug Groups**

2x3 ANOVA
Day, p=0.023

---

**Figure 3.4 A)** Mean (±SD) cigarette smoked per day. **B)** Mean (±SD) alcoholic drinks consumed per week.
The 2x3 ANOVA for cigarette consumption showed a main effect of day associated with a decreased number of cigarettes smoked at the end of study compared to baseline [F(2,21)=14.15, p<0.001]. See Figure 3.4-A. In addition, the 2x3 ANOVA for alcohol consumption showed a main effect of day associated with a decreased number of drinks consumed at the end of study compared to baseline [F(2,21)=4.52, p=0.023]. See Figure 3.4-B.

Although the daily diary prompted participants for information on time of first cigarette, situation of each cigarette, and time of waking up, majority of the participants did not complete those details. Instead of evaluating time of first cigarette in terms of nicotine dependence, the FTND score is used instead. The 2x2 ANOVA for FTND nicotine dependence showed a main effect of day associated with a decreased nicotine dependence score at the end of study compared to baseline [F(1,22)=30.41, p<0.001].

3.4.2 Nicotine and Cotinine Analysis

The 2x2s ANOVA for plasma nicotine, cotinine levels and the 3HC/Cotinine ratio did not show any significant main effects or interactions. These values are displayed in Table 3.4.2.

<table>
<thead>
<tr>
<th></th>
<th>Nicotine Baseline (ng/mL)</th>
<th>Nicotine End of Study (ng/mL)</th>
<th>Cotinine Baseline (ng/mL)</th>
<th>Cotinine End of Study (ng/mL)</th>
<th>3HC/Cotinine Ratio Baseline (ng/mL)</th>
<th>3HC/Cotinine Ratio End of Study (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>13.3 (±4.6)</td>
<td>14.1 (±5.9)</td>
<td>109.3 (±65.8)</td>
<td>112.8 (±94.3)</td>
<td>0.50 (±0.3)</td>
<td>0.49 (±0.3)</td>
</tr>
<tr>
<td>Varenicline</td>
<td>13.9 (±6.5)</td>
<td>10.7 (±5.1)</td>
<td>90.4 (±60.9)</td>
<td>59.0 (±35.6)</td>
<td>0.59 (±0.2)</td>
<td>0.59 (±0.2)</td>
</tr>
</tbody>
</table>
3.5 Tertiary Outcomes

3.5.1 Adverse Events

One way ANOVA analysis at the end of study showed no significant differences between varenicline and placebo group for all of the subcategories. This is shown in Figure 3.5.1-A.

**Figure 3.5.1-A. Comparison of HSCL-90 Components Between Groups**

![Graph showing mean scores of HSCL-90 categories.](image)

**Figure 3.5.1-A.** Mean (±SD) scores of HSCL-90 categories. 1: mid-study; 2: end of study. Soma: somatization; Obcom: obsessive-compulsive; Intsens: interpersonal sensitivity; Dep: depression; Anx: anxiety; Anghos: anger-hostility; Phoanx: phobic-anxiety; Psycho: psychoticism; Paranid: paranoia; Sleepdiff: sleep-difficulty.
There were no significant associations between drug group and any of the common adverse events: nausea (Fisher’s Exact, $p=0.185$), vomiting (Fisher’s Exact, $p=0.565$), insomnia (Fisher’s Exact, $p=0.300$), gas [$X^2(1)=0.001$, $p=0.973$], and constipation (Fisher’s Exact, $p=0.585$). This is shown in Figure 3.5.1-B.

**Figure 3.5.1.-B. Comparison of Common Adverse Events Between Groups**

![Graph comparing common adverse events between placebo and varenicline groups](image)

**Figure 3.5.1-B.** Percentages of reported common adverse events in all subjects.
3.5.2 Beck Depression Inventory (BDI)

The 4x2 repeated ANOVA for the Beck Depression Inventory showed no significant main effects or interactions. Varenicline did not influence participants’ depression symptoms throughout the 21-days study period. This is shown in Figure 3.5.2.

Figure 3.5.2 Comparison of Beck Depression Inventory Between Groups

![Figure 3.5.2 Comparison of Beck Depression Inventory Between Groups](image)

**Figure 3.5.2 Mean (±SD) bars for BDI scores.** No significant differences between drug groups at all days and no significant changes in BDI scores before and after treatment.
3.5.4 Cognitive Measures

3.5.4.1 Digital Symbol Substitution Task (DSST)

The varenicline group had significantly higher DSST scores compared to the placebo group for both baseline \([t(22)=2.59, p=0.017]\) and end of treatment \([t(22)=2.36, p=0.028]\). The 2x2 ANOVAs showed no significant main effects or interactions. The two-week varenicline treatment did not affect participants’ speed of information processing, attention and memory. This is shown in Table 3.5.4.1.

Table 3.5.4.1 The DSST Scores of All Participants

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Completed</td>
<td>Correct</td>
</tr>
<tr>
<td>Placebo</td>
<td>21.36 (±4.8)</td>
<td>20.73 (±4.9)</td>
</tr>
<tr>
<td>Varenicline</td>
<td>25.77 (±3.5)</td>
<td>25.38 (±3.5)</td>
</tr>
</tbody>
</table>

3.5.4.2 Modified Stroop Task

The 2x2x3 repeated ANOVA analysis showed a main effect of day associated with a decreased reaction time (milliseconds) at the end of study compared to baseline \([F(2,21)=4.86, p=0.038]\). There was also a main effect of word-type associated with different reaction times amongst tobacco, alcohol and neutral words \([F(2,21)=3.41, p=0.042]\). This is shown in Figure 3.5.4.2.
3.5.5 End of Study Information

Medication compliance was confirmed using a pill count box and self-report. Unused medications were returned to the study pharmacy. Furthermore, subjects were prompted to guess whether they were randomized to placebo or varenicline at study completion. Only 1 subject could not guess whether they’ve received varenicline or placebo. For those in the varenicline group, 69.2% guessed correctly due to the presence of adverse events. Similarly, 54.5% of the placebo group guessed they received placebo. Lastly, a total of two subjects in the sample of twenty-four who completed this study enrolled themselves as clients at the Nicotine Dependence Clinic of CAMH to receive treatment for smoking cessation.
4. Discussion, Conclusions, & Recommendations

4.1 General Discussion

This study aimed to investigate the effect of a 2-week varenicline administration on cue-induced tobacco and alcohol cravings and cigarette and alcohol consumption in daily smokers who are also heavy drinkers. It was found that two weeks of varenicline administration reduced cue-induced craving for cigarettes. Two weeks of varenicline decreased alcohol craving after smoking a cigarette compared to abstinence condition, but it alcohol cue-induced craving was not affected. Also, all participants decreased in cigarette and alcohol consumption at the end of study compared to baseline.

There were no significant differences in baseline and demographics between medication groups with the exception that participants in the placebo group smoked for significantly longer and had a trend towards a longer history of drinking. This was likely related to the placebo group being approximately 8 years older; while not statistically significant there was a trend in age differences. Despite the age difference between groups there were no differences in baseline levels of nicotine and alcohol dependence, or consumption. Hence this is not likely to have impacted other findings reported here. There was also a difference in baseline 12-hour abstinence cigarette craving on the VAS such that the varenicline group had greater level of craving. Baseline abstinence craving according to the QSU was similar to that reported by the VAS, although there were no statistically significant differences between the groups. It is possible that baseline cigarette craving differences between the varenicline and placebo groups influenced results related to cigarette cravings. However, all subjects reported very similar cravings
after smoking one cigarette and hence they entered the cue conditions with similar craving levels. It is also possible that subjects in the varenicline group were more perceptive to cigarette cravings. Nicotine withdrawal for all subjects reduced significantly after smoking one cigarette compared to the abstinence condition; for both the baseline and the end of treatment study days. This particular result showed that by administrating the cigarette break, we eliminated any ceiling effects of nicotine withdrawal in these daily smokers. In addition, the MNWS scores were not significantly different between the neutral to tobacco-alcohol cue conditions for both baseline and the end of treatment. This suggests that nicotine withdrawal was not differentially affecting responses during the two cue conditions.

The finding that varenicline was associated with decreased craving is consistent with previous studies that showed varenicline reduces general background smoking urges and craving (Gonzales, Rennard et al. 2006; Jorenby, Hays et al. 2006; West, Baker et al. 2008). However, we also reported that varenicline was associated with decreases in cue-induced cigarette craving. In fact, to our knowledge, there has been only one study that evaluated the impact of varenicline on cigarette cue-provoked craving in smokers not interested in quitting (Niaura, Hitsman et al. 2007). In the study by Niaura and colleagues, acute varenicline administration decreased background nicotine craving but had no effect on cue-induced nicotine craving. This is in contrast to our findings. One possible explanation of the divergent results could be the usage of a single dosage of varenicline in the study by Niaura et al. Despite the fact that Niaura and colleagues had assessed cue-reactivity 4 hours after dosing (in order for varenicline to reach maximum
plasma concentrations), it is possible that even at peak concentration single doses of varenicline are not able to influence cue-induced craving. This study utilized a multiple dosing strategy that allowed for varenicline to reach steady state (which occurs after four days). Hence, the results from Niaura and colleagues concerning varenicline’s influence on cue-induced cigarette cravings may be due to inadequate dosing. Another possible factor that influenced the divergent result in the present study may be the comorbidity with tobacco and alcohol. Research has consistently agreed on the complex relationship in cue-induced cravings of cigarettes and alcohol (Field, Mogg et al. 2005; Sayette, Martin et al. 2005; Erblich, Montgomery et al. 2009). In particular, alcohol has been shown to increase cognitive biases, urges to smoke, emotional valence, and incentive salience of smoking cues in smokers (Robinson and Berridge 1993; Burton and Tiffany 1997; Mogg, Bradley et al. 2003; Field, Mogg et al. 2004; Field, Mogg et al. 2005). Furthermore, alcohol alone was found to dose-dependently increase urge to smoke in heavy social drinking smokers who are not nicotine dependent (King, McNamara et al. 2009). Drinking cues have also induced cigarette craving as well as alcohol craving (Rohsenow, Monti et al. 1997; Erblich, Montgomery et al. 2009; King, McNamara et al. 2009). In addition to conditioning effects of mixed tobacco-alcohol cues, the importance of alcohol in tobacco craving may be due to a shared neurobiological mechanism since both drinking and smoking activate dopaminergic neurotransmission in the ventral tegmental area (Pomerleau 1992).

In relation to other smoking cessation aids, varenicline may be more effective in curbing craving. Nicotine patch (Tiffany, Cox et al. 2000; Havermans and Jansen 2003;
Morissette, Palfai et al. 2005; Rohsenow, Monti et al. 2007) and bupropion (Durcan, Deener et al. 2002; Hussain, Zawertailo et al. 2009) were found to reduce only background craving but not in vivo visual and olfactory cue-induced cravings. Nicotine gum and lozenge (Durcan, De'Ath et al. 2003; Shiffman, Shadel et al. 2003; Niaura, Sayette et al. 2005) studies have yielded mixed results, however they are likely to be used as rescue aids in reducing the intensity of craving episodes while they arise rather than functioning as preventing cue-induced cravings in smokers.

Our results with regards to alcohol are consistent with previous studies of heavy drinkers and alcohol dependent individuals that have demonstrated that alcohol cues can elicit alcohol related craving (Drummond, Cooper et al. 1990; Childress, Hole et al. 1993; Glautier and Drummond 1994; Streeter, Gulliver et al. 2002; Fox, Bergquist et al. 2007). Subjects who received varenicline decreased in alcohol cravings after smoking a cigarette compared to abstinence. This suggests that varenicline may decrease alcohol cravings in smokers who usually pair cigarettes and alcohol together. In addition, we found varenicline had no effects on cue-induced alcohol cravings. However, the power calculation in the present study was based on cigarette cue-induced cravings and thus may not be powered to detect alcohol cue-induced cravings.

To our knowledge, there are no previous randomized clinical trials that have evaluated the influence of a two-week varenicline administration on tobacco and alcohol mixed cue-induced alcohol cravings. In a behavioural paradigm, McKee et al. found that one week of varenicline administration reduced alcohol self-administration and alcohol
rewarding effects (McKee, Harrison et al. 2009). Based on their findings one may expect to see a decrease in alcohol craving associated with varenicline administration. However, our results do not support this. Furthermore, heavy-drinking smokers are often exposed to mixed cues in their natural environments. Thus, the present study’s cue-paradigm may be better in reflecting real life situations. While McKee’s sample of heavy-drinking smokers had similar cigarette use and dependence, smokers in the present study scored considerably higher in alcohol use scores (varenicline group AUDIT: 14.9 ± 3.8) compared to McKee’s smokers (varenicline group AUDIT: 10.3 ± 4.2). Also, McKee’s study had excluded participants with alcohol dependence and treatment seeking for either alcohol or smoking, whereas the current study did not hold such criteria. Hence, it is plausible to infer that the current study may better reflect the nature of the heavy-drinking smokers and can thus be more generalized to such population.

Our results support previous research in that visual, tactile and olfactory stimuli cues can reliably elicit strong urges to smoke (Niaura, Shadel et al. 1998; Carter and Tiffany 1999; Sayette, Martin et al. 2001; Bailey, Goedeker et al. 2009) and alcohol cravings (Drummond, Cooper et al. 1990; Childress, Hole et al. 1993; Glaunier and Drummond 1994) under laboratory conditions. This is also supported by evidence from functional neuroimaging studies in that visual and olfactory cues associated with nicotine, alcohol and other drug use have elicited robust activations in the nucleus accumbens and ventral striatum (David, Munafo et al. 2005; Franklin, Wang et al. 2007). Our results not only support the evidence that repeated days of smoking cue exposure induces urge to smoke on separate days (Miranda, Rohsenow et al. 2008), they also confirm the same for
alcohol. Since previous studies found that smoking imagery induced both cigarette and alcohol cravings (Gulliver, Rohsenow et al. 1995; Drobes 2002; Field, Mogg et al. 2005; Erblich, Montgomery et al. 2009), we combined the tobacco and alcohol cues together in this study to address the comorbid nature of the population of smokers who consume alcoholic drinks heavily. Thus, it is possible that daily smoking heavy drinkers experience more craving from mixed tobacco and alcohol cues, and they may have a stronger response to varenicline’s effects.

Varenicline administration (two weeks) did not influence cigarette or alcohol consumption in this study compared to placebo. Analysis of the one week baseline data (pre-medication) also did not reveal significant changes in either cigarette or alcohol consumption. There was a general decrease in self-reported cigarette and alcohol consumption in all participants; this may be due to placebo effects. A possible explanation for the reduction in consumption is that subjects needed to be interested in quitting smoking to participate. Therefore, the subjective reports of cigarette reduction in both groups could be due to self-motivation. Measuring blood cotinine levels is an objective method to supplement the subjective diary reports of cigarette consumption. There appears to be a decrease in cotinine levels for subjects who received varenicline at the end of study compared to baseline, but this did not reach significance in the ANOVA. There were no significant differences in 3HC/Cotinine ratios with small variability between groups, indicating all participants had similar speed of nicotine metabolism.
To our knowledge, there is no previous research that investigated the influence of varenicline on alcohol consumption over multiple days. Our results do not support preclinical studies that found varenicline reduced alcohol seeking and consumption (Steensland, Simms et al. 2007), or its effects in cognitive interactions (Ericson, Lof et al. 2009). Steensland had argued that since varenicline reduces nicotine reward as a partial agonist on the $\alpha 4\beta 2$ nAChR, it could play a role in the modulation of alcohol consumption. One reason could be that the varenicline dosage used was recommended for smoking cessation and it is possible a different dosing strategy would be required to show alcohol related effects in humans. Preclinical investigations still have not found dose-effect relationships with varenicline in alcohol consumption or dopamine response (Steensland, Simms et al. 2007). In another pre-clinical study, Le and colleagues investigated the effects of dihydro-beta-erythroidine (DH$\beta$E), a competitive nicotinic antagonist on alcohol consumption in rats (Le, Corrigall et al. 2000). They found DH$\beta$E failed to influence alcohol consumption and it was suggested that alcohol-tobacco interaction may not be mediated by the $\alpha 4\beta 2$ receptor subtype (Le, Corrigall et al. 2000).

Our results are similar to a recent longitudinal community study that found quitting smoking is associated with reduced heavy drinking (Karlamangla, Zhou et al. 2006). Since alcohol drinks are often consumed together with cigarettes in participants of the current study, there was also a reduction in alcohol consumption. In support, a clinical trial testing the efficacy of a smoking cessation treatment using nicotine replacement therapy in a large sample of heavy drinkers suggested that initiation of smoking cessation can provide an opportunity for heavy drinkers to change alcohol
consumption (Kahler, Metrik et al. 2008). Another possible contributing factor could be the synergistic rewarding effects associated with alcohol and nicotine are co-administration (Tizabi, Copeland et al. 2002). Hence, it is possible that reducing cigarette consumption may also decrease alcohol consumption.

Adverse events experienced by subjects in the current study were not serious and reports did not differ between those who received varenicline or placebo. Also, there were no differences between groups in depressive symptoms (BDI) or psychological distress (HSCL-90) across the time-course of the study. Furthermore, no subject discontinued the study due to adverse events. Recently there have been some concerns that varenicline may be associated with neuropsychiatric effects (Food 2009) with a report of a psychotic relapse in one schizophrenic patient (Freedman 2007). The present study, along with previous clinical studies contrasts such concerns in that varenicline administration did not worsen symptoms of depression or psychiatric distress. In support, Stapleton and colleagues recently examined varenicline in smokers with psychiatric conditions and found that it was well tolerated with no exacerbation of mental conditions (Stapleton, Watson et al. 2008). Similarly, an 8-week treatment of varenicline in depressed smokers revealed a significant improvement in depression at the end of treatment (Philip, Carpenter et al. 2009). Another supporting study by Sofuoglu et al. showed that varenicline compared to placebo had been reported to enhance positive mood measures when intravenous nicotine was administered in humans (Sofuoglu, Herman et al. 2009). Preclinical work has also demonstrated that varenicline has antidepressant-like activities in animal models (Rollema, Guanowsky et al. 2009). It is important to note that
a much larger sample than that in this study would likely be needed to detect rare adverse neuropsychiatric effects related to varenicline use. Nonetheless, our findings contribute to the literature in that a 2-week varenicline administration may be well tolerated in heavy drinking smokers without inducing depressive and psychotic symptoms.

4.2 Strength & Limitations

There are several strengths to note in this study. This is the first placebo-controlled randomized trial to examine the effects of varenicline on both cue-induced cigarette and alcohol cravings. The major advantage of using this cue-paradigm is that the mixed tobacco and alcohol cues are presented to heavy drinking smokers. Since heavy drinking smokers often consumed tobacco and alcohol together, the present cue-paradigm can closer represent cues experienced in the natural environment. It is difficult to understand smoking cessation in heavy drinkers without acknowledging the presence of alcohol. The mixed tobacco-alcohol cue-paradigm used in this study can significantly increase both cigarette and alcohol craving scores. Specifically, the visual image portion of the cue-paradigm is validated by several previous studies (Wrase, Grusser et al. 2002; van Hanswijck de Jonge and Gormley 2005; Wrase, Schlagenhauf et al. 2007; Hussain, Zawertailo et al. 2009), and the tactile/olfactory portion has also been used to reliably induce tobacco and alcohol craving (Colby, Rohsenow et al. 2004; Donny, Griffin et al. 2008; Ferguson and Shiffman 2009). Hence, our cue-presentation paradigm was both well validated and a close representation of cue-exposure in a smoker who also drinks may experience in daily life.
Some limitations of the study are also worth noting. First, findings of the current study must be considered in light of the small sample size. A post-hoc power analysis revealed a power of 0.71 with an effect size of 0.93, an alpha of 0.05 and a sample size of 24. If we aim for a power of 0.95 (as in the sample size calculation) with an alpha of 0.05, the effect size of 0.93 would need a sample size of 52. It is also possible that our study lacks power to detect an influence of varenicline on alcohol related cue reactivity or consumption, as the sample size calculations were performed using cigarette related measures.

Second, the majority of participants in the study were male. There were not enough female participants to perform gender analyses on craving. One study by Udo and colleagues examined acute alcohol intoxication on self-reported arousal in response to alcohol-related picture cues with 36 social drinkers (16 women) (Udo, Bates et al. 2009). Udo et al. found men had a significantly dampened emotional arousal during alcohol intoxication and it could account for differences in reactivity to alcohol-related picture cues compared to women (Udo, Bates et al. 2009). However, Udo and colleagues’ findings may not be generalizable to the present study since they only examined social drinkers and only 11 participants reported cigarette use. In contrast, emerging literature on cue-reactivity studies suggest that gender does not influence cigarette and alcohol craving (Colamussi, Bovbjerg et al. 2007; Erblich, Montgomery et al. 2009; Hussain, Zawertailo et al. 2009). Colamussi and colleagues found that women reported higher stress-induced cigarette craving, but they produced no difference in laboratory imagery cue-induced cigarette craving compared to men (Colamussi, Bovbjerg...
et al. 2007). Erblich et al. also found the exposure of drinking cues in smokers who drink alcohol socially did not differ among men and women (Erblich, Montgomery et al. 2009). Also, Hussain et al. found consistent evidence that cigarette cue reactivity in daily smokers was not affected by gender (Hussain, Zawertailo et al. 2009).

A third limitation is that we did not record adverse events before the study medication was distributed in order to eliminate any pre-existing adverse events. Also, participants’ motivation to quit smoking can be measured by the Contemplation Ladder (Biener and Abrams, 1991). Finally, the majority of participants enrolled were not alcohol dependent and thus our findings are not generalizable to an alcohol-dependent population.

### 4.3 Conclusions

Two-week administration of varenicline (0.5-2mg) reduced tobacco cue-induced cigarette cravings in a group of heavy-drinking smokers but varenicline did not influence cue-induced alcohol cravings. Varenicline also appears safe for use as a smoking cessation aid in heavy drinking smokers, as it did not produce serious adverse events or influence symptoms of depression over two weeks in our sample. In addition, our results highlight the importance that cue-reactivity research may have in the development of smoking cessation treatments in heavy-drinking smokers.
4.4 Future Directions

Based on the current study, varenicline shows potential as a smoking cessation aid in heavy-drinking smokers since it reduced mixed tobacco-alcohol cue-induced cigarette craving with minimal adverse events and no influence on depression or mood. However, more research is needed to replicate this finding in smokers who are alcohol dependent, since people with alcohol use disorders are often heavily nicotine dependent (Hughes and Kalman 2006). Alcohol dependent subjects who are daily smokers can be recruited in a future study with a larger sample size in order to examine whether varenicline influenced alcohol and cigarette cue reactivity utilizing the same cue paradigm of the current study. As more studies investigate the influence of varenicline administration in heavy drinking smokers, a meta-analysis could be performed to detect more rare but serious adverse events. Future studies can also examine the effect of open-label varenicline combined with pre-existing alcohol treatments for inpatients that are alcohol and nicotine dependent. Additional research is needed to further explore the relationships between cue-induced craving intensity and subsequent tobacco and alcohol use or dependence, and whether craving intensity is predictive of cessation success in cigarette and alcohol dependence. Future smoking cessation studies can compare levels of cue-induced tobacco and alcohol cravings with rates of cessation success after 12 weeks of varenicline, NRT, or placebo administration. Since previous studies have identified familial and genetic patterns that predict cue-induced cigarette craving in smokers (Erblich, Lerman et al. 2005; Colamussi, Bovbjerg et al. 2007), it will be intriguing to find if these patterns may also emerge for alcohol craving in smokers who drink heavily.
Also, examining cue-reactivity with mixed tobacco and other drugs may provide insight on smoking cessation and episodes of cue-induced relapse in smokers who use other drugs. Findings from these studies may further clarify the important mechanisms underlying the tobacco-alcohol comorbid addiction, and ultimately benefit associated treatment interventions.
REFERENCES


Drummond, D. C. (2000). "What does cue-reactivity have to offer clinical research?" *Addiction* 95 Suppl 2: S129-44.


bupropion for smoking cessation: a randomized controlled trial." Jama 296(1): 56-63.


Picciotto, M. R., N. A. Addy, et al. (2008). "It is not "either/or": activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors related to nicotine addiction and mood." Prog Neurobiol 84(4): 329-42.


APPENDIX 1

Study Advertisement
HEALTHY VOLUNTEERS NEEDED FOR A RESEARCH STUDY

. Do you smoke cigarettes?  
Do you drink alcohol?  

YOU MAY BE ELIGIBLE TO PARTICIPATE.  

Financial compensation provided.

We are currently conducting a research study on the effects of a medication (varenicline) on smoking and alcohol drinking.

You will be required to take this medication and attend CAMH to complete questionnaires and computerized tests.

Please call:  
Greg at 416-535-8501 ext. 6346  
or  
Shan at 416-535-8501 ext. 6522

Must be available weekdays, with no current health problems.  
ALL QUERIES ARE STRICTLY CONFIDENTIAL.

CAMH provides other treatment options for mental illness or addiction.  
For more information call CAMH at 416-535-8501.

CAMH is a Pan American Health Organization/ World Health Organization Collaborating Centre  
Affiliated with the University of Toronto.
APPENDIX 2

Telephone Pre-screening Form
# VAT Study

**CAMH**

**Telephone Pre-screening Form**

<table>
<thead>
<tr>
<th>Date: ___________________</th>
<th>Time: ______________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form Completed by: ______________</td>
<td></td>
</tr>
</tbody>
</table>

**Name:**

**Date:**

**Sex:**

- [ ] Male
- [ ] Female

**Age:**

**DOB:**

**Telephone:**

- [ ] Home
- [ ] Work
- [ ] Cell
- [ ] Pager

**May I leave a message at this number:**

- [ ] Yes
- [ ] No

**Other number:**

- [ ] Home
- [ ] Work
- [ ] Cell
- [ ] Pager

**How did you find out about this study:**

### SMOKING SCREENING:

<table>
<thead>
<tr>
<th>Are you currently smoking?</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you currently interested in quitting smoking?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Are you interested in quitting smoking in the next 30 days?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>On average, how many cigarettes do you smoke per day?</td>
<td>0-10</td>
<td>11-15</td>
</tr>
<tr>
<td>Are you currently in treatment for tobacco dependence?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>If NO, Were you ever in treatment for tobacco dependence?</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

### Administer Fagerstrom Test for Nicotine Dependence (FTND):

<table>
<thead>
<tr>
<th>Question</th>
<th>Answers</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How soon after you wake up do you smoke your first cigarette?</td>
<td>Within 5 minutes</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6-30 minutes</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31-60 minutes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>After 60 minutes</td>
<td>0</td>
</tr>
<tr>
<td>2. Do you find it difficult to refrain from smoking in places where it is forbidden? (e.g. movie theatre, church, library)</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>3. Which cigarette would you hate to give up the most?</td>
<td>The first one in the morning</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>All others</td>
<td>0</td>
</tr>
<tr>
<td>4. How many cigarettes do you smoke a day?</td>
<td>10 or less</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21-30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31 or more</td>
<td>3</td>
</tr>
<tr>
<td>5. Do you smoke more frequently during the first hours after waking than during the rest of the day?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>
6. Do you smoke even if you are so sick that you are in bed most of the day?  
<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

**Fagerstrom test score = **

**FTND <3**  
**FTND >3**

**ALCOHOL SCREENING:**

<table>
<thead>
<tr>
<th>Have you consumed any alcohol in the past 12 months?</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often do you drink alcohol?</td>
<td>□ Never</td>
<td>□ Monthly or less □ 2-4 times/month □ 2-3 times/week □ 4 or more times/week</td>
</tr>
<tr>
<td>On those occasions that you do drink alcohol, how many drinks do you usually have?</td>
<td>□ 1-2</td>
<td>□ 3-4</td>
</tr>
<tr>
<td>In the past 12 months, have you ever consumed 5 or more drinks on any one occasion?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>If yes, how often does that happen?</td>
<td>□ Monthly or less</td>
<td>□ 2-4 times/month</td>
</tr>
<tr>
<td>In total, how many drinks do you consume per week?</td>
<td>&gt; 70 (male)</td>
<td>&lt; 70 (male)</td>
</tr>
</tbody>
</table>

**Heavy Drinker Group:**  
Consume >= 25 drinks/week (male)  
Consume >= 20 drinks/week (female)

**Social Drinkers Group:**  
Consume <= 14 drinks/week (male)  
Consume <= 9 drinks/week (female)

**DEPRESSION SCREENING:**

<table>
<thead>
<tr>
<th>Are you currently being treated for or receiving medication for the treatment of depression?</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>2. In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time?</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

If 1 or 2 is NO, skip following questions and move to next section of screen
If 1 or 2 is YES, ask the following questions

<table>
<thead>
<tr>
<th>Over the past two weeks, when you felt depressed or uninterested:</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was your appetite decreased or increased nearly every day? Did your body weight decrease or increase without trying intentionally (i.e., by ± 5% of body weight or ± 8 lbs or ± 3.5kgs, for a 160 lbs/70kg person in a month)?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>2. Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>
sleeping excessively)?

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Did you talk or move more slowly than normal or were you fidgety, restless or having trouble sitting still almost every day?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>4. Did you feel tired or without energy almost every day?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>5. Did you feel worthless or guilty almost every day?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>6. Did you have difficultly concentrating or making decisions almost every day?</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

If **3 or more** are marked **YES**, exclude from study.

### MEDICAL HISTORY:

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMEN: Are you currently pregnant or lactating?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Are you colour blind?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Do you have normal or corrected to normal vision?</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Do you have insulin-dependent diabetes?</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

In the past 3 months, have you used any recreational drugs such as marijuana, cocaine, speed, sleeping pills, heroin, or any other medications or substances for your own pleasure or need?

If YES:

- **What:** ___________________________________________________
- **How much:** _______________________________________________
- **How often:** _______________________________________________

### ELIGIBLE GROUP

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HD: Heavy Smoker, Heavy Drinker</td>
<td>YES</td>
</tr>
<tr>
<td>SD: Heavy Smoker, Social Drinker</td>
<td>HD</td>
</tr>
</tbody>
</table>

Assessment day: Date ________________  Time ________________
APPENDIX 3

Informed Consent Form
Subject Information
And
Informed Consent

Sept 17th, 2008
(Version 2.1)

Study Name: Effect of Varenicline on reactivity to smoking and drinking cues in individuals with concurrent tobacco dependence and alcohol use

Principal Investigator: Usoa Busto, PharmD (416) 535-8501 x.6812
Co-Principal Investigator: Laurie Zawertailo, Ph.D. (416) 535-8501 x.7422
Co-Investigator: Peter Selby, M.B.B.S. (416) 535-8501 x.6859
Graduate Students: Shan Wang, Hon.B.Sc. (416) 535-8501 x.6522
Gregory Staios, Hon.B.Sc. (416) 535-8501 x.6346

This study will take place at the Centre for Addiction and Mental Health – Russell St. Site under the supervision of Dr. U. Busto. This study is the M.Sc. research project of Shan Wang and Gregory Staios both under the supervision of Dr. U. Busto. There will be 80 people enrolled in this study. This study is funded by the Canadian Institutes of Health Research.

You are being asked to participate in this study because:

**You are a current smoker who is interested in quitting who also drinks alcohol**

Please take the time to read this information sheet carefully and ask any questions that you may have before deciding whether you wish to participate in this study.

Purpose of the Study:
The purpose of this study is to test how varenicline, a drug used to help people quit smoking, affects your responses to various pictures and environments.

Medication Information: As a participant in this study you will either receive the active medication or an inactive version called a placebo. You will be given a set of instructions on how to take the medication throughout the study. Neither you nor the investigator will know whether you are taking the active form of the medication or the placebo. The dosage and the way you take this medication will be identical to that which
you would receive if you went to your own family doctor and received this prescription. Specifically, you will be asked to take one 0.5mg capsule once a day for 3 days, and then take one 0.5mg capsule twice a day for 4 days followed by a 1 mg capsule taken twice daily for the remainder of the study. The total length of time you will take this medication is 2 weeks.

**Procedures**

**Assessment Day:** Before the study begins you will be asked to come in for an assessment visit. At this time, you will be asked to provide informed consent, undergo a medical exam and a brief psychiatric assessment to determine if you are eligible to participate in the study. General information about you will be collected at this time including questions about:

- Demographics (e.g.: your age, education, occupation)
- Your smoking history
- Your alcohol use history
- Your past and current drug use
- Current medications
- Psychiatric symptoms and history

Also, a blood sample will be collected for a general medical assessment and to obtain measures about your smoking. Also a urine sample will be required to screen for drug use and pregnancy in women. This visit will take about two hours. At the end of this assessment you will be provided a diary to take home that you will need to complete each day for one week. This diary will include questions about your smoking and alcohol consumption.

**Study Day Procedures:** One week after your assessment you will be asked to attend the laboratory having eaten a light breakfast. You may consume one cup of coffee or tea with your breakfast, if so desired. You will also be asked to keep from smoking cigarettes and drinking any alcohol for 12 hours before the study session. You also will have not taken any psychoactive drug for 24 hours prior to the start of the study. Your diary will also be collected at this time. To verify that you have not smoked any cigarettes or drank any alcohol, breath samples will be taken at the beginning of the test session. In order to be able to undergo testing on the study day, your breath samples must show that you have no alcohol in your blood. During this study session, you will be shown a slide show on a computer and will answer some questions about how you are feeling. You will also be asked to complete some computerized tests. A sample of blood (approx. 5ml or 1 teaspoon of blood) will also be drawn to determine your level of smoking. Once you have finished all the required tasks you will be provided with study medication for the following week and a new diary that you will be asked to complete each day. This day will take approximately 4 hours of your time.

You will return to CAMH in one weeks time to give back your medication bottle and diary and receive another 1-week supply of study medication and instructions as well as another diary. During this visit you will also be asked to complete some questionnaires about any side effects you may be experiencing due to the drug and your mood. This visit will last about 1 hour.
After taking the medication for another week you will attend CAMH for a final study visit where you will undergo the same procedure described above which includes a sample of blood (approx. 5ml or 1 teaspoon) being drawn to measure smoking levels. You will also be asked to complete a questionnaire about any side effects you may be having from your study medication. This visit should take approximately 4 hours of your time.

Upon completion of the study, you will be given the opportunity to continue with treatment for smoking cessation through the Nicotine Dependence Clinic at CAMH. Your total treatment time in the Nicotine Dependence Clinic will be for 12-weeks should you choose to continue with treatment. If you agree, you will be contacted after your 12-week treatment is completed to undergo a procedure similar to the assessment day procedure outlined above.

Risks and Discomforts
To participate in this study you will be required to stop smoking for a period of 12 hours prior to the start of each study day. You must also not drink any alcohol for 12 hours or take any psychoactive drugs for 24 hours prior to the start of the study. Discontinuation of these drugs may cause you some discomfort. During this study you will also be required to provide blood samples, which may also cause you some discomfort. The additional risks associated with this study are due to the medications used. Varenicline, the drug being given in this study, may produce some side effects including nausea, sleep disturbances, constipation and vomiting. Of the individuals taking this medication at a 1 mg dose, 30% experienced nausea, 18% experienced sleep disturbances, 8% experienced constipation and 5% experienced vomiting whereas those taking placebo experienced the above-mentioned side effects at 10%, 13%, 3% and 2% respectively. Generally, these symptoms only lasted for a short while. There have also been reports of individuals having episodes of depressed mood, agitation, changes in behaviour and thoughts of suicide while taking this medication. If at anytime during this study you begin having such feelings, you should contact both the study investigators and your family physician immediately. If these feelings are severe and impairing, you should discontinue this medication and contact the study physician immediately. If you are unable to contact the study physician, you should go to your local emergency room for treatment.

Time Commitment:
The preliminary screening visit (today) will last approximately 2 hours. Each of the study visits will last approximately 4 hours and the mid-study visit will last about 1 hour. Your total time commitment for this study will be approximately 12 hours.

Benefits:
The potential benefit to you by being in this study is having access to a study drug that may assist you in your attempt to quit smoking. Additionally, you will help contribute to information about the effects of this drug in smokers who also drink alcohol.

Compensation:
In consideration of your participation in this study you will receive $200.00 at the end of the study. If you decide to drop out of the study, your compensation will be pro-rated (see attached payment schedule).

**Voluntary Participation:**

Your participation in this study is completely voluntary and you can withdraw from the study at any time and for any reason. The investigators, at their discretion, may terminate your involvement in the study at any time. This could be due to medical reasons or for not following study procedures. If you decide to withdraw or are withdrawn from the study, this will not affect your current or any future care at the Centre for Addiction and Mental Health in any way.

**Confidentiality:**

Your identity will be kept strictly confidential to the full extent provided by law. All information collected during the course of this study will be kept secure and confidential and will only be made available to the researchers in this study. The data will be identified by your initials and a coding number only and not by your name. Published reports and presentations at scientific meetings will refer only to a code number or grouped data, and not a name or initial. As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board and, if applicable, by the Health Canada Therapeutics Products Programme. A person from the research ethics team may contact you (if your contact information is available) to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you must maintain your confidentiality to the extent permitted by law.

**Additional Information:**

Please feel free to ask any relevant questions regarding this form or the study if you are unclear. Consider this form as long as necessary before making a decision.
INFORMED CONSENT

I, _______________________________ have read (or had read to me) the information sheet for the study “Effect of Varenicline on reactivity to smoking and drinking cues in individuals with concurrent tobacco dependence and alcohol use”. The purpose of this research, the procedures and the risks associated with it have been fully explained to me. I have had the opportunity to ask questions and my questions have been answered to my satisfaction. I understand that I am able to withdraw from this study for any time and for any reason. I understand that my withdrawal from this study would in no way affect any current or future treatment at the Centre for Addiction and Mental Health. I voluntarily consent to participate in this research study.

In addition, I have been given a copy of this informed consent and information sheet to keep for my own records. If I have any further questions I understand that I can contact the Principal Investigator Dr. U. Busto at (416) 535-8501 x. 6812 or the Study Coordinators Shan Wang at (416) 535-8501 x.6522 or Greg Staios at (416) 535-8501 x. 6346. If I have any questions regarding my rights as a subject in this research I may contact Dr. Padraig Darby at (416) 535-8501 x. 6876.

Participant’s Signature     Date   Time

________________________________________
Participant’s Name

________________________________________
Investigator’s/Designate’s Signature     Date   Time

________________________________________
Investigator’s/Designate’s Name

I agree to be contacted at the end of 12-weeks of treatment for reassessment.

________________________________________
Participant’s Signature     Date   Time

________________________________________
Participant’s Name
APPENDIX 4

Study Diary Sample Pages
Date ______________

Today I woke up at: ______________ am / pm

**Cigarettes I Smoked**

<table>
<thead>
<tr>
<th>Time</th>
<th>Situation (e.g. in the car, with a coffee…etc.)</th>
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<tbody>
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</tbody>
</table>
*** Please make sure you wrote down time of your 1st cigarette***

Total number of cigarettes I had today: ___________

Total number of alcohol drinks I had today: __________

Please answer the following questions on a scale from 0 to 6, where 0 = not at all, 6 = very much.

1. Did you experience any the following?
   a. Nausea 0 1 2 3 4 5 6
   b. Vomiting 0 1 2 3 4 5 6
   c. Insomnia 0 1 2 3 4 5 6
   d. Gas 0 1 2 3 4 5 6
   e. Constipation 0 1 2 3 4 5 6
   f. Cigarette craving 0 1 2 3 4 5 6
   g. Alcohol craving 0 1 2 3 4 5 6

2. Did you experience other side effects today that you think are due to the study medication?
   □ Yes If yes, please describe ________________________________
   □ No

3. What time(s) did you take your study medication?

   ______ am / pm               ______ am / pm
APPENDIX 5

Single-Item Visual Analogue Scale Sample
I have a craving for cigarettes...

Click on the slider scale to move the slider button until the black vertical line appears in a position to indicate how you are feeling RIGHT NOW...

not at all  a little  moderately  quite a bit  extremely
APPENDIX 6

Cue Environment & Visual Sample
<table>
<thead>
<tr>
<th>Cue Type</th>
<th>Neutral Cues</th>
<th>Alcohol &amp; Tobacco Cues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual</td>
<td>• Neutral interview room</td>
<td>• simulated bar environment</td>
</tr>
<tr>
<td></td>
<td>• Neutral slide-show</td>
<td>• alcohol &amp; tobacco slide-show</td>
</tr>
<tr>
<td>Auditory</td>
<td>silence</td>
<td>bar type jazz music</td>
</tr>
<tr>
<td>Olfactory</td>
<td>cup filled with water</td>
<td>cup filled with alcohol of choice *</td>
</tr>
<tr>
<td>Tactile paraphernalia</td>
<td>pencil</td>
<td>cigarette</td>
</tr>
</tbody>
</table>

* Alcoholic choices provided for olfactory cues: beer, vodka, rum, gin, and whiskey
APPENDIX 7

ANOVA of Tobacco and Alcohol Cravings and Nicotine Withdrawal: Primary and Confirmatory Analyses
<table>
<thead>
<tr>
<th>Main Craving Outcome Measures</th>
<th>Primary Analysis 2x2x4 ANOVA</th>
<th>Confirmatory Analyses: 2x2x2 ANOVAs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 (varenicline, placebo) x 2 (baseline, end of study) x 4 (abstinence, after 1 cigarette, neutral cues, tobacco-alcohol cues)</td>
<td>Part 1: 2 (varenicline, placebo) x 2 (baseline, end of study) x 2 (abstinence, after 1 cigarette) Part 2: 2 (varenicline, placebo) x 2 (baseline, end of study) x 2 (neutral cues, tobacco-alcohol cues)</td>
</tr>
</tbody>
</table>

**Tobacco Craving & Nicotine Withdrawal**

<table>
<thead>
<tr>
<th></th>
<th>day, p=0.009</th>
<th>time-point, p&lt;0.001</th>
<th>day x drug, p=0.017</th>
<th>time-point, p&lt;0.001</th>
<th>day x time-point, p=0.010</th>
<th>day x drug, p=0.014</th>
<th>time-point, p=0.036</th>
<th>day x time-point, p=0.041</th>
<th>day, p=0.003</th>
<th>time-point, p=0.003</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS Cigarette Craving</td>
<td>day, p=0.001</td>
<td>time-point, p&lt;0.001</td>
<td>day, p=0.004</td>
<td>time-point, p&lt;0.001</td>
<td>day x time-point, p=0.010</td>
<td>day, p=0.004</td>
<td>time-point, p&lt;0.001</td>
<td>day x time-point, p=0.041</td>
<td>day, p=0.003</td>
<td>time-point, p=0.028</td>
</tr>
<tr>
<td>QSU Factor 1</td>
<td>day, p=0.001</td>
<td>time-point, p&lt;0.001</td>
<td>day, p=0.004</td>
<td>time-point, p&lt;0.001</td>
<td>day x time-point, p=0.010</td>
<td>day, p=0.004</td>
<td>time-point, p&lt;0.001</td>
<td>day x time-point, p=0.041</td>
<td>day, p=0.003</td>
<td>time-point, p=0.003</td>
</tr>
<tr>
<td>QSU Factor 2</td>
<td>day, p=0.005</td>
<td>time-point, p&lt;0.001</td>
<td>day, p=0.027</td>
<td>time-point, p&lt;0.001</td>
<td>day x time-point, p=0.010</td>
<td>day, p=0.004</td>
<td>time-point, p&lt;0.001</td>
<td>day x time-point, p=0.041</td>
<td>day, p=0.007</td>
<td>time-point, p=0.003</td>
</tr>
<tr>
<td>MNWS</td>
<td>day, p=0.004</td>
<td>time-point, p=0.002</td>
<td>day, p=0.014</td>
<td>time-point, p&lt;0.001</td>
<td>day x time-point, p=0.010</td>
<td>day, p=0.004</td>
<td>time-point, p&lt;0.001</td>
<td>day x time-point, p=0.041</td>
<td>day, p=0.003</td>
<td>time-point, p=0.003</td>
</tr>
</tbody>
</table>

**Alcohol Craving**

<table>
<thead>
<tr>
<th></th>
<th>time-point, p&lt;0.001</th>
<th>day x time-point x drug, p=0.047</th>
<th>time-point, p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACQ Method 1</td>
<td>time-point, p&lt;0.001</td>
<td>No significant effects</td>
<td>time-point, p&lt;0.001</td>
</tr>
<tr>
<td>ACQ Method 2</td>
<td>time-point, p&lt;0.001</td>
<td>No significant effects</td>
<td>day x time-point, p=0.041</td>
</tr>
<tr>
<td>VAS Alcohol Craving</td>
<td>time-point, p=0.002</td>
<td>No significant effects</td>
<td>day x time-point, p=0.002</td>
</tr>
<tr>
<td></td>
<td>day x time-point, p=0.030</td>
<td>No significant effects</td>
<td>day x time-point, p=0.002</td>
</tr>
</tbody>
</table>