EFFECT OF VARENICLINE VS. PLACEBO ON REACTIVITY TO TOBACCO AND ALCOHOL CUES IN SMOKERS WHO ARE LIGHT DRINKERS

by

Gregory Staios

A thesis submitted in conformity with the requirements for the degree of

Master of Science

Graduate Department of Pharmacology and Toxicology

University of Toronto

© Copyright by Gregory Staios (2010)
Varenicline is used to treat tobacco dependence. While varenicline decreases craving during a quit attempt, no studies have investigated its effect on cue-induced craving. Varenicline has also been shown to decrease alcohol consumption in animal and humans. This double-blind, randomized, placebo-controlled trial investigated the effect of varenicline on tobacco and alcohol cue-induced craving and alcohol consumption in dependent smokers/light drinkers. Tobacco and alcohol craving were assessed at baseline and after 2-weeks of drug administration using the QSU and ACQ. Significant decreases in cigarette and alcohol craving were observed between the pre- and post-drug session in the varenicline group on QSU Factor 1 (87.58±11.66 vs. 70.58±20.79, p=0.008) and ACQ Total (3.37±1.16 vs. 2.66±1.15, p=0.004) scores. This effect remained significant after correction for craving during neutral cues in the alcohol but not tobacco condition. No significant decreases in alcohol consumption were seen. These results suggest varenicline decreases overall craving, but not cue-induced craving specifically.
Acknowledgements

This thesis is dedicated to the memory of Gregory Staios Sr., my grandfather and namesake, who made the difficult decision with my grandmother, Eugenia Staios, to move to Canada approximately 45 years ago. The decision they made have provided me with opportunities that would not have been available to me otherwise.

While my grandfather only had a grade 6 education, he always valued higher learning. His high regard for education and the sacrifices he made working in deplorable conditions inspired me to pursue higher education and take full advantage of the opportunities this country offers me. Grandpa, I love you and I miss you. I hope I’ve made you proud.

First, I’d like to thank my parents Chris and Theodota Staios for always being supportive. You’ve always been there for me and always encouraged me no matter what obstacle I would face. Even though there were times were you wouldn’t see much of me for days, you always understood why. You truly are the best parents a child could ever ask for.

To my sister Gina, thanks for listening to my odd mumblings about science (it’s ok, I realize you had no idea what I was talking about half the time) and laughing at my cheesy science jokes. While I finish this degree, you embark on a new voyage of education yourself. Just remember, I’ll always be there for you, just like how you’ve always been there for me.

To my supervisor, Dr. Usanda Busto, thank you for teaching me to be an independent and critical thinker. Thanks to your efforts, I look at the world differently now. You have provided me a unique opportunity to learn clinical pharmacology and
science in general. Thank you for giving me the opportunity to learn. You are a wonderful person and I applaud you for breaking the mould of the stereotypical scientist. Thank you for taking the time to make your students feel like part of the family.

I will forever remember that even though you were in the hospital, you made every effort to try and come to my defense. Even though you couldn’t attend, the efforts you went to were touching. The phone calls you made to me before my defense giving pointers and telling me that I’d do great really put me at ease. You truly made me feel special and your words warmed my heart that day. Thank you for everything you have provided me.

To Dr. Bruna Brands, well, where do I begin? I could write a book larger than this thesis to describe how much I appreciate everything you have done for me; however, I’ll keep it concise, just like how you taught me. Bruna, throughout the years, I have had the pleasure of getting to know and you have become a good friend of mine. I cannot even being to describe how much I appreciated you. Your door was always open, and you always knew exactly what to say to make me feel better when things weren’t going exactly as planned. No matter how many things were going on in your life, you always had time for me, and for that I will always be grateful. You are my mentor and you are the type of scientist I aspire to become. Thank you!

To Dr. Laurie Zawertailo, my advisor, thank you for always providing me with constructive input on all aspects of my work. You have always been available to look over whatever I’ve sent your way and you always gave me great feedback. Thank you for always helping with all the study issues and being available whenever I had questions.
To Kathryn Knight and Alain MacDonald, thank you both for always being so caring and considerate. Kathryn, thank you for always answering my questions about research binders and other administrative details and Alain, thanks for working tirelessly to ensure our computer programs were always working properly. This degree could have never been completed without both of your help.

To my lab mates, Dr. Alex Elkader, Shan Wang, Lina Chiuccariello, Vlad Kushnir, Lindsay Steinberg, Kim DeSousa, Anne Marie Tremblay, Dr. Laurie Sellings, Dr. Xavier Balducci and all other that I may have forgotten. You guys weren’t only the people I worked with, you were like family. I knew I could always turn to you guys no matter what problem I was having and you guys would come running to help. I honestly couldn’t have gotten through this experience without each and every one of you. You are all great people and I hope all your dreams and aspirations come true. I’m certain our paths will cross again.

To my friend Steven Lo, my brother from a different mother and father! We started grad school on the same day, and ended on the same day. It truly was an interesting experience. I appreciate all the help and the moral support you would provide about school and life in general. Thanks for always being there for me. You’re a great guy and I know you can overcome any obstacle. Keep on going bud, one day we’ll get to our final destination, hopefully working side by side!

Finally, to all my participants who come down to CAMH, sometimes under terrible weather conditions to make my study sessions. I can honestly say without a doubt that this research would not have been possible if it were not for you. Thank you for allowing research like this to take place.
# Table of Contents

Abstract ii  
Acknowledgements iii  
Table of Contents vi  
List of Tables xiii  
List of Figures xiv  
List of Abbreviations xvii  
List of Appendices xviii  

## 1.0 Introduction 1  
1.1 Statement of the Problem 1  
1.2 Overall Purpose and Objectives 2  
1.3 Rationale and Hypotheses 2  
1.4 Review of the Literature 3  
1.4.1 Tobacco and Alcohol Interactions 3  
1.5 Alcohol and Nicotine Consumption 5  
1.5.1 Animal Studies 5  
1.5.2 Human Studies 6  
1.6 Alcohol Consumption and its Effect on Tobacco Craving 7  
1.7 Cue-Induced Craving 8  
1.7.1 Animal Studies 9  
1.7.2 Human Studies 11  
1.8 Neural Substrates of Cue-Induced Craving 13  
1.9 Role of Cue-Induced Craving on Smoking Cessation Success 14
1.10 Alcohol and Nicotine – Cross Reactive Cue-Induced Craving 16
1.11 Nicotinic Acetylcholine Receptor Antagonists and Tobacco Cue-Induced Craving 17
1.12 Nicotinic Acetylcholine Receptors (nAChRs) 18
1.13 Interaction of Ethanol with Nicotinic Acetylcholine Receptors 19
1.13.1 Animal Studies 19
1.13.2 Human Studies 21
1.14 Varenicline 22
1.14.1 Initial Development 22
1.14.2 Pharmacology 24
1.14.2.1 Absorption 24
1.14.2.2 Distribution 25
1.14.2.3 Metabolism 25
1.14.2.4 Excretion 25
1.14.3 Preclinical Studies 26
1.14.4 Clinical Studies 29
1.14.4.1 Phase II Studies 29
1.14.4.2 Phase III Studies 30
1.14.5 Long Term Studies 31
1.14.6 Studies Comparing Varenicline to NRT 32
1.14.7 Safety and Efficacy of Varenicline in Populations with Psychiatric Disorders 32
1.14.7.1 Efficacy in Populations with Psychiatric Disorders 32
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.14.7.2</td>
<td>Safety of Varenicline in Populations with Psychiatric Disorders</td>
<td>33</td>
</tr>
<tr>
<td>1.14.8</td>
<td>Varenicline and Depression</td>
<td>36</td>
</tr>
<tr>
<td>1.14.8.1</td>
<td>Animal Studies</td>
<td>36</td>
</tr>
<tr>
<td>1.14.8.2</td>
<td>Human Studies</td>
<td>37</td>
</tr>
<tr>
<td>1.14.9</td>
<td>Effect of Varenicline on Alcohol Consumption</td>
<td>39</td>
</tr>
<tr>
<td>1.14.9.1</td>
<td>Animal Studies</td>
<td>39</td>
</tr>
<tr>
<td>1.14.9.2</td>
<td>Human Studies</td>
<td>41</td>
</tr>
<tr>
<td>1.15</td>
<td>Overall Summary</td>
<td>42</td>
</tr>
<tr>
<td>2.0</td>
<td><strong>Materials and Methods</strong></td>
<td>43</td>
</tr>
<tr>
<td>2.1</td>
<td>Study Design</td>
<td>43</td>
</tr>
<tr>
<td>2.2</td>
<td>Subject Selection</td>
<td>44</td>
</tr>
<tr>
<td>2.2.1</td>
<td>Inclusion Criteria</td>
<td>44</td>
</tr>
<tr>
<td>2.2.2</td>
<td>Exclusion Criteria</td>
<td>44</td>
</tr>
<tr>
<td>2.3</td>
<td>Subject Recruitment</td>
<td>46</td>
</tr>
<tr>
<td>2.4</td>
<td>Subject Assessment</td>
<td>46</td>
</tr>
<tr>
<td>2.4.1</td>
<td>Pre-Screening Procedures</td>
<td>46</td>
</tr>
<tr>
<td>2.4.2</td>
<td>Assessment Day Procedures</td>
<td>47</td>
</tr>
<tr>
<td>2.5</td>
<td>Study Day Procedures</td>
<td>48</td>
</tr>
<tr>
<td>2.5.1</td>
<td>Baseline Visit (Pre-Drug Session)</td>
<td>48</td>
</tr>
<tr>
<td>2.5.2</td>
<td>Mid Study Visit</td>
<td>50</td>
</tr>
<tr>
<td>2.5.3</td>
<td>Final Visit (Post-Drug Session)</td>
<td>51</td>
</tr>
<tr>
<td>2.6</td>
<td>Cue-Presentation Procedures</td>
<td>51</td>
</tr>
</tbody>
</table>
2.6.1 Neutral Cues 51
2.6.2 Tobacco and Alcohol Cues 52
2.7 Description of Scales 52
2.7.1 Alcohol Use Disorder Identification Test 52
2.7.2 Beck Depression Inventory 53
2.7.3 MINI International Neuropsychiatric Interview 53
2.7.4 Questionnaire of Smoking Urges 54
2.7.5 Alcohol Craving Questionnaire 54
2.7.6 Visual Analogue Scale 55
2.7.7 Obsessive Compulsive Drinking Scale 55
2.7.8 Minnesota Nicotine Withdrawal Scale 55
2.8 Description of Tasks 56
2.8.1 Nicotine/Alcohol Stroop Task 56
2.8.2 Digit Symbol Substitution Test 56
2.9 Measurement of Outcome Variables 56
2.9.1 Reactivity to Smoking and Alcohol Cues 56
2.9.2 Daily Craving Measures and Consumption 57
2.9.3 Assessment of Adverse Events 57
2.10 Medications 58
2.10.1 General Medication Information 58
2.11 Randomization Information 59
2.12 Regulatory Information 59
2.13 Sample Size Justification 59
2.14 Data Analysis

3.0 Results

3.1 Study Participants

3.2 Effectiveness of Cue Paradigm to Induce Craving

3.3 Subjective Tobacco Craving Results

3.3.1 Questionnaire of Smoking Urges

3.3.1.1 Desire to Smoke subscale

3.3.1.2 Anticipation of Positive Outcome subscale

3.3.1.3 Relief of Withdrawal or Negative Affect subscale

3.3.1.4 Intention to Smoke subscale

3.3.1.5 Factor 1 subscale

3.3.1.6 Factor 2 subscale

3.3.2 Visual Analogue Scale – Cigarette Craving

3.3.3 Corrected Craving Measures

3.4 Subjective Alcohol Craving Results

3.4.1 Alcohol Craving Questionnaire

3.4.1.1 Urge and Desire to Use Alcohol subscale

3.4.1.2 Intent to Use Alcohol subscale

3.4.1.3 Anticipation of Positive Outcome subscale

3.4.1.4 Anticipation of Relief from Withdrawal from Negative Outcomes subscale

3.4.1.5 Lack of Control Over Use subscale

3.4.1.6 Total Score
3.4.2 Visual Analogue Scale – Alcohol Craving
3.4.3 Corrected Craving
3.5 Obsessive and Compulsive Behaviours with Respect to Alcohol Consumption
3.5.1 Obsessive Compulsive Drinking Scale
3.6 Measures of Nicotine Withdrawal
3.6.1 Minnesota Nicotine Withdrawal Scale
3.7 Tobacco Consumption Measures
3.7.1 Self-Reported Tobacco Consumption
3.7.2 Biochemical Measures of Tobacco Consumption
3.8 Alcohol Consumption Measures
3.8.1 Self-Reported Alcohol Consumption
3.9 Cognitive Processing Measures
3.9.1 Digit Symbol Substitution Test
3.10 Measures of Attentional Bias
3.10.1 Stroop Task
3.10.1.1 Incongruent Colour Words
3.10.1.2 Congruent Colour Words
3.10.1.3 Smoking Related Words
3.10.1.4 Positive Smoking Effect Words
3.10.1.5 Negative Smoking Effect Words
3.10.1.6 Neutral Words
3.10.1.7 Alcohol Words
3.11 Summary of Adverse Events 86

3.12 Assessment of Compliance 86

4.0 Discussion 88

4.1 Subjective Tobacco Craving 89

4.2 Subjective Alcohol Craving 93

4.3 Attentional Bias 95

4.4 Limitations 96

4.5 Conclusions 100

4.6 Recommendations for Future Studies 100

5.0 References 103

6.0 List of Publications and Abstracts 112

Appendices 113
## List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Subject Demographics</td>
<td>62</td>
</tr>
</tbody>
</table>
## List of Figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Outline of overall study design</td>
<td>43</td>
</tr>
<tr>
<td>2.2</td>
<td>Assessment Flowchart</td>
<td>46</td>
</tr>
<tr>
<td>2.3</td>
<td>Study Day Procedure</td>
<td>50</td>
</tr>
<tr>
<td>3.1</td>
<td>Comparison of Questionnaire of Smoking Urges Desire to Smoke subscale scores compared between varenicline and placebo during all four conditions</td>
<td>64</td>
</tr>
<tr>
<td>3.2</td>
<td>Comparison of Questionnaire of Smoking Urges Anticipation of Positive Outcome subscale scores between varenicline and placebo during all four conditions</td>
<td>65</td>
</tr>
<tr>
<td>3.3</td>
<td>Comparison of Questionnaire of Smoking Urges Relief of Withdrawal or Negative Affect subscale scores between varenicline and placebo during all four conditions</td>
<td>66</td>
</tr>
<tr>
<td>3.4</td>
<td>Comparison of Questionnaire of Smoking Urges Intention to Smoke subscale scores between varenicline and placebo during all four conditions</td>
<td>67</td>
</tr>
<tr>
<td>3.5</td>
<td>Comparison of Questionnaire of Smoking Urges Factor 1 subscale scores between varenicline and placebo during all four conditions</td>
<td>68</td>
</tr>
<tr>
<td>3.6</td>
<td>Comparison of Questionnaire of Smoking Urges Factor 2 subscale scores between varenicline and placebo during all four conditions</td>
<td>69</td>
</tr>
<tr>
<td>3.7</td>
<td>Comparison of Visual Analogue Scale “I crave a cigarette” scores between varenicline and placebo during all four conditions</td>
<td>70</td>
</tr>
<tr>
<td>3.8</td>
<td>Comparison of Alcohol Craving Questionnaire Urge and Desire to Use Alcohol subscale scores between varenicline and placebo during all four conditions</td>
<td>72</td>
</tr>
<tr>
<td>3.9</td>
<td>Comparison of Alcohol Craving Questionnaire Intent to Use Alcohol subscale scores between varenicline and placebo during all four conditions</td>
<td>73</td>
</tr>
</tbody>
</table>
3.10 Comparison of Alcohol Craving Questionnaire Anticipation of Positive Outcome subscale scores between varenicline and placebo during all four conditions

3.11 Comparison of Alcohol Craving Questionnaire Anticipation of Relief from Withdrawal from Negative Outcomes subscale scores between varenicline and placebo during all four conditions

3.12 Comparison of Alcohol Craving Questionnaire Total Scores between varenicline and placebo during all four conditions

3.13 Comparison of Visual Analogue Scale (alcohol craving) scores were compared between varenicline and placebo during all four conditions

3.14 Comparison of Minnesota Nicotine Withdrawal Scale scores between varenicline and placebo during all four conditions

3.15 Self-reported tobacco consumption measures compared between varenicline and placebo during the entire study period

3.16 Measures of nicotine, cotinine and 3HC in the varenicline and placebo groups in the pre- and post-drug sessions

3.17 Self-reported alcohol consumption measures compared between varenicline and placebo during the entire study period

3.18 Visual representation of mean reaction times when presented with congruent colour words between varenicline and placebo groups

3.19 Visual representation of mean reaction times when presented with smoking related words between varenicline and placebo groups

3.20 Visual representation of mean reaction times when presented with negative smoking effect words between varenicline and placebo groups
Visual representation of mean reaction times when presented with alcohol words between varenicline and placebo groups
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3HC</td>
<td>3-hydroxycotinine</td>
</tr>
<tr>
<td>ACQ</td>
<td>Alcohol Craving Questionnaire</td>
</tr>
<tr>
<td>AOPO</td>
<td>Anticipation of Positive Outcome</td>
</tr>
<tr>
<td>AORFWONO</td>
<td>Anticipation of Relief from Withdrawal from Negative Outcomes</td>
</tr>
<tr>
<td>AUDIT</td>
<td>Alcohol Use Disorder Identification Test</td>
</tr>
<tr>
<td>BDI</td>
<td>Beck Depression Inventory</td>
</tr>
<tr>
<td>DSST</td>
<td>Digit Symbol Substitution Test</td>
</tr>
<tr>
<td>DTS</td>
<td>Desire to Smoke</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>ITS</td>
<td>Intention to Smoke</td>
</tr>
<tr>
<td>ITUA</td>
<td>Intent to Use Alcohol</td>
</tr>
<tr>
<td>LCOU</td>
<td>Loss of Control Over Use</td>
</tr>
<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
</tr>
<tr>
<td>MNWS</td>
<td>Minnesota Nicotine Withdrawal Scale</td>
</tr>
<tr>
<td>nAchR</td>
<td>Nicotinic Acetylcholine Receptor</td>
</tr>
<tr>
<td>OCDS</td>
<td>Obsessive Compulsive Drinking Scale</td>
</tr>
<tr>
<td>QSU</td>
<td>Questionnaire of Smoking Urges</td>
</tr>
<tr>
<td>ROWONE</td>
<td>Anticipation of Relief from Nicotine Withdrawal or from Withdrawal Associated Negative Affect</td>
</tr>
<tr>
<td>UADTUA</td>
<td>Urge and Desire to Use Alcohol</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
</tbody>
</table>
# List of Appendices

<table>
<thead>
<tr>
<th>Appendix</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Informed Consent Form</td>
<td>113</td>
</tr>
<tr>
<td>2</td>
<td>Study Advertisements</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>Telephone Screening Form</td>
<td>123</td>
</tr>
<tr>
<td>4</td>
<td>Examples of Cue Pictures</td>
<td>127</td>
</tr>
</tbody>
</table>
Section 1: Introduction

1.1 Statement of the Problem

Tobacco cues have been shown to increase craving for tobacco and have been implicated in relapses to smoking (Shiffman 1982; Bliss, Garvey et al. 1989; Shiffman, Paty et al. 1996). Although a variety of medications, such as nicotine replacement therapy and bupropion decrease craving associated with abstinence from tobacco, medications used in this context have either not been effective at attenuating cue-induced craving or they have not been investigated in this context. Varenicline, a partial agonist of the α4β2 nicotinic acetylcholine receptor has been found to be effective at decreasing tobacco craving during a quit attempt (Gonzales, Rennard et al. 2006; Jorenby, Hays et al. 2006), however no studies have been published addressing the ability of this medication to decrease tobacco-cue induced craving. Recent studies in both animals (Kamens, Andersen et al.; Steensland, Simms et al. 2007) and humans (McKee, Harrison et al. 2009) show that varenicline can reduce alcohol consumption but further studies confirming these results are needed. Furthermore as tobacco and alcohol are substances that are commonly consumed together, it is likely that many of the cues that induce cravings to smoke may also influence craving to alcohol and vice versa (Drobes 2002; Erblich, Montgomery et al. 2009). Therefore studies investigating the effect of varenicline on alcohol cue-induced craving are also required. These gaps in the understanding of the mechanism of this medication suggest that further research is required to elucidate the effect of varenicline on both tobacco and alcohol cue-induced craving, while also investigating the effect of this medication on alcohol consumption.
1.2 Overall Purpose and Objectives

The purpose of this study was to investigate whether varenicline tartrate (Champix®, Pfizer, New York, NY) administered at a therapeutic dose over a two week period could decrease the subjective craving experienced by cigarette smokers and light alcohol drinkers after exposure to tobacco and alcohol cues compared to placebo. Light drinkers are defined as individuals who drink less than 14 drinks per week if male, or less than 9 drinks per week if female and do not consume more than 2 drinks per drinking occasion (Adlaf, Ialomiteanu et al. 2008). The secondary outcome measure was to determine whether varenicline could also decrease consumption of both of these substances.

1.3 Rationale and Hypotheses

There is a paucity of literature investigating the influence of varenicline on tobacco cue-induced craving in regular smokers. Only one study, of which only an abstract has been published, has investigated this effect (Niaura, Hitsman et al. 2007). This group did not find any decreases in cue-induced tobacco craving, but their study sessions were conducted after only a single dose of varenicline. As varenicline has a half-life of approximately 24 hours, this suggests that this effect was measured at sub-therapeutic doses of varenicline. Measurement of tobacco cue-induced craving at therapeutic concentrations of this medication could yield different results. Furthermore, mecamylamine, a nicotinic acetylcholine receptor antagonist, has been shown to decrease cue-induced craving however this was with respect to cocaine cues (Reid, Mickalian et al. 1999), but this effect has not been investigated with tobacco cues. In addition, as alcohol is postulated to mediate some of its effects through the nicotinic acetylcholine receptor (Le, Corrigall et al. 2000; Larsson, Svensson et al. 2002), it may be possible that
varenicline can influence alcohol cue-induced craving and consumption. While mecamylamine has been shown to reduce cue-induced craving the specific receptor subtype involved in this effect has not been elucidated. Varenicline was used in the present study to investigate the specific influence of the $\alpha_4\beta_2$ nAChR on tobacco and alcohol cue-induced craving. The aim of the present study was investigate whether therapeutic concentrations of varenicline compared to placebo can decrease tobacco and alcohol cue-induced craving using a mixed tobacco and alcohol cue presentation procedure.

**Hypotheses:**

1) **At therapeutic concentrations, varenicline will decrease tobacco and alcohol cue-induced craving compared to placebo.**

2) **Varenicline will decrease tobacco and alcohol consumption compared to placebo.**

1.4 Review of the Literature

1.4.1 Tobacco and Alcohol Interactions

Alcohol and tobacco are strongly associated with one another as they are often used together. This association is bidirectional as approximately 80% of individuals with alcohol dependence smoke cigarettes while 30% of smokers are alcohol dependent (Miller and Gold 1998). Furthermore, heavy smoking has been observed to be a predictor of undiagnosed alcohol abuse or dependence (Kozlowski, Jelinek et al. 1986). A lifetime diagnosis of nicotine dependence has shown a odds ratio of 4.69 for alcohol dependence, while having smoked 30 or more cigarettes per day, commencing smoking at 17 years of age or younger and endorsing particular DSM-IV nicotine dependence
criteria were associated with an odds ratio of 4.0 or higher for alcohol dependence (John, Meyer et al. 2003).

Studies have also linked alcohol consumption with failure of smoking cessation treatment with heavy drinking days being associated with a higher probability of relapse to smoking (Leeman, McKee et al. 2008). Similarly, studies investigating real-time reports during a concurrent alcohol and tobacco cessation program also showed that the frequency of alcohol craving was increased after smoking a cigarette (Cooney, Litt et al. 2007). While acute tobacco deprivation prior to exposure to alcohol cues was not observed to increase the urge to drink alcohol in alcohol-dependent smokers (Cooney, Cooney et al. 2003) or moderate to heavy drinking young adults (Colby, Rohsenow et al. 2004), administration of a priming drink during an experimental session has been shown to hamper the ability of subjects to resist smoking a cigarette and these subjects smoked a greater number of cigarettes compared to those given a placebo drink (McKee, Krishnan-Sarin et al. 2006). These findings suggest that an association exists between alcohol use disorder and nicotine dependence and that alcohol consumption may influence smoking cessation outcomes.

Summary Points:

- Alcohol and tobacco use are strongly linked as supported by the high prevalence of co-occurring alcohol use disorders and nicotine dependence
- Alcohol consumption has been linked with smoking cessation failures and increases in tobacco craving
1.5 Alcohol and Nicotine Consumption

1.5.1 Animal Studies

Pre-treatment of rats with nicotine, while initially decreasing alcohol consumption, causes increased alcohol consumption and operant responding for alcohol (Le, Corrigall et al. 2000). Furthermore, when nicotine was administered concurrently with alcohol, nicotine both increased alcohol self-administration and reinstated alcohol seeking when administered after extinction of alcohol seeking behaviour (Le, Wang et al. 2003). Similarly, in a study where animals were administered nicotine during a forced abstinence from alcohol, it was observed that nicotine administration increased alcohol consumption compared to those administered vehicle alone (Alen, Gomez et al. 2009). In a study where nicotine was administered to rats for 5 days during an alcohol-deprivation period, the nicotine-treated animals consumed more alcohol than those administered saline when allowed to freely administer alcohol (Lopez-Moreno, Trigo-Diaz et al. 2004).

Unfortunately, studies investigating the role of alcohol on nicotine consumption are limited in animal models. This mostly stems from difficulties in ensuring patency of intravenous lines used to self-administer nicotine. As these lines would have to be placed prior to alcohol self-administration training, lack of use during the alcohol training phase may cause blockage of many of these lines thus not allowing these animals to self-administer nicotine after alcohol administration. Even with these difficulties, a recent study has examined the effects of co-administration of both alcohol and nicotine using a rat model. In this study, it was shown that while animals will co-administer nicotine and alcohol, concurrent access to alcohol significantly decreased nicotine self-administration and extinction of alcohol seeking behaviour was slower in the presence of nicotine.
However, administration of a priming dose of nicotine or alcohol in animals trained to self-administer both substances reinstated both alcohol and nicotine seeking behaviours (Le, Lo et al.).

**Summary Points:**

- Administration of nicotine increases alcohol consumption and operant responding for alcohol in rats.
- When nicotine and alcohol are co-administered, nicotine increases alcohol self-administration
- In animals trained to administer both substances, a priming dose of either drug will reinstate alcohol and nicotine seeking behaviour

**1.5.2 Human Studies**

Consumption of alcohol has been shown to increase smoking behaviours such as puff volume, duration and number of puffs compared to placebo beverage in a laboratory setting (King, McNamara et al. 2009). In a study of 42 smokers who were also heavy social drinkers, alcohol administration increased subjective craving for tobacco in both male and female smokers, however an increase in smoking was only observed in male smokers (King, McNamara et al. 2009). In contrast to the results of this study, an increase in smoking was not seen in a study of 10 nicotine-dependent smokers pre-administered alcohol, although these differences may be due to the relative light drinking patterns of those included in this study (Zacny, Mitchell et al. 1997). A further study monitoring the naturalistic consumption of both of these substances found that while occasional smokers and regular smokers drank similar amounts of alcohol during the study period, occasional smokers delayed their smoking until they consumed more drinks
(i.e. had a higher blood alcohol level) than the regular smoker group who began smoking after having consumed fewer drinks (Harrison, Hinson et al. 2009).

Administration of nicotine has also been shown to increase alcohol consumption. Alcohol consumption increased in non-dependent occasional smokers who smoked regular cigarettes compared to de-nicotinized cigarettes whereas water consumption was not influenced by cigarette type (Barrett, Tichauer et al. 2006). Studies in light smoker-social drinkers showed that administration of transdermal nicotine prior to an alcoholic priming drink increased alcohol consumption compared to placebo patch using an alcohol drink vs. monetary reinforcement paradigm. However, this effect was specific to men, as an increase in alcohol consumption was not observed in females (Acheson, Mahler et al. 2006). Conversely, in a similar study conducted in heavy-drinking smokers, it was observed that transdermal nicotine patches increased the time to first drink and fewer drinks were consumed during a self-administration period compared to placebo patch (McKee, O'Malley et al. 2008). These results suggest that nicotine may have differential effects on alcohol consumption based on an individual’s level of nicotine dependence and that further research is required to elucidate the mechanism of this effect.

**Summary Points:**

- Alcohol consumption increases smoking behaviour and subjective craving for tobacco
- Nicotine administration also increase alcohol self-administration and consumption

### 1.6 Alcohol Consumption and its Effect on Tobacco Craving

Burton and Tiffany (1997) published one of the first reports documenting the effects of alcohol consumption on craving to smoke. In their study, administration of
alcohol to regular smokers who consumed at least one drink weekly increased tobacco craving. Specifically, alcohol consumption did not have an effect on tobacco cue-induced craving but rather increased craving for cigarettes under both the neutral and tobacco cue condition (Burton and Tiffany 1997). More recent studies have observed similar results with this effect being observed in both heavy smokers (Sayette, Martin et al. 2005); heavy drinking, light smokers (Ray, Miranda et al. 2007) and occasional social smokers (chippers) (Sayette, Martin et al. 2005; Epstein, Sher et al. 2007). Furthermore, a study investigating the effect of an acute alcohol dose on attentional biases to smoking related cues determined that alcohol increased both craving for tobacco and increased the time individuals maintained focus on smoking cues (Field, Mogg et al. 2005). A recent study by King et al. (2010) investigating the neural correlates associated with this response using functional magnetic resonance imaging (fMRI). In this study, ventral striatal activation was measured following alcohol administration during presentation of neutral and smoking cues. Their main findings, similar to those above, was that alcohol increased self-reported measures of tobacco craving and significantly increased ventral striatum activity during exposure to smoking cues compared to neutral cues (King, McNamara et al.).

**Summary Point:**

- Alcohol consumption increases craving for cigarettes. This effect is seen in heavy smokers, heavy drinking-light smokers and occasional social smokers.

### 1.7 Cue-Induced Craving

Cue-induced craving is thought to develop over a period of time when drugs of abuse are consumed in the presence of neutral or environmental contents that are reliably
associated with drug uses. After repeated drug administrations, these stimuli or cues become paired to the unconditioned drug stimulus. Once this pairing has occurred, these previously neutral stimuli become conditioned stimuli that evoke a conditioned response commonly manifested as a craving to consume the drug of abuse (Carter and Tiffany 1999). A variety of evidence supports this theory in both animals and humans studies. The main findings from these studies are summarized below.

1.7.1 Animal Studies

The role of cues in animal drug seeking behaviours is typically investigated using a conditioned reinforcement paradigm. Briefly, this procedure involves an animal self-administering drug by pressing on one of two levers with only one providing a drug infusion. When the active lever is depressed, a brief stimulus such as illumination of a cue light is presented prior to drug administration. With repeated pairings of drug administration with stimulus presentation, this light becomes a conditioned stimulus predicting drug availability. Once stable responding to drug has been achieved, an extinction of this behaviour occurs where drug is no longer administered by depressing the active lever while the inactive lever remains inactive. After repeated lever pressing without drug administration, this behaviour is eventually extinguished. Once extinguished, presentation of the environmental cue (i.e.: a cue light) previously paired with drug administration can reinstate lever pressing on the active lever (Shippenberg and Koob 2008). This paradigm provides a model of relapse analogous to relapse that is often observed in humans following exposure to cues that have been paired with drug use, and serve as a method to investigate a construct similar to cue-induced craving in humans using animal models.
Using the above mentioned paradigm it has been shown that environmental cues such as a visual stimulus that have been paired with nicotine administration reinstate lever pressing on an active lever even after extinction of this behaviour (Liu, Caggiula et al. 2006). Furthermore, the presentation of environmental cues during acquisition increase the rate of lever pressing in drug naïve rats compared to those given nicotine without pairing of a cue (Caggiula, Donny et al. 2002). In a similar study, although either nicotine or cue alone had weak reinforcing properties, when they were combined a synergistic increase in lever pressing was observed (Palmatier, Evans-Martin et al. 2006) indicating that nicotine acts to increase the reinforcing properties of environmental stimuli which in turn increase the reinforcing properties of nicotine itself. In animals where response to nicotine has been extinguished, a priming dose and exposure to cues associated with drug administration or presentation of cues alone were sufficient to reinstate drug-seeking behaviour. As no significant differences were observed between administration of a priming dose and cues or cues alone, this provides further evidence of the importance of cues in reinstatement of drug-seeking behaviour (LeSage, Burroughs et al. 2004).

In addition to the direct effects of nicotine, it has been shown that after animals have been trained on a conditioned reinforcement task (visual stimulus and water administration on one lever, no response on the other), an acute dose of nicotine given prior to an administration session can increase responding on the active lever (Olausson, Jentsch et al. 2004). A similar increase in active lever pressing was also observed when nicotine was administered for 15 days prior to conditioning training (Olausson, Jentsch et al. 2004). Studies investigating the effect of more distal or contextual stimuli on drug
extinction or reinstatement have observed that after pairing of nicotine self-administration in a particular environment, extinction time was longer when conducted in this environment compared to a novel environment, although similar levels of responding were eventually reached in both contexts. When animals were primed with nicotine or presented with cues associated with drug administration, reinstatement of nicotine-seeking behaviour was slower when in the novel environment compared to the original environment, however only trend level significance was observed. Furthermore, when animals were placed in their original environment after extinction in the novel environment, significant reinstatement of nicotine-seeking was seen (Wing and Shoaib 2008).

**Summary Points:**

- Environmental cues paired with nicotine administration can reinstate nicotine seeking after extinction in rats
- Presentation of cues with nicotine administration increase rates of lever pressing
- After extinction, presentation of paired cues are sufficient to reinstate drug seeking behaviour
- After pairing of a particular environment with nicotine self-administration, extinction of self-administration is prolonged

**1.7.2 Human Studies**

Studies conducted where cues were presented in a smoker’s natural environment have shown that presentation of smoking cues evoke greater craving than neutral cues (Warthen and Tiffany 2009). These increases in craving in response to tobacco cues were also observed in functional magnetic resonance imaging studies. When levels of
activation were examined it was seen that activation remained similar between satiated and 12 hour abstinent conditions (McClernon, Hiott et al. 2005), but was greater than the satiated condition when examined after 24-hours of abstinence (McClernon, Kozink et al. 2009). Cue presentations in the laboratory environment have also shown to increase craving to smoke using in vivo (Shadel, Niaura et al. 2001; Erblich and Bovbjerg 2004), imaginal (Drobes and Tiffany 1997; Erblich and Bovbjerg 2004), imagery (Alsene, Li et al. 2003) and virtual reality (Bordnick, Graap et al. 2004; Carter, Bordnick et al. 2008) cue presentation techniques. Cue presentations have also been shown to reliably evoke craving to smoke even after repeated presentations (Miranda, Rohsenow et al. 2008). These results suggest that paradigms where cues are presented to individuals in a laboratory environment over multiple study sessions are a valid method to investigate cue-induced craving and potential treatments to attenuate these cravings.

Reactivity to in vivo smoking cues in non-treatment seeking smokers has been associated with smoking rate, whereby a positive association is observed between absolute craving (unadjusted for reactivity to neutral cues) on the QSU Total score and increases in smoking. However, when controlling for reactivity to neutral cues, this effect no longer remained significant (Carpenter, Saladin et al. 2009). In a study of 225 smokers comparing imaginal to in vivo smoking cues, greater reactivity to the in vivo, but not the imaginal cues was related to both shorter recent quit durations and short maximum quit durations and was marginally related to higher perceived quit difficulty (Erblich and Bovbjerg 2004).
Summary Points:

- Cue-induced craving paradigms are valid techniques to investigate this type of craving
- Reactivity to cues has been associated with smoking rate and quit duration

1.8 Neural Substrates of Cue-Induced Craving

While no specific studies investigating the neural substrates of tobacco cue-induced craving have been conducted, recent evidence from both human (Volkow, Wang et al. 2006) and animal (Schiffer, Liebling et al. 2009) studies has shown that presentation of cues paired with cocaine administration can induce dopamine release in the striatum. While these studies suggest a role of dopamine in cue-induced craving and reinstatement, other studies suggest that other neural substrates are also involved. In another animal study investigating reinstatement to cocaine self-administration after presentation of cues paired with this drug in rats, it was seen that administration of volinanserin, a 5-HT2A antagonist, was able to attenuate cue-induced reinstatement following extinction.

Studies investigating the neural substrates of alcohol cue-induced craving and reinstatement have found other pathways that may also be involved. Studies conducted in alcohol-dependent patients have found that administration of nalrexone, an opioid antagonist, was able to decrease alcohol cue-induced activation in the ventral striatum. Further studies in alcohol-dependent individuals administered memantine, a NMDA receptor antagonist, showed that memantine was able to dose-dependently attenuate alcohol cue-induced craving.
The results of these studies suggest that while cue-induced craving is influenced by dopamine, other neurotransmitters may play a significant role in cue-induced craving and further studies investigating these neural substrates are required.

**Summary Point:**
- While dopamine is believed to be the main neurotransmitter involved in cue-induced craving, other neurotransmitter systems such as the 5-HT, glutamine and the opioid system are likely involved

1.9 Role of Cue-Induced Craving on Smoking Cessation Success

While greater generalized craving after abstinence is associated with decreased smoking cessation success (Killen and Fortmann 1997; Shiffman, Engberg et al. 1997), results are both limited and mixed regarding whether the degree of cue-induced craving is predictive of relapse after a smoking cessation attempt. Many individuals attribute their relapses to smoking after a cessation attempt to viewing smoking cues or being in the presence of other smokers (Shiffman 1982; Bliss, Garvey et al. 1989; Shiffman, Paty et al. 1996). In a study investigating the effect of cue-induced craving on smoking relapse, it was found that when individuals who relapsed were compared to those who maintained abstinence and never smokers, those in the relapse group experienced significantly greater craving after a cue-presentation procedure than either those who maintained abstinence or non-smokers. However, a further experiment investigating the association between prospectively determined cue-induced craving and smoking cessation outcomes at 6 months found that while abstainers rated their anxiety levels lower than those who relapsed, no differences were observed on self-reported urge to smoke measures (Abrams, Monti et al. 1988).
In an additional study that stratified a cohort of individuals into those who relapsed vs. those who maintained abstinence, no difference in pre-cessation urge measures were observed between groups, although craving was numerically higher in those who relapsed (Niaura, Abrams et al. 1989). A more recent study smoking cessation study of 62 smokers where cue-induced craving was assessed prior to enrollment found that although smoking rate at end-of-treatment was predicted by score on the Fagerstrom Tolerance Questionnaire and heart rate during cue presentation, reactivity to smoking cues did not influence end-of-treatment smoking rates (Payne, Smith et al. 2006).

A recent study (N=1110) investigating smokers’ reactions to the smell of tobacco smoke encountered in their daily activities and its association to smoking relapse was conducted in a consecutive sample of individuals who had attended a smoking cessation clinic for treatment who had maintained smoking abstinence for one week. Those who found the smell of smoke tempting during the first two weeks had a greater rate of relapse during the following week. This relationship was not significant during the 4th and final week of the study, suggesting that this effect dissipated over time. When baseline characteristics were accounted for, age and temptation rating during the first week of the study predicted abstinence at weeks 2 and 3 whereas 4th week abstinence was predicted by level of dependence and age. However, when an individual’s mood and physical symptoms related to their urge to smoke were accounted for, this factor replaced temptation as a significant predictor while temptation no longer remained significant (McRobbie, Hajek et al. 2008).
Summary Points:

- Cue-induced craving has been shown to predict smoking cessation success, although some evidence suggests otherwise.
- Those who rated cues as tempting during a smoking cessation attempt had greater rates of relapse compared to those who did not

1.10 Alcohol and Nicotine – Cross Reactive Cue Induced Craving

As mentioned, alcohol and tobacco are commonly co-abused substances. It can therefore be hypothesized that over time, the common use of both substances causes the presentation of alcohol cues to elicit craving to smoke and vice versa. Previous studies have demonstrated that presentation of alcohol cues can increase urge to smoke in both alcohol-dependent (Gulliver, Rohsenow et al. 1995; Rohsenow, Monti et al. 1997), and non-alcohol-dependent (Drobes 2002) smokers. In a study conducted in nicotine-dependent light drinkers (defined as individuals who consumed at least one alcoholic beverage over the past month), presentation of social drinking relevant scripts induced craving for both alcohol and tobacco. This effect was observed to be stronger in those who reported frequent consumption of alcohol in social contexts. Furthermore, in the same study, presentation of smoking-related scripts also induced craving for both tobacco and alcohol (Erblich, Montgomery et al. 2009). Similarly, Drobes (2002) observed a similar effect in that alcohol-dependent smokers exhibited strong cravings to smoke or drink after being presented with either alcohol or tobacco cues (Drobes 2002).

Examination of electronic diary reports completed by alcohol-dependent smokers after discharge from a combined tobacco/alcohol treatment found that frequency of alcohol urges increased after smoking a cigarette (Cooney, Litt et al. 2007).
Summary Points:

- Presentation of alcohol cues can elicit craving to smoke.
- This effect is observed in both light social drinkers and alcohol dependent individuals.
- Alcohol urges increase after smoking episodes in alcohol-dependent individuals.

1.11 Nicotinic Acetylcholine Receptor Antagonists and Tobacco Cue-Induced Craving

While only limited evidence exists on the role of mecamylamine, a nicotinic acetylcholine receptor antagonist, on attenuation of cue-induced craving, animal data suggest that pretreatment with mecamylamine prior to presentation of conditioned stimuli associated with nicotine self-administration after extinction can decrease active lever presses (Liu, Caggiula et al. 2006) and can dose-dependently attenuate drug-seeking behaviour towards nicotine but does not alter food-seeking and consumption responses (Liu, Caggiula et al. 2007). Furthermore, a study investigating cue-induced cocaine craving in human cocaine-dependent individuals found that mecamylamine attenuated cue-induced subjective increases in craving after presentation of cocaine cues, but did not influence objective craving measures such as skin conductance (Reid, Mickalian et al. 1999). In a further study investigating the effect of mecamylamine on cue-induced craving in both individuals with schizophrenia and controls found that pretreatment with mecamylamine was able to dose-dependently reduce cue reactivity in smokers with schizophrenia. While mecamylamine was able to slightly decrease cue-reactivity in healthy controls, this decrease was not significant (Fonder, Sacco et al. 2005).
results of these studies, while limited, provide some evidence for the involvement of the cholinergic system in cue-induced craving.

Summary Points:

- Animal studies show that nAchR antagonists can decrease lever pressing after presentation of cues paired with nicotine administration.
- Human studies suggest nAchR antagonists can attenuate craving after presentation of cocaine cues.

1.12 Nicotinic Acetylcholine Receptors (nAChRs)

Nicotinic acetylcholine receptors are ligand-gated ion channels that contain five subunits that combine to create a functional receptor. Upon binding of one of the endogenous agonists, acetylcholine or an exogenous ligand such as nicotine, the channel opens allowing for the entry of ions such as calcium to enter (Benowitz 2008). These receptors are either heteromeric and composed of both α and β subunits or homomeric and contain only α subunits (Fowler, Arends et al. 2008). The most abundant subtypes in the human brain are the α4β2, α3β4, and α7 of which the α4β2 subtype is postulated to be the main receptor mediating tobacco dependence (Benowitz 2008). It is postulated that nicotine mediates its effect by promoting dopamine release in the nucleus accumbens by binding to nAChRs found on dopaminergic cell bodies in the ventral tegmental area. Blockade of these receptors with nAchR antagonists almost completely blocks the ability of nicotine to release dopamine in the nucleus accumbens thus providing further evidence that these receptors are mediating dopamine release (Pierce and Kumaresan 2006). Further evidence implicating the importance of the α4β2 nAchR on tobacco dependence has been elucidated using knockout mice lacking the gene that encodes the β2 subunit.
These animals did not exhibit the typical behavioural effects of nicotine, including self-administration (Picciotto, Zoli et al. 1998). Additional evidence implicating the β2 subunit to nicotine’s effects were observed when this gene was reinserted selectively into the ventral tegmental area in β2 knockout mice behavioural responses to nicotine were restored (Maskos, Molles et al. 2005).

1.13 Interaction of Ethanol with Nicotinic Acetylcholine Receptors

1.13.1 Animal Studies

Administration of ethanol has been shown to cause dopamine release in the nucleus accumbens using microdialysis techniques in both mouse (Middaugh, Szumlinski et al. 2003) and rat (Blomqvist, Engel et al. 1993; Ericson, Blomqvist et al. 1998; Gonzales and Weiss 1998) models. Existing evidence suggests that this effect may be mediated in part through the actions of ethanol on the nicotinic acetylcholine receptors. Studies using mecamylamine, a non-selective competitive nicotinic acetylcholine receptor antagonist, have found that while administration of mecamylamine alone did not have any effect on dopamine release compared to baseline levels, pretreatment with mecamylamine was able to attenuate the dopamine release observed following ethanol administration (Blomqvist, Engel et al. 1993; Ericson, Blomqvist et al. 1998) and also decrease ethanol self-administration (Ericson, Blomqvist et al. 1998) in a rat model. Further evidence linking ethanol to the nAchRs comes from studies in which nicotine and ethanol were co-administered. Blomqvist and his group showed that subchronic treatment of rats with nicotine significantly increased ethanol self-administration and an acute nicotine challenge increased locomotor activity in animals treated with nicotine for 10 days compared to animals treated with vehicle alone (Blomqvist, Ericson et al. 1996).
Administration of subthreshold doses of nicotine and ethanol administered concurrently had an additive effect on dopamine release. Administration of higher doses of nicotine and alcohol resulted in slightly increased levels of dopamine release compared to the administration of either substance alone, indicating that this effect was not additive (Tizabi, Copeland et al. 2002). A limitation of these studies is that both nicotine and ethanol were not self-administered and therefore may not represent the most valid model to compare these effects in the context of human consumption.

A further study conducted by Le and colleagues (Le, Corrigall et al. 2000) found that nicotine pretreatment enhanced alcohol self-administration while administration of mecamylamine significantly reduced alcohol consumption. In an attempt to elucidate the role of particular receptor subtypes on this effect, rats were pretreated with dihydro-β-erythroidine (DHβE), a selective α4β2 nAChR antagonist or mecamylamine. DHβE had no effect on alcohol consumption while mecamylamine (2mg/kg) significantly reduced alcohol consumption, suggesting that the α4β2 nAChR may not have a significant influence on alcohol consumption in rodents. A dose effect was also observed with mecamylamine with larger doses being associated with decreased alcohol consumption. A further study conducted in male mice given an α7 nAChR antagonist methyllycaconitine citrate or DHβE found that neither drug reduced the locomotor stimulatory effects. Administration of either of these compounds also had no effect on ethanol-induced dopamine overflow, whereas mecamylamine administration completely antagonized this effect (Larsson, Svensson et al. 2002).
Summary Points:

- Ethanol administration has been shown to cause dopamine release in the nucleus accumbens and this effect may be mediated in part through the nicotinic acetylcholine receptor since pretreatment with nicotine increases ethanol self-administration.

- Mecamylamine blocks any ethanol induced increase in dopamine release and self-administration.

- Receptor subtype mediating this effect is still not fully elucidated.

1.13.2 Human Studies

In a double-blind, within-subject, placebo-controlled, crossover design study (N=20) conducted in healthy, non-dependent subjects, administration of mecamylamine decreased the stimulant effects of ethanol compared to placebo and decreased blood alcohol concentrations (Blomqvist, Hernandez-Avila et al. 2002). In a similarly designed study (N=27) of moderate social drinkers (minimum of three drinks per week and consuming at least three drinks on any one occasion) who were not tobacco dependent, mecamylamine significantly decreased the stimulant effect of alcohol but did not alter subjective ratings of euphoria or sedation compared to placebo. No objective measures, including vital signs or blood alcohol concentration, were altered after mecamylamine administration (Chi and de Wit 2003). In another study of non-problem social drinkers (N=24) given an alcoholic drink after being administered placebo, alcohol was able to increase measures of euphoria and stimulation as measured by the Addiction Research Center Inventory (ARCI). Administration of mecamylamine prior to alcohol administration attenuated this increase. A behavioural economic analysis of this study
showed that although mecamylamine did not change alcohol consumption when the entire sample was analyzed together, when subjects were stratified according to whether they experienced stimulant effects from alcohol, those in the high stimulation group decreased their choice for alcohol compared to monetary reward (Young, Mahler et al. 2005).

**Summary Points:**

- Mecamylamine is able to decrease stimulant effects of alcohol
- Behavioural economic analysis showed that in a subset of non-problem social drinkers, mecamylamine was able to decrease choice for alcohol compared to monetary reward.

1.14 Varenicline

1.14.1 Initial Development

The initial development of varenicline was based on the structural design of the nicotinic acetylcholine receptor partial agonist (-)-cytisine. Although cytisine was investigated as a smoking cessation aid in the 1960s, it did not exhibit strong efficacy and therefore did not gain widespread appeal. Although cytisine has limited efficacy as a smoking cessation aid, it has been shown to block the effect of acetylcholine at the α4β2 receptor while still providing some agonist effect when administered alone (Papke and Heinemann 1994). These results suggested that a more potent partial agonist at the α4β2 nAChR receptor may be more efficacious as a smoking cessation aid.

Further positive yet limited evidence was obtained from studies investigating combined agonist and antagonist therapy. Three randomized, double-blind, placebo controlled studies investigating the combined use of nicotine replacement therapy and
mecamylamine have been conducted with mixed results. One study (N=80) investigating the effect of pre-cessation treatment with mecamylamine and nicotine patch, mecamylamine alone, nicotine alone or placebo, found that pre-cessation mecamylamine (mec + nic and mec alone vs. nicotine only and placebo) was significantly more effective at increasing continuous abstinence rates. However, pre-cessation treatment did not have any effect on 6-month point prevalence or continuous abstinence rates, although post-hoc comparisons showed that mecamylamine and nicotine continuous abstinence rates were greater than pooled data from the three other treatment groups (Rose, Behm et al. 1998). In another study (N=48) individuals were administered nicotine patch (started either 2 weeks prior to or on the target quit date for 6 to 8 weeks total treatment duration) and either mecamylamine (5 weeks total treatment started 2 weeks prior to target quit date) or placebo. It was seen that continuous and point prevalence abstinence after 7 weeks of treatment was greater in the groups administered mecamylamine vs. those administered placebo (Rose, Behm et al. 1994). While these studies suggest a beneficial effect of mecamylamine on smoking cessation outcomes, a more recent study (N=540) investigating the efficacy of a combined nicotine/mecamylamine patch did not find significantly different continuous abstinence rates after 4 weeks of treatment between those receiving mecamylamine and nicotine vs. those receiving nicotine alone (Glover, Laflin et al. 2007). These studies suggest that mecamylamine was no more effective than nicotine alone at increasing abstinence rates. While the findings from these studies do not agree, they did provide evidence that nicotinic acetylcholine receptor partial agonism through a single partial agonist may be an effective smoking cessation pharmacotherapy.
Based on these studies, varenicline, a synthetic compound which is a partial agonist of the α4β2 nicotinic acetylcholine receptor, the main receptor subtype implicated in nicotine dependence was made by making substitutions to (-) – cytisine. This drug demonstrated greater efficacy and potency than an agonist/antagonist combination treatment.

Summary Points:

- Varenicline is a partial agonist of the α4β2 nicotinic acetylcholine receptor, the main receptor subtype implicated in tobacco dependence.

- Varenicline is based on the structural design of (-)-cytisine, which only exhibited only limited efficacy as a smoking cessation aid.

- Combined agonist/antagonist (nicotine patch/mecamylamine) therapy provided results suggestive of greater efficacy as smoking cessation aid of dual therapy compared to each alone.

1.14.2 Pharmacology

1.14.2.1 Absorption

A single-dose pharmacokinetic study (N=102) found that a dose of up to 3mg was tolerated in smokers and 1mg in non-smokers however nausea and vomiting occurred at the higher doses (Faessel, Smith et al. 2006). In a multiple dose pharmacokinetic study (N=44) doses of varenicline up to and including a dose of 2mg daily were well tolerated. Mean plasma varenicline concentrations were higher after repeat dosing compared to single dose administration indicating drug accumulation following once or twice-daily oral administration. Maximum plasma concentration was achieved approximately 2 to 4
hours post-dose. Steady-state concentrations were reached after 4 days of repeated twice per day dosing (Faessel, Gibbs et al. 2006).

1.14.2.2 Distribution

Varenicline has a low level of binding to plasma proteins (≤ 20%). This effect is independent of both renal function and age (Canadian Pharmaceutical Association).

1.14.2.3 Metabolism

Varenicline is excreted mostly unchanged in urine, with 81% of the drug being excreted as the parent compound and 99% of a dose is recovered in the urine. The major metabolites in humans are a N-formyl conjugate, N-carbamoyl glucuronide, N-hexose conjugate and an unidentified metabolite of the parent compound (Obach, Reed-Hagen et al. 2006).

1.14.2.4 Excretion

The half-life of varenicline ranges between 16 to 27 hours after a single dose and between 18 to 43 hours after repeat dosing (Faessel, Gibbs et al. 2006; Faessel, Smith et al. 2006). Varenicline is excreted mainly by renal elimination through glomerular filtration and active tubular secretion via OCT2, an organic cationic transporter (Canadian Pharmaceutical Association).

Summary Points:

- Peak plasma concentrations of varenicline are reached after 2-4 hours.
- Steady state concentrations are reached after 4 days of dosing.
- Varenicline is excreted mostly unchanged in urine.
- Half-life ranges between 18 and 43 hours after repeat dosing.
1.14.3 Preclinical Studies

Varenicline displays high binding affinity and selectivity for the rat $\alpha_4\beta_2$ nAchR over other nAchR subtypes investigated. Compared to nicotine, varenicline was able to evoke 32% of the maximal response seen with nicotine, while cytisine evoked 40% of this response. Further investigation using in vivo methods to examine the ability of these drugs to attenuate the effect of nicotine on mesolimbic dopamine (determined by co-administering these agents with 1mg/kg sc of nicotine) showed that (-)-cytisine reduced nicotine-induced increase in dopamine by 36% while varenicline attenuated this effect by 66% at the maximal tolerated dose (5.6mg/kg). Furthermore, varenicline was able to fully attenuate the effect of nicotine on dopamine release and uptake to a level that was similar to varenicline alone (Coe, Brooks et al. 2005).

A further assessment of the pharmacological properties of varenicline conducted by Rollema et al. (Rollema, Chambers et al. 2007) showed that varenicline exhibited approximately a 20-fold higher affinity for human $\alpha_4\beta_2$ nAchR than nicotine while exhibiting a low binding affinity to other non-nicotinic neurotransmitter receptors, and other non-receptor sites including ion channels, modulatory binding sites, enzyme and transporter sites.

In vitro patch clamp of HEK293 cells stably transfected with human $\alpha_4\beta_2$ and $\alpha_3\beta_4$ nAchR found that the intrinsic agonist efficacy of varenicline at the $\alpha_4\beta_2$ nAchR was 45% relative to nicotine. These findings are similar to those observed in xenopus oocytes as reported by Coe et al. (2005). Furthermore, the acute application of varenicline during the continuous application of nicotine at a concentration of 10$\mu$M caused a concentration-dependent but partial, inhibition of nicotine-evoked currents. In
vitro assays using rat striatal slices showed that varenicline produced concentration-dependent increases in $[^{3}\text{H}]$-dopamine release that were significantly lower than those induced by 10μM nicotine and which reached only 51% of the maximal nicotine effect. Furthermore, when combined with nicotine, varenicline reduced the nicotine-evoked $[^{3}\text{H}]$-dopamine release by 53%, a level similar to that seen when varenicline was administered alone (Rollema, Chambers et al. 2007).

In vivo microdialysis studies investigating the time courses associated with maximally effective doses of nicotine and varenicline showed that varenicline-induced increases in the extracellular level of dopamine and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) are smaller than nicotine-induced effects observed at 0.5 to 1 hour after drug administration. Furthermore, confirming the in vitro results, in vivo results show that extracellular levels of dopamine, DOPAC and HVA are significantly decreased with varenicline compared to those seen with nicotine administration, to a level approximately 40 – 60% of the maximal nicotine response. When varenicline was co-administered with a maximally effective dose of nicotine, dopamine turnover and release were significantly reduced compared to that seen with nicotine alone and similar to those seen when varenicline was administered alone (Rollema, Chambers et al. 2007).

Behavioural experiments conducted in rats trained to self-administer nicotine according to a fixed-ratio 5 schedule showed that pretreatment with varenicline (subcutaneous or oral administration) reduced nicotine intake to a level similar to that seen with saline substitution. This observed effect was specific to nicotine intake, as a separate group of nicotine experienced rats did not decrease their responses for food
when pretreated with varenicline. Although the response rate observed was greater in these animals, it was not associated with increased locomotor activity or food intake. In experiments conducted using a progressive-ratio schedule nicotine supported a higher break point than saline. Varenicline administration produced significantly fewer infusions than nicotine treatment and exhibited a significantly lower breakpoint than nicotine (Rollema, Chambers et al. 2007).

Studies of drug discrimination using rats taught to distinguish nicotine found that varenicline was able to significantly and dose-dependently increase the response rate and fully substitute for nicotine, suggesting that these drugs both have similar drug effects.

The results of these studies all suggest that varenicline is able to block dopamine release following nicotine administration while maintaining the ability to release some dopamine on its own. The partial agonist properties of varenicline could therefore be useful in attenuating cravings in a therapeutic context.

**Summary Points:**

- Varenicline displays high binding affinity and selectivity for \( \alpha_4\beta_2 \) over other nAchRs.
- Varenicline administered alone causes approximately 50% of dopamine release compared to a full agonist e.g.: nicotine
- Varenicline attenuated the effect of nicotine on dopamine release similar to the level when varenicline was administered alone
- Pretreatment with varenicline reduces nicotine intake, and varenicline exhibits lower breakpoints than nicotine
1.14.4 Clinical Studies

1.14.4.1 Phase II Studies

The safety and efficacy of varenicline has been investigated in two Phase 2 clinical trials. Nides et al (2006) (N=638) compared three different doses (0.3mg once daily, 1mg once daily or 1mg twice daily) of varenicline to sustained release bupropion hydrochloride (150mg twice daily) or placebo. Continuous abstinence rates during any 4 weeks of treatment were greater for varenicline 1mg twice daily and 1mg once daily doses than for placebo (48.0%, 37.3% and 17.1%, respectively). Carbon-monoxide (CO) confirmed continuous abstinence rates during 4 to 52 weeks of treatment were also significantly greater in the varenicline 1mg twice daily group compared to the placebo group (14.4% vs. 4.9%) (Nides, Oncken et al. 2006). In another study by Oncken et al. (2006) (N=647), the optimal dosing regimen to maximize efficacy and minimize adverse events was investigated. Participants were randomized to one of five groups consisting of different doses and schedules (0.5mg or 1mg twice daily either titrated or not titrated over the first week of treatment) of varenicline or placebo for 12 weeks, with a 40 week unmedicated follow-up period. CO confirmed 4 week continuous abstinence rates for weeks 9-12 and continuous abstinence rates from 9-52 weeks were greater in the 1mg dose compared to the 0.5mg dose and placebo (49.4%, 44.0% and 11.6% and 22.4%, 18.5% and 3.9% respectively). Titration of these doses decreased the incidence of nausea (Oncken, Gonzales et al. 2006).

Summary Points:

- Continuous abstinence rates at end of treatment were greater in the varenicline group compared to placebo
• The greatest efficacy was observed at a dose of 1mg. Dose titration decreased the incidence of nausea.

1.14.4.2 Phase III Studies

Three Phase III clinical trials were subsequently conducted to further investigate efficacy and safety of varenicline. Two of these trials (Gonzales, Rennard et al. 2006; Jorenby, Hays et al. 2006) were double-blind, randomized, placebo and active-treatment controlled studies investigating the efficacy of 12-weeks of varenicline therapy compared to sustained-release bupropion and placebo. Results of the Gonzales et al. study (n=1025) showed that varenicline was significantly more efficacious than both bupropion SR and placebo at maintaining continuous abstinence during both the last 4 weeks of treatment (44.0%, 29.5% and 17.7%, respectively) and at maintaining abstinence up to 52 weeks (21.9% vs. 8.4%) (Gonzales, Rennard et al. 2006). A similarly designed Phase III study (N=1027) conducted by Jorenby et al found comparable results. In this study, varenicline was significantly more efficacious at maintaining continuous abstinence during the last four weeks of treatment compared to both bupropion SR and placebo (43.9%, 29.8% and 17.6%, respectively) and at the end of 52 weeks after treatment (23.0% for varenicline vs.14.6% for bupropion SR and 10.3% for placebo) (Jorenby, Hays et al. 2006).

The third Phase III trial (Tonstad, Tonnesen et al. 2006) was 12-week open-labeled study of varenicline followed by a double-blind, randomized, placebo controlled trial of an additional 12-weeks of treatment of either varenicline or placebo in those who maintained abstinence during the open-label segment of the study (N=1210). The aim of this study was to investigate the efficacy of varenicline maintenance therapy for
continued abstinence beyond the first 12 weeks of treatment. The results of this study demonstrated that CO-confirmed continuous abstinence was significantly higher for varenicline (43.6%) vs. placebo (36.9%) between weeks 13 and 52 of treatment (Tonstad, Tonnesen et al. 2006).

These studies suggest that varenicline is more effective than Bupropion SR after 12 weeks of treatment and is effective at maintaining abstinence up to 52 weeks after a quit date in those who were successful at maintaining abstinence for 12 weeks on varenicline.

Studies investigating the effectiveness of varenicline conducted in the general population have shown similar smoking cessation rates as those observed in efficacy trials (Blak, Wilson et al.; Ramon and Bruguera 2009), confirming the utility of this medication as a smoking cessation pharmacotherapy.

**Summary Points:**

- Varenicline is significantly more effective than sustained-release bupropion and placebo at maintaining abstinence at end of treatment and follow-up.
- Extended course of varenicline was effective in those who successfully maintained abstinence at 12 weeks to maintain smoking abstinence up to 52 weeks.

**1.14.5 Long-term Studies**

A study (N=375) of a 52-week course of varenicline showed 7-day point prevalence abstinence rates to be 36.7% for varenicline and 7.9% for placebo at 52 weeks (Williams, Reeves et al. 2007), suggesting that long-term treatment with varenicline may be an effective option for maintaining smoking abstinence.
1.14.6 Studies comparing varenicline to NRT

Studies comparing the efficacy of varenicline to nicotine replacement therapy showed that varenicline is a more efficacious smoking cessation aid. One recent open-label trial (N=757) comparing 12 weeks of varenicline treatment to 10 weeks of nicotine replacement therapy found that the continuous abstinence rate during the last 4 weeks of treatment was greater for varenicline compared to NRT (55.9% vs. 43.2, p<0.001) but not significantly different at 1 year (26.1% vs. 20.3%, p=0.056) (Aubin, Bobak et al. 2008).

Summary Points:

- Varenicline is more effective at maintaining continuous abstinence during the last 4 weeks of treatment, but not at 52 weeks compared to NRT.

1.14.7 Safety and Efficacy of Varenicline in Populations with Psychiatric Disorders

1.14.7.1 Efficacy in Populations with Psychiatric Disorders

To date, only a limited number of studies have investigated the efficacy of varenicline in a population with psychiatric disorders. A recent retrospective review of veterans with a high prevalence of mental illness prescribed varenicline found that those with underlying mental illness were more likely to fail a smoking cessation attempt (Purvis, Mambourg et al. 2009) suggesting that a sustained smoking cessation attempt is more difficult in those with mental illness. A study comparing varenicline (N=208) to NRT (N=204) in individuals with (N=112) and without (N=300) mental illness, found that varenicline exhibited a similar advantage over NRT as a smoking cessation aid in both those with and without mental illness (Stapleton, Watson et al. 2008). A case series investigating the effectiveness of varenicline as a treatment in smokers with schizophrenia reported that 13 of the 18 patients who remained in treatment were able to
quit smoking within 10 to 21 days of starting varenicline and were able to maintain self-reported abstinence for greater than 12 weeks (Evins and Goff 2008). In a case study reported by Ochoa (Ochoa 2009) varenicline treatment was able to decrease smoking behaviour in an individual diagnosed with bipolar disorder, not otherwise specified. These studies provide limited evidence of the efficacy of varenicline in populations with mental illness, therefore further studies in this population are required.

Summary Points:

- Varenicline is effective as a smoking cessation pharmacotherapy in populations with psychiatric disorders, however evidence is limited and further studies are required to establish effectiveness in this population.

1.14.7.2 Safety of Varenicline in Populations with Psychiatric Disorders

No significant increases in the incidence of exacerbations of psychiatric symptoms have been reported in studies conducted in populations with psychiatric disorders. In a study by Purvis et al (2009), (N=50) 5 patients experienced increases in psychiatric symptoms while taking varenicline and of these 4 discontinued treatment due to increases in motor and cognitive disturbances; however all returned to baseline after the discontinuation of varenicline therapy. All 4 of these individuals had a history of psychiatric illness. No reports of suicidal ideation were observed in the entire patient sample. In contrast, Stapleton et al (2008) did not observe any greater rate of adverse symptoms in those with mental illness than in those without, although one participant did experience a neuropsychiatric reaction consisting of feelings of anxiety, paranoia, confusion and impaired motor control (Stapleton, Watson et al. 2008). Evins and Goff (2008) also did not report signs of psychotic relapse or significant worsening of
psychiatric symptoms (Evins and Goff 2008) and Ochoa (2009) did not observe any increase of any symptoms of psychosis, mania or hypomania.

Although these studies only reported limited exacerbations of mental illness, a pivotal report by the Institute for Safe Medication Practices documented the incidence of neuropsychiatric and other adverse effects including accidents, vision problems and problems with glycemic control (Moore, Cohen et al. 2008), prompting further investigation of these adverse reactions by public health agencies. However, it should be noted that this report was not peer reviewed and the incidence of reported neuropsychiatric events may have been exaggerated because it was based, in part, on symptoms disclosed by individuals calling a Pfizer sponsored quit line and therefore may have been related to nicotine withdrawal.

Other case reports documenting cases of exacerbation of psychiatric disorders have been reported. Individuals with bipolar disorder have experienced episodes of mania, irritability, suicidal ideation and psychotic symptoms after taking varenicline (Kohen and Kremen 2007; Morstad, Kutscher et al. 2008; Alhatem and Black 2009; DiPaula and Thomas 2009). Similarly, individuals with schizophrenia or schizoaffective disorder have experienced episodes of psychotic relapse and manic episodes (Freedman 2007; Liu, Tsai et al. 2009). Furthermore, individuals with a history of depression or depression and other psychiatric disorders including post traumatic stress disorders, drug or alcohol abuse, generalized anxiety disorder and borderline personality disorder have reported symptoms such as decrease mood, suicidal ideation, severe anxiety, irritability, paranoia, and visual hallucinations (Lyon 2008; Pirmoradi, Roshan et al. 2008; Pumariega, Nelson et al. 2008; Spirling, Stapleton et al. 2008; Raidoo and Kutscher
In all these case reports, these psychiatric symptoms resolved upon the discontinuation of varenicline. In some cases, individuals who had no previously documented mental health issues reported neuropsychiatric symptoms while taking varenicline or upon discontinuation (Kutscher, Stanley et al. 2009; Laine, Marttila et al. 2009). These symptoms included paranoia, anxiety, suicidal ideation and visual hallucinations. Furthermore, one case of a completed suicide without any known history of depression has been reported and was attributed to varenicline as no other drugs or alcohol were quantified in a blood drug screen (Kintz, Evans et al. 2009). However the precipitating factor or other reasons that may have prompted this suicide attempt were unknown.

These reported adverse events prompted the US Food and Drug Administration (FDA) to release a black box warning for both varenicline and bupropion regarding the incidence of changes of behaviour such as depressed mood, suicidal thoughts or actions. Health Canada also released a similar warning stating that individuals who have concomitant psychiatric conditions, even if currently well controlled, or those who have a history of psychiatric symptoms, should be monitored closely by their physician while taking varenicline.

**Summary Points:**

- In studies conducted in populations with psychiatric disorders, no significant increases in the incidence of exacerbations of psychiatric symptoms were reported, although some exacerbations were reported by individual patients.
- Case reports of exacerbations of psychiatric illness have been reported, however most of these symptoms subsided upon discontinuation of varenicline.
• These reports prompted the FDA and Health Canada to issue warnings informing physicians and patients of possible changes in behaviour such as depressed mood, suicidal thoughts or actions while taking varenicline.

1.14.8 Varenicline and Depression

1.14.8.1 Animal Studies

One of the main symptoms of concern while taking varenicline includes depressive symptoms and suicidal ideation. In a preclinical study investigating the effects of varenicline on mouse mobility on the forced swim test, varenicline significantly reduced immobility in both C57BL/6J and CD-1 mice at most doses investigated, however this effect was more prominent in the C57BL/6J mice. Varenicline also did not increase locomotor activity. Varenicline produced similar swim scores as sertraline (a selective serotonin reuptake inhibitor), and the co-administration of varenicline and sertraline resulted in a swim time that was greater than that recorded for sertraline alone. The swim scores obtained when these drugs were co-administered were comparable to those seen after the administration of amitriptyline (a tricyclic antidepressant) (Rollema, Guanowsky et al. 2009).

Summary Points:

• Varenicline significantly reduced immobility in forced swing test in mice
• Forced swim test times were similar to those with sertraline and conadministration of varenicline and sertraline resulted in swim times that were greater than sertraline alone and similar to amitriptyline.
1.14.8.2 Human Studies

Patterson, et al (2009) investigated the role of varenicline on mood and cognition using a double-blind, within-subject crossover design. Individuals (N=67) were required to abstain from smoking for 3 days after taking varenicline or placebo for 10 days. The varenicline group reported lower levels of withdrawal symptoms (p=0.04), smoking urges (p<0.001), negative affect (p=0.013) and greater positive affect (p=0.046) compared to placebo (Patterson, Jepson et al. 2009). Two recent studies have been conducted investigating the effect of varenicline in depressed smokers. In one open label study, 18 depressed smokers currently on a stable dose of antidepressants or mood stabilizers who still experienced persistent depressive symptoms demonstrated significant improvement in depressive symptoms after varenicline compared to baseline (p<0.001). Furthermore, although no explicit smoking cessation interventions were provided during this study, 8 participants were able to achieve abstinence and 9 were able to reduce their levels of smoking (Philip, Carpenter et al. 2009). In a large multicentre study (N=1,117), mood and the prevalence and intensity of treatment related side-effects as well as abstinence was investigated in individuals either with or without a probable history of major depressive disorder (MDD) who were receiving varenicline as a smoking cessation aid. Mean change in depressive symptoms from baseline to each follow up were greater in the group without a history of MDD than in those with a history at 21 days (-0.19 in the depression history positive group vs. -0.33 in the depression history negative group, p<0.001) and at 3 months (-0.22 for history of depression positive vs. -0.32 for history of depression negative, p=0.02). However it should be noted that there was a significant increase in depressive symptom scores in individuals with a history of depression (9.7%)
compared to those without a history of depression (7.9%) at 21 days (p=0.33).

Compared to the depression negative group, the severity of adverse reactions reported in those with a history of depression were slightly worse confusion, nausea and trouble sleeping as well as reports of recent tension or agitation, irritability or anger, confusion and depression at 21 days (McClure, Swan et al. 2009). It should be kept in mind however that the characterization of history of MDD was completed using only a single item from the DSM-IV criteria, specifically participants were asked “if they had ever in their lifetime experienced a period of two weeks or more when they felt down, depressed or hopeless or had little interest or pleasure in doing things”. An answer of yes to this question was indicative of a history of major depression for this study. A diagnosis of MDD in the DSM-IV requires that this criteria be met, and that individuals exhibit three of 7 criteria during that aforementioned two week period: Based on this study’s methodology, it is likely that MDD may have been over-reported.

Summary Points:

- Administration of varenicline is able to decrease negative and increase positive affect compared to placebo during short term abstinence.
- Varenicline was able to significantly decrease depressive symptoms compared to placebo in individuals experiencing persistent depressive symptoms.
- In those taking varenicline with or without a probable history of major depressive disorder, a significant increase in depressive symptoms was observed in those with a probable history compared to those without a history of MDD.
1.14.9 Effect of Varenicline on Alcohol Consumption

1.14.9.1 Animal Studies

A pivotal study conducted in rats trained to self administer alcohol under a fixed-ratio (FR3) schedule of reinforcement showed that varenicline (0.3, 1 or 2 mg/kg s.c.) was able to attenuate operant self-administration of 10% ethanol compared to vehicle when administered 30 minutes prior to the study session. While a variety of doses were tested, the decrease in alcohol self-administration was observed most robustly at the 1 and 2mg/kg doses. This decrease was not observed in the self-administration of 5% sucrose suggesting that the vehicle does not change locomotor behaviour per se. In the same study, alcohol consumption was measured using the continuous 2-bottle choice drinking paradigm. After the rats were maintained at a stabilized level of 10% ethanol consumption over 8 weeks, either 1 or 2 mg/kg varenicline sc was administered 30 minutes prior to ethanol access. Varenicline decreased ethanol consumption for up to 6 hours after administration (although this effect was more pronounced at 30 minutes than at 6 hours). This effect was specific only to alcohol as water consumption was not affected. Both water and alcohol consumptions returned to baseline 24 hours after varenicline treatment. Chronic administration of varenicline (2mg/kg sc daily for 6 days) reduced ethanol consumption compared to baseline, and when treatment was discontinued, alcohol consumption levels returned to baseline (Steensland, Simms et al. 2007). In another study in mice, varenicline was able to decrease ethanol consumption for 3 hours post dose, but had no significant effect on water consumption. When mice were examined 23 hours after drug administration, no residual effect on alcohol
consumption was noted. Varenicline also did not have any effect on saccharin or food consumption (Kamens, Andersen et al.).

Other studies investigating the effects of varenicline on dopamine release associated with alcohol administration showed that when rats were administered a 1.5mg/kg sc dose of varenicline concomitantly with alcohol, varenicline was able to prevent the dopamine release observed when each substance was administered alone. A further experiment investigating the effect of varenicline (1.5mg/kg s.c. daily for 5 days) vs. saline on dopamine release after nicotine, alcohol or concomitant administration of both substance showed that while varenicline was able to attenuate an increase in dopamine release after an acute administration of nicotine, it did not prevent this increase when alcohol was administered alone or in combination with nicotine (Ericson, Lof et al. 2009).

Studies investigating the effect of varenicline on ethanol-induced deficits in learning have also observed a positive effect of varenicline. In this study, mice that were given a paired conditioned (30s of white noise)-unconditioned stimulus (2 s foot shock) in a particular environment were found to freeze upon presentation of the environment (associated with hippocampus-dependent contextual learning) but not upon presentation of the noise (associated with hippocampus-independent cued learning) when administered alcohol. However when varenicline was administered, mice froze to both the environment and to the cue; when both varenicline and ethanol were given, animals froze significantly more after presentation of the environment and the cue compared to animals given alcohol alone. These results suggest that varenicline may play a role in
alleviating some of the learning deficits observed after ethanol administration (Gulick and Gould 2008).

Summary Points:

- Administration of varenicline was able to decrease self-administration of ethanol compared to vehicle.
- Using a 2-bottle choice drink paradigm, varenicline decreased ethanol consumption while no effect was observed on water consumption.
- Varenicline decreased dopamine release after nicotine administration but not after ethanol was administered alone or in combination with nicotine.

1.14.9.2 Human Studies

To date, only a single human study (N=20) has been conducted investigating the role of varenicline on alcohol consumption. In this double-blind, placebo controlled study, varenicline was administered for 7 days according to an accelerated titration schedule (0.5mg daily for 2 days, 0.5 mg twice daily for 3 days, followed by 1mg twice daily for 2 days). Subjects then participated in a laboratory session where they were given a priming dose of alcohol followed by a period where they were allowed to drink up for four drinks or receive a monetary reward for each drink they chose not to consume. Varenicline significantly decreased the number of drinks consumed during the self-administration period and also decreased the subjective effects of alcohol compared to placebo. Varenicline also reduced the number of cigarettes smoked during the designated cigarette breaks and attenuated the increase in alcohol craving observed after administration of the priming drink (McKee, Harrison et al. 2009).
Summary Points:

- Varenicline significantly decreased number of drinks consumed after administration of a priming drink of alcohol and decreased the subjective effects of alcohol compared to placebo.

1.15 Overall Summary:

Based on the review of the literature, pharmacotherapeutic interventions to attenuate cue-induced craving are limited. While no specific studies have been published regarding the efficacy of varenicline on attenuating tobacco cue-induced craving, studies using mecamylamine have shown decreases in cocaine cue-induced craving. These results suggest that the cholinergic system may influence cue-induced craving and therefore further studies investigating this effect with varenicline, a novel α4β2 nicotinic acetylcholine receptor partial agonist, are required.

The limited number of studies investigating the influence of varenicline on alcohol consumption do show a decrease in consumption however further studies are required to confirm this effect.
Section 2: Materials and Methods

2.1 Study Design

This was a randomized, double-blind, placebo controlled trial investigating the efficacy of varenicline in reducing cue-induced craving after exposure to tobacco and alcohol cues. Secondary outcome measures included self-reported changes in consumption of tobacco and alcohol. A total of 24 subjects were included in this study. Throughout the study, self-reported measures of tobacco and alcohol consumption were determined through the completion of a daily diary. The total duration of the study was 3 weeks and included 4 visits comprising of an assessment visit, a baseline study day, a mid-study visit and a final study day. The overall study design is summarized in figure 2.1 below. This study was approved by the CAMH Research Ethics Board and was conducted in accordance with the Declaration of Helsinki. The study was registered on as a clinical trial on www.clinicaltrials.gov.

Figure 2.1: Outline of overall study design. Subjects attended the laboratory on 4 separate occasions over a 3 week period. First visit (not shown) was an assessment day where eligibility was determined.
2.2 Subject Selection

2.2.1 Inclusion Criteria

Subjects were eligible to participate if they were 1. Treatment seeking smokers; 2. Were 18 to 65 years old; 3. Smoked greater than 10 cigarettes per day; 4. Scored greater than 3 on the Fagerstrom Test for Nicotine Dependence (FTND); 4. Scored less than 8 on the Alcohol Use Disorder Identification Test; 5. Drank less than 14 standard alcoholic drinks per week for males or less than 9 drinks per week for females and 6. Were able to provide informed consent (See Appendix 1).

2.2.2 Exclusion Criteria

Exclusion criteria included 1. Any medical condition requiring immediate investigation or treatment; 2. A Beck Depression Inventory score of greater than 16; 3. Currently taking insulin for diabetes mellitus; 4. Drinking more than 14 standard alcoholic drinks per week for males or greater than 9 standard drinks per week for females and also maintain a pattern of consuming not more than 2 to 3 drinks per occasion; 5. Pregnancy or lactation; 6. Any current diagnosis of DSM-IV Axis 1 psychiatric disorder or 7. any regular use of any therapeutic or recreational psychoactive drug use during the last three months or other substance use disorder with the exception of tobacco.

2.3 Subject Recruitment

Subjects were recruited by placing advertisements in NOW Magazine, Metro Toronto newspapers, craigslist.org and through placement of advertisements in the downtown Toronto area, the University of Toronto St. George campus and the 4 CAMH campuses.
Of the 673 individuals who responded to our advertisements, 447 were able to be contacted. Of these, 66 met initial criteria as assessed through the telephone prescreening form and were requested to attend CAMH to have a full assessment. Thirty seven assessments were conducted. Eleven individuals were not eligible at the end of this assessment. Two individuals refused to sign the consent form due to concerns regarding the adverse events associated with varenilcine. A total of 26 participants were eligible to participate in the study, however 2 withdrew from the study prior to study day 1 due to unexpected work commitments and 1 subject missed their first study day and was unable to be contacted. See recruitment flowchart below in figure 2.2.
Figure 2.2: Assessment Flowchart. Six hundred and seventy three calls were received by participants interested in participating in this study, however after completing all screening procedures only 26 were eligible of which 24 completed the study.

### 2.4 Subject Assessment

#### 2.4.1 Pre-Screening Procedure

Subject eligibility was initially determined through a telephone interview. During this interview, subjects were provided with information regarding the study and were asked questions regarding their smoking history, alcohol use over the past year, depressive symptoms experienced over the past two weeks and their current drug use.
Nicotine dependence was assessed using the Fagerstrom Test for Nicotine Dependence (Heatherton, Kozlowski et al. 1991), a 6 item questionnaire used to assess severity of nicotine dependence. Preliminary screening for alcohol use was conducted using a modification of the alcohol component of the CAMH Monitor (Adlaf, Ialomiteanu et al. 2008). To determine whether a major depressive episode was present, the depression section of the MINI International Neuropsychiatric Interview (Sheehan, Lecrubier et al. 1998) was administered and individuals were asked about their current use of any antidepressants. General questions regarding pregnancy or lactation in females, colour blindness, diagnosis of insulin-dependent diabetes and a brief drug use history were also administered at this time.

2.4.2 Assessment Day Procedures

Subjects who met the screening criteria were invited to attend CAMH for a full detailed assessment. At the beginning of the interview, subjects were provided further information about the study and if they were still interested in participating at this time, informed consent was obtained. To ensure that the informed consent was not obtained while the subject was under the influence of alcohol, a breath sample was obtained using a breathalyzer (Alco-Sensor IV, Intoximeters Inc, St. Louis, MO). A blood alcohol concentration of 0.000 was required to proceed. After demographic information was collected, the Alcohol Use Disorders Identification Test (AUDIT) and the Beck Depression Inventory (BDI) were administered to screen for any alcohol use disorders over the past 12 months and any depressive symptoms over the past 2 weeks, respectively. A detailed substance use history was obtained, including lifetime and current drug use. A general mental health assessment was then conducted using the
MINI International Neuropsychiatric Interview (Sheehan, Lecrubier et al. 1998) to rule out any undiagnosed past or current psychiatric condition. Subjects who remained eligible at this time had blood and urine samples collected for basic biochemistry, haematology and a urine toxicology screening. Following collection of these samples, subjects were taken to the Nicotine Dependence Clinic at CAMH where a medical assessment was conducted.

If subjects were eligible and deemed healthy to participate, an appointment was made for them to return to the laboratory in one week’s time to attend their first study day. Subjects were provided a daily diary where there were asked to record the total number of cigarettes and alcoholic drinks consumed per day, any adverse events they may have experienced, and the time that they took the study medication during the upcoming week. They were also given a wallet-sized card containing an emergency number that could be accessed in case a subject experienced an adverse drug reaction and their treating physician required information about what medication was given to the subject. Results for haematology, biochemistry and the urine drug screen were not available until after completion of the assessment day. The physician reviewed all laboratory results in order to determine continued eligibility for the study.

2.5 Study Day Procedures

2.5.1 Baseline Visit (Pre-Drug Session)

The evening prior to the scheduled study day, subjects were called and given instructions to refrain from smoking a cigarette and/or drinking any alcohol for 12 hours prior to the beginning of the study day. They were also reminded to eat a light breakfast and to limit their caffeine consumption to only one cup of coffee or tea, and to return
their daily diary. Subjects were asked to attend the Clinical Neuroscience laboratory at 10:00am on the following morning. Smoking abstinence was confirmed by measuring levels of breath carbon monoxide using a smokerlyzer (Micro III Smokerlyzer, Bedfont Instruments, Kent, England) and was required to be less than 10 ppm. Alcohol abstinence was confirmed by obtaining a breath sample and was required to be 0.000 mg/dL. If the obtained values were within these parameters, the subject could proceed. In cases where the following parameters were not met, the subject was re-scheduled to return on the next available study day.

Subjects were then requested to complete the Beck Depression Inventory (Beck, Ward et al. 1961) to assess for any depressive symptoms. A baseline measurement of craving was conducted using the Questionnaire of Smoking Urges (Tiffany and Drobes 1991), and the 47 item version of the Alcohol Craving Questionnaire (Singleton, Tiffany et al. 1995). Compulsive thoughts and obsessive behaviours regarding alcohol use were then assessed using the Obsessive Compulsive Drinking Scale (Anton, Moak et al. 1995). Withdrawal from tobacco was measured using the Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami 1986). Upon completion of these questionnaires, a blood sample was taken from each subject to measure the concentration of nicotine, cotinine and 3-hydroxycotinine. After this procedure, subjects were allowed to smoke a single cigarette after which the above named questionnaires, excluding the Obsessive Compulsive Craving Questionnaire, were re-administered. Subjects were then allowed a 1 hour rest break, after which the neutral cue presentation paradigm was presented (described in further detail in Cue Presentation Procedure below). After completing the paradigm, the craving and withdrawal questionnaires were administered. Subjects were
then relocated to a simulated bar environment, where a tobacco and alcohol cue presentation paradigm was administered followed by the craving and withdrawal questionnaires. Upon completion of these questionnaires and while in the bar environment, subjects were requested to complete a modified nicotine/alcohol Stroop task (Stroop 1935) and Digit Symbol Substitution Test (Wechsler 1958) to assess attentional bias and memory, respectively.

Subjects were then randomized to receive either varenicline or placebo and were provided a one week supply of study medication. They were instructed to take a one 0.5mg capsule once daily on days 1 to 3 and one 0.5 mg capsule twice daily on days 4 to 7. Subjects were provided a daily diary to record their smoking and drinking patterns. They were given an appointment to return in exactly one week’s time. A schematic diagram of the study day procedures is outlined below (Figure 2.3).

Figure 2.3: Study Day Procedures. Subjects underwent a craving assessment consisting of the Questionnaire of Smoking Urges, Alcohol Craving Questionnaire, Minnesota Nicotine Withdrawal Scale and a Visual Analogues Scale on 4 separate occasions.

2.5.2 Mid-Study Visit

During this visit, subjects returned any unused medication and their completed diaries. A 45-item symptom checklist and the 90-item version of the Hopkins Symptom Checklist (Lipman, Covi et al. 1979) were administered to assess for the presence of any adverse events and the Beck Depression Inventory was administered to assess for depressive symptoms. If subjects reported any adverse events, further detailed information regarding the symptoms was collected. Information regarding concomitant medication was also collected at this time. Upon completion of these tasks, subjects were
provided with study medication, and instructed to take one 1mg capsule twice daily for this week. Individuals randomized to placebo were given identical instructions. Subjects were given a new daily diary to complete each day for the upcoming week.

2.5.3 Final Visit (Post-Drug Session)

At the end of the 2-week treatment session, subjects attended CAMH for their final study session. This session was conducted in an identical manner as the baseline visit, however, in addition to the questionnaires administered on the baseline visit, the symptom checklists (as described above) were also administered. Subjects were asked about adverse events and any concomitant medication use. At the completion of this and all other study days, subjects were encouraged to seek treatment through the Nicotine Dependence Clinic at CAMH where 12-weeks of varenicline treatment would be provided free-of-charge.

2.6 Cue Presentation Procedure

2.6.1 Neutral Cues

While subjects were seated in a neutral environment, which consisted of a room devoid of any smoking or drinking cues, they were presented with a slide show of neutral pictures consisting of objects such as lamps, airplanes, and faces of people of a variety of ages (Lang, Bradley et al. 1997). A total of 44 pictures were presented for a duration of 7 seconds each. The total time of the slide show was 5 minutes 8 seconds. Upon completion of the slide show, subjects were requested to pick up a pen and hold it as if they were writing. They were also requested to pick up a cup containing tap water and smell it for 2 minutes. Subjects were then asked to complete the questionnaires described
previously (see Study Day Procedures above). A sample of neutral cues presented are shown in Appendix 4.

**2.6.2 Tobacco and Alcohol Cues**

Tobacco and alcohol cues were presented in a simulated bar environment which had a variety of alcohol and tobacco cues present, including alcoholic beverage containers, ashtrays, lighters and cigarette packs. Light jazz music was broadcast over a speaker system at a low volume. While seated at the bar, subjects were presented a slideshow consisting of alcohol and tobacco cues which included pictures of individuals and groups smoking cigarettes, pictures of glasses of wine, mugs of beer, etc. The slideshow consisted of 22 tobacco related pictures (Hussain, Zawertailo et al.; van Hanswijck de Jonge and Gormley 2005) and 22 alcohol related pictures(Wrase, Grusser et al. 2002). Each picture was presented for 7 seconds each. Tobacco and alcohol pictures were presented for a total of 2 minutes 34 seconds each. The total duration of the slideshow was 5 minutes 8 seconds. The presentation of multiple cue-types during this study was done in order to ensure that craving would be elicited by these cues. Furthermore, these cues were presented in combination in a bar in an effort to replicate a naturalistic environment. A sample of tobacco and alcohol cues presented are shown in Appendix 4.

**2.7 Description of Scales**

**2.7.1 Alcohol Use Disorders Identification Test**

The Alcohol Use Disorder Identification Test (Babor, Higgins-Biddle et al. 2001) is a 10-item questionnaire that is used to identify individuals with hazardous and harmful patterns of alcohol consumption. Hazardous alcohol use is assessed by examination of
the frequency of drinking, typical quantity of drinking and the frequency of heavy
drinking. Presence of dependence symptoms are examined in questions pertaining to
impaired control over drinking, increased salience of drinking and morning drinking
whereas harmful alcohol use is determined through questions regarding the feelings of
guilt after drinking, presence of blackouts after heavy drinking sessions, alcohol-related
injuries and others expressing concern about their drinking patterns. The recommended
cutoff score for non-problem drinking is 8, a score of 8 -15 represents a medium level of
alcohol problems and scores of 16 and above represent a high level of alcohol problems.

2.7.2 Beck Depression Inventory

The Beck Depression Inventory (Beck, Ward et al. 1961) is a validated, 21-
question, multiple-choice, self-report questionnaire used to measure severity of
depression. Questions relate to symptoms associated with depression including
hopelessness, guilt, irritability etc. Physical symptoms associated with depression
including weight loss, fatigue and lack of interest in sex are also examined. Greater
scores are associated with greater severity of depression with scores greater than 16 being
associated with borderline clinical depression.

2.7.3 MINI International Neuropsychiatric Interview

The MINI International Neuropsychiatric Interview is a validated, short structured
psychiatric interview, composed of questions designed to detect the presence of 18 Axis 1
DSM-IV disorders. This tool investigates a current diagnosis of psychiatric or substance
use disorder and current and lifetime criteria for bipolar and psychotic disorders.
2.7.4 Questionnaire of Smoking Urges

The Questionnaire of Smoking Urges (Tiffany and Drobes 1991) is a 32-item questionnaire which measures four distinct conceptualizations of smoking urges. The four subscale are the Desire to Smoke, Anticipation of Positive Outcomes from smoking, Anticipation of Relief from Nicotine Withdrawal or from Withdrawal-Associated Negative Affect and Intention to Smoke. Subjects are asked questions and requested to indicate on a Likert-type scale how strongly they agree or disagree with the question presented. Scores range from 1 (strongly disagree) to 7 (strongly agree). Scoring of this questionnaire can be through the presentation of scores for each separate subscale or through a two factor scoring method composed of categories titled Factor 1 and Factor 2. Factor 1 is composed primarily of questions related the intention and desire to smoke, and anticipation of pleasure from smoking while the factor 2 scale is primarily composed of questions related to the anticipation of relief from negative affect and nicotine withdrawal, and an urgent and overwhelming desire to smoke.

2.7.5 Alcohol Craving Questionnaire

The 47-item version of the Alcohol Craving Questionnaire (Singleton, Tiffany et al. 1995) was utilized in this study. This questionnaire measures acute alcohol craving on dimensions labeled Urge and Desire to Use alcohol, Intent to Use alcohol, Anticipation of Positive Outcome, Anticipation of Relief from Withdrawal from Negative Outcomes, Lack of Control Over Use and Total Score. Questions are scored on a Likert-type scale from 1 (strongly disagree) to 7 (strongly agree) with some questions being reverse coded.
2.7.6 Visual Analogue Scale

Visual Analogue Scales are commonly used to determine momentary changes in mood and other physical symptoms (Folstein and Luria 1973). In this study, the Visual Analogue Scale was used to assess overall craving for tobacco and alcohol during each craving assessment. Subjects were presented the question, “I crave a cigarette” and “I crave alcohol” and they were asked to select how much they agreed with this statement on a 100-point scale, with 0 representing subjects having no craving while 100 represents the most intense craving they have ever experienced.

2.7.7 Obsessive Compulsive Drinking Scale

The Obsessive Compulsive Drinking Scale (Anton, Moak et al. 1995) is a validated self-report scale composed of 14 multiple-choice questions. This instrument is used to determine the level of obsessive and compulsive characteristics of drinking-related thoughts, urges to drink, and the ability to resist though thoughts and urges in our study population. The scores from this scale are reported on two different subscales, the obsessive subscale (questions 1-6) and the compulsive subscale (questions 7-14), as well as a total score composed of both measures.

2.7.8 Minnesota Nicotine Withdrawal Scale

The Minnesota Nicotine Withdrawal Scale is a questionnaire composed of 8-questions regarding the presence of DSM-IV symptoms of nicotine withdrawal including irritability, restlessness, depression, anxiety, urge to smoke, difficulty concentrating, increased appetite and insomnia. Subjects were asked to rate these withdrawal symptoms on a 5 point Likert-type scale ranging from none to severe.
2.8 Description of Tasks

2.8.1 Nicotine/Alcohol Stroop Task

During the Stroop task (Stroop 1935), subjects are presented with alcohol and tobacco related or neutral words in four colours; red, blue, green or yellow. Names of colours were also presented either in the correct or incorrect colour, for example the word green would be written in green or in blue. The objective of this task was to name the colour of the word and not the word itself as quickly and as accurately as possible. The reaction time to name the colour of the words is an indicator of attentional bias. It would be expected that individuals who are dependent on a substance would spend a greater amount of time processing words related to that drug, thus leading to a slower reaction time to those words.

2.8.2 Digit Symbol Substitution Test

The Digit Symbol Substitution Test (Wechsler 1958) is a task used to measure basic cognitive functioning. During this task, subjects were presented with a series of symbols along the top of the screen with number corresponding to each symbol. In the centre of the screen, subjects are presented a number. In a blank box below the number, the subjects are asked to duplicate the symbol that corresponds to the number presented above in that box. Subjects are requested to complete the task as quickly and as accurately as possible.

2.9 Measurement of Outcome Variables

2.9.1 Reactivity to Smoking and Alcohol Cues

Reactivity was assessed using two methods. The first method consisted of presentation of cues as described earlier followed by completion of the questionnaire
assessing craving for tobacco and alcohol. These questionnaires included the Questionnaire of Smoking Urges (Tiffany and Drobes 1991), a 32-item questionnaire that assess craving for tobacco and provide a measure of responsiveness towards the tobacco related cues and the 47-item Alcohol Craving Questionnaire (Singleton, Tiffany et al. 1995), provided a measure of responsiveness to the alcohol based cues. These measures of tobacco and alcohol craving were also quantified using the Visual Analogue Scale (Folstein and Luria 1973). The second method of assessing reactivity was through the assessment of attentional bias via the modified Stroop test which was composed of tobacco, alcohol and neutral words presented to subjects in a random order. In this task, words were presented in four colours and subjects were requested to name the colour of the word as quickly as possible while maintaining accuracy. Additionally, the digit symbol substitution test, a task where subjects were require to substitute symbols for a random assortment of numbers was administered to assess speed of information processing, attention and memory.

2.9.2 Daily craving measures and consumption

Assessment of craving and consumption of both tobacco and alcohol throughout the study was assessed using questions presented in the daily diary.

2.9.3 Assessment of Adverse Events

Adverse events were recorded on Study Day 2 and 3. Depressive symptoms were assessed using the Beck Depression Inventory. Information about adverse events was collected using a 45-item symptom checklist. General neurological symptoms were assessed using the 90-item Hopkins Symptoms Checklist. Subjects were required to rate the severity of symptoms presented on a scale from 1 to 5 (with 1 being not at all and 5
being extremely). Subjects’ daily diaries also contained a section to document adverse events. After review of the adverse events reported in these measures, subjects were requested to provide further detail regarding these symptoms to the study investigators.

2.10 Medications

Varenicline tartrate (Pfizer Pharmaceuticals) tablets were encapsulated in a plain generic capsule which was indistinguishable from the placebo capsules. Any additional space within the capsule was occupied by filler composed of lactose monohydrate. Placebo capsules were composed of only lactose monohydrate. Subjects that were randomized to active compound received doses of 0.5 mg and 1mg. Subjects were given instructions to take one 0.5mg capsule once daily for the first three days and one 0.5mg capsule twice a day for the next 4 days. Subjects returned at the completion of this dosing regime and were provided with 1mg capsules that they were instructed to take twice daily for the next 7 days. Subjects randomized to placebo were given identical instructions regarding administration of study medication.

2.10.1 General Medication Information

Varenicline tartrate was provided by the Nicotine Dependence Clinic at CAMH and was encapsulated by Pharmacy.ca (Toronto, ON). Medication was dispensed by the CAMH Russell St pharmacy. To assist subjects in maintaining this dosage regimen, medications were provided to subjects in a blister pack. If a subject forgot a dose, they were instructed to leave that dose within this package. Blister packs were collected and medication counts were conducted at each study visit to assess for compliance.
2.11 Randomization Information

The randomization table was prepared by the CAMH research pharmacist. Randomizations were conducted using a block design (blocks of 4). The randomization code was kept within a secure location at the CAMH Russell St. site pharmacy. The on-call pharmacist had access to the randomization codes after hours should an adverse event occur and a treating physician require that the blind be broken.

2.12 Regulatory Information

This study was approved by the CAMH Research Ethics Board (Study Number: 114/2008). All participants provided written informed consent before participating in this study. Upon completion of the study, subjects were compensated either $200 (prior to VAT108) or $350 (Compensation was increased after reexamination of the time commitments required for this study i.e.: time required to complete the diary, etc). This study was registered with Clinicaltrials.gov (Identifier: NCT00873535)

2.13 Sample Size Justification

Since no previous studies have been conducted investigating the relationship between varenicline administration and cue-reactivity, an *a priori* sample size calculation was conducted using results from a study investigating the role of bupropion on cue-reactivity (Brody, Mandelkern et al. 2004). It was assumed that a difference in cue-reactivity between those receiving placebo and varenicline towards cigarette cues would be similar to those seen comparing bupropion (cigarette cue scan: 1.4±1.4, neutral scan: 1.1±1.4) to an untreated (cigarette cue scan: 4.1±1.6, neutral scan: 2.9±1.6) group. As such, a sample size of 16 per group would be sufficient to provide a power of 0.95 to detect a significant difference between groups with an alpha of 0.05.
2.14 Data Analysis

Subject demographics were analyzed using a $\chi^2$ to assess for differences between groups with respect to gender. Other parametric demographic variables were compared using independent samples t-tests. QSU, ACQ, VAS and MNWS data were analyzed using repeated measure ANOVAs with condition (abstinent, after cigarette, neutral cue, tobacco/alcohol cue) and day (day 1, day 2) as within-subject factors and drug (varenicline, placebo) as between-subject factors. To confirm that similar results would be seen when only the neutral and tobacco/alcohol cue conditions were included in the analysis, an additional repeated measures ANOVA was conducted using the same variables as above however the condition factor only included neutral and tobacco/alcohol cue terms. Significant differences in the ANOVAs were analyzed using post hoc t-tests. Differences within groups from the pre- to post-drug session were examined using paired samples t-tests whereas between group differences during each condition on each study day were compared using independent samples t-tests. All post hoc results were Bonferroni corrected to account for the multiple (8) comparisons made. Measures that were only taken once each study day (OCDS, DSST, nicotine/cotinine/3-hydroxycotinine) were compared using an ANOVA with day being the within-subject factor and drug as the between-subject factors. Significant findings on the ANOVAs were analyzed using post hoc t-tests where comparisons between pre- and post-drug session were conducted using paired samples t-tests while comparisons between groups were conducted with independent samples t-tests. Tobacco and alcohol consumption measures were analyzed using an ANOVA where day was entered as the within-subject factor and drug was the between-subject factor. Stroop mean reaction time values were
analyzed by first determining the reaction times to different word types after removal of incorrect trials and individual reaction times that were <200ms. A mean reaction time was then calculated and individual reaction times that were >3 standard deviations from the mean were removed. These remaining valid responses were then used to calculate reaction times for each word type.

Differences between groups with respect to adverse events reporting were analyzed using a Fischer’s Exact Test, whereas changes in depressive symptoms experienced during the study were analyzed using an ANOVA with day as the within-subjects factor and drug as the between-subjects factor. Results were reported as being significant if p<0.05 was observed.
Section 3: Results

3.1 Study Participants

A total of 24 subjects completed the study. No significant differences between participants randomized to the varenicline of placebo group were observed with respect to age, cigarettes smoked per day, FTND scores, alcoholic beverages consumed per week, or AUDIT scores. While no statistically significant differences in gender were observed between the drug groups, the varenicline group had 9 males and 3 females, while the placebo group had 6 males and 6 females. A summary of participant characteristics can be seen in Table 3.1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 24)</th>
<th>Varenicline (n = 12)</th>
<th>Placebo (n = 12)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.17 (9.91)</td>
<td>31.08 (7.39)</td>
<td>35.25 (11.89)</td>
<td>NS</td>
</tr>
<tr>
<td>No. cigarettes per day</td>
<td>14.75 (5.67)</td>
<td>14.00 (5.63)</td>
<td>15.50 (5.85)</td>
<td>NS</td>
</tr>
<tr>
<td>Fagerstrom Test for Nicotine Dependence (FTND) score</td>
<td>5.25 (1.45)</td>
<td>5.33 (1.16)</td>
<td>5.17 (1.75)</td>
<td>NS</td>
</tr>
<tr>
<td>No. alcoholic drinks per week</td>
<td>9.38 (3.80)</td>
<td>9.00 (3.10)</td>
<td>9.75 (4.50)</td>
<td>NS</td>
</tr>
<tr>
<td>AUDIT score</td>
<td>6.25 (1.54)</td>
<td>5.75 (0.97)</td>
<td>6.75 (1.87)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 3.1: Subject Demographics.

3.2 Effectiveness of Cue Paradigm to Induce Craving

In order to assess the effectiveness of the cue paradigm in inducing craving, scores for all subjects during the neutral condition were compared to those obtained during the tobacco/alcohol cue condition on study day 1, prior to the administration of any medication. Results from this comparison showed significantly greater scores during
the tobacco/alcohol cue condition than neutral cue condition on all measures of the Questionnaire of Smoking Urges (DTS, p=0.001; AOPO, p=0.001; ROWONE, p=0.011; ITS, p=0.004, Factor 1, p=0.010; Factor 2, p<0.001). Similar increases were also observed on all measures, with the exception of the Lack of Control Over Use subscale, of the Alcohol Craving Questionnaire (ITUA, p=0.001; AOPO, p=0.003; AORFWORO, p=0.001; Total Score, p=0.001). Similarly, VAS measures also showed similar effects (VAS Cigarette, p<0.001; VAS Alcohol, p=0.001). These results suggest that the cue paradigm was effective in inducing craving in this population.

3.3 Subjective Tobacco Craving Results

3.3.1 Questionnaire of Smoking Urges

3.3.1.1 Desire to Smoke subscale

An overall effect of cycle was observed on this subscale when comparing all four conditions (ie: abstinence, after a cigarette, neutral cue and tobacco/alcohol cue conditions) (F(3,66) = 53.792, p<0.001). Furthermore, a significant day x cycle x drug interaction (F(3,66) = 3.572, p=0.019) was also observed. When comparing only neutral and tobacco/alcohol cue conditions, a significant cycle (F(1,22) = 16.102, p=0.001), day x drug (F(1,22) = 7.830, p=0.01) and day x cycle (F(1,22) = 5.010, p=0.036) interaction were observed. Post-hoc analysis showed a significant decrease in subscale scores during the tobacco/alcohol cue condition between the pre-drug vs. post-drug condition in the varenicline group (p=0.008), however this result did not remain significant after Bonferroni correction (see Figure 3.1). No significant differences between the placebo and varenicline groups were observed at any time points.
Figure 3.1: Comparison of Questionnaire of Smoking Urges Desire to Smoke subscale scores compared between varenicline and placebo during all four conditions. Significant effect of cycle (p<0.001) and day x cycle x drug (p=0.019) were observed.

3.3.1.2 Anticipation of Positive Outcome subscale

An overall effect of day (F(1,22) = 7.196, p=0.014), cycle (F(3,66) = 43.312, p<0.001) and a day x cycle x drug (F(3,66) = 3.817, p = 0.014) interaction were observed when comparing all 4 conditions. A significant day (F(1,22) = 5.615, p =0.027), cycle (F(1,22) = 25.355, p<0.001), cycle x drug (F(1,22) = 7.706, p = 0.011) and day x cycle (F(1,22) = 4.466, p = 0.046) interaction were observed when only the neutral and tobacco cues were compared. Post-hoc tests showed a significant decrease in subscale scores in the placebo group between pre- and post-drug conditions (p=0.014) in the after cigarette condition and a significant decrease between pre- and post-drug conditions in the varenicline group in the tobacco/alcohol cue condition (p=0.018). These results did not remain significant after Bonferroni correction (see Figure 3.2). No significant differences between placebo and varenicline groups were observed at any time point.
Figure 3.2: Comparison of Questionnaire of Smoking Urges Anticipation of Positive Outcome subscale scores between varenicline and placebo during all four conditions. Significant effects of day (p=0.014), cycle (p<0.001) and day x cycle x drug (p=0.014) were observed.

3.3.1.3 Relief of Withdrawal or Negative Affect subscale

An overall effect of cycle (F(3,66) = 25.730, p<0.001) was observed when comparing all four conditions, while a significant cycle (F(1,22) = 20.155, p< 0.001) and day x drug (F(1,22) = 9.867, p=0.005) interaction were observed when comparing only the neutral and tobacco/alcohol cue conditions. Post-hoc tests showed a significant decrease in subscale score in the varenicline group during the neutral cue condition (p=0.008), however this effect did not remain significant after Bonferroni correction (see Figure 3.3). No significant differences between varenicline and placebo groups were observed at any time point.
Figure 3.3: Comparison of Questionnaire of Smoking Urges Relief of Withdrawal or Negative Affect subscale scores between varenicline and placebo during all four conditions. A significant effect of cycle (p<0.001) was observed.

### 3.3.1.4 Intention to Smoke subscale

An overall main effect of day (F(1,22) = 5.852, p=0.024) and cycle (F(3,66) = 49.670, p<0.001) were observed when comparing all four conditions, while a cycle (F(1,22) = 9.163, p=0.006) and a day x drug (F(1,22) = 4.955, p=0.037) interaction were observed when only the neutral and tobacco/alcohol cue conditions were investigated. Post-hoc tests showed a significant decrease in subscale score from pre- to post-drug in the varenicline group during the tobacco and alcohol condition (p=0.009), however this effect did not remain significant after Bonferroni correction. A statistically significant difference was also observed between the varenicline and placebo group in the post-drug condition in the after cigarette condition (p=0.020) (See Figure 3.4).
Figure 3.4: Comparison of Questionnaire of Smoking Urges Intention to Smoke subscale scores between varenicline and placebo during all four conditions. A significant effect of day (p=0.024) and cycle (p<0.001) were observed.

3.3.1.5 Factor 1 subscale

An overall main effect of day (F(1,22)=6.016, p=0.023), cycle (F(3,66)=47.573, p<0.001) and a day x cycle x drug interaction (F(3,66)=2.742, p=0.05) was observed upon examination of all 4 study conditions. When only the neutral and tobacco/alcohol conditions were examined, a significant day (F(1,22)=4.887, p=0.038), cycle (F(1,22)=13.968, p=0.001) and day x drug interaction (F(1,22)=5.998, p=0.023) was observed. Post-hoc tests revealed a significant decrease in subscale scores between the pre- vs. post-drug condition in the varenicline group during the tobacco/alcohol cue paradigm condition (p=0.008). The subscale scores were also observed to be significantly decreased in the varenicline group compared to the placebo group in the after cigarette condition in the post-drug session (p=0.04). Neither of these effects remained significant after Bonferroni correction (see Figure 3.5).
3.3.1.6 Factor 2 subscale

An overall main effect of cycle \((F(3,66)=43.210, p<0.001)\) and a day x cycle x drug interaction \((F(3,66)=3.366, p=0.024)\) was observed when examining all four cycles. When only the neutral and tobacco/alcohol condition were examined a significant main effect of cycle \((F(1,22)=26.587, p<0.001)\) and a day x drug \((F(1,22)=7.456, p=0.012)\) interaction was observed. Post-hoc tests revealed a significant increase in subscale scores in the placebo group between pre- and post-drug sessions under the neutral cue condition \((p=0.009)\). These statistically significant results did not remain significant after Bonferroni correction. No significant differences between placebo and varenicline were observed at any time point (see Figure 3.6).
Figure 3.6: Comparison of Questionnaire of Smoking Urges Factor 2 subscale scores between varenicline and placebo during all four conditions. A significant effect of cycle (p<0.001) and a day x cycle x drug (p=0.024) interaction were observed.

3.3.2 Visual Analogue Scale – Cigarette Craving

An overall main effect of day (F(1,22)=4.598, p=0.043) and cycle (F(3,66)=43.091, p<0.001) was observed when all 4 conditions were examined with a repeated measures ANOVA. A day x drug (F(1,22)=10.163, p=0.004), day x cycle (F(3,66)=6.175, p=0.001) and day x cycle x drug (F(3,66)=4.571, p=0.006) interaction terms were also observed. When only the neutral and tobacco/alcohol cue conditions were examined, a significant main effect of day (F(1,22)=8.066) and cycle (F(1,22)=27.883, p<0.001) were observed. Furthermore, a significant day x drug interaction (F(1,22)=15.308, p=0.001) was also observed. Post-hoc tests showed significant decreases in craving in the varenicline group between pre- and post-drug session during the abstinence (p=0.025), neutral (p=0.008) and tobacco/alcohol (p=0.003) conditions. Significant differences between the varenicline and placebo group were observed during the post-drug session in the neutral (p=0.002) and tobacco/alcohol
(p=0.018) cue condition. Only the within subject comparison between the varenicline group on the tobacco/alcohol condition and the between subject comparison in the post-drug session in the neutral cue condition remained significant after Bonferroni correction (see figure 3.7).

Figure 3.7: Comparison of Visual Analogue Scale “I crave a cigarette” scores between varenicline and placebo during all four conditions. Significant effects of day (p=0.043) and cycle (p<0.001) were observed. Significant day x drug (p=0.004), day x cycle (p=0.001) and day x cycle x drug (p=0.006) interactions were observed. *p=0.002, **p=0.018. Results in red remained significant after Bonferroni correction.

3.3.3 Corrected Craving Measures

A conservative method for measuring cue-induced craving is to subtract a participant’s score during the tobacco/alcohol cue condition from those seen during the neutral cue presentation. For the purpose of this thesis, the results from this method will be called corrected craving.

When examining differences in the Questionnaire of Smoking Urges responses, the only statistically significant differences that was observed was a decrease in Factor 2 subscale scores in the placebo group between the pre- and post-drug sessions (p=0.020).
When varenicline and placebo groups were compared, a significant difference was observed on the anticipation of positive outcome subscale score in the pre-drug condition (p=0.048). These measures did not remain significant after Bonferroni correction.

No statistically significant differences were seen on the visual analogue scale scores.

3.4 Subjective Alcohol Craving Results

3.4.1 Alcohol Craving Questionnaire

3.4.1.1 Urge and Desire to Use Alcohol subscale

An overall main effect of cycle (F(3,66)=14.189, p<0.001) was observed when all 4 conditions were examined with a repeated measures ANOVA. A day x cycle (F(3,66)=4.285, p=0.008) and day x cycle x drug F(3,66)=4.446, p=0.007) interaction was also observed. When only neutral and tobacco/alcohol cues conditions were examined, a significant main effect of cycle (F(1,22)=14.326, p=0.001) and a day x drug (F(1,22)=4.313, p=0.05), day x cycle (F(1,22)=11.218, p=0.003) and day x cycle x drug (F(1,22)=10.271, p=0.004) interaction were observed. Post-hoc tests showed a significant increase in subscale scores between pre- and post-drug were seen in the placebo group both in the after cigarette (p=0.028) and neutral cue (p=0.024) conditions. A significant decrease in subscale scores was observed in the varenicline group in the tobacco/alcohol cue condition between the pre- and post-drug sessions (p=0.016). No significant between group differences were observed. These statistically significant results did not remain significant after Bonferroni correction (see figure 3.8).
3.4.1.2 Intent to Use Alcohol subscale

A significant main effect of cycle (F(3,66)=14.368, p<0.001) was observed when all four conditions were entered into repeated measures ANOVA. A day x cycle (F(3,66)=3.930, p=0.012) and day x cycle x drug (F(3,66)=5.067, p=0.003) interaction were also observed. When only the neutral and alcohol cue conditions were examined in an ANOVA a significant main effect of cycle (F(1,22)=17.162, p<0.001) was observed. A day x drug (F(1,22)=5.468, p=0.029), day x cycle (F(1,22)=5.179, p=0.033) and day x cycle x drug (F(1,22)=8.331, p=0.009) interaction were also observed. Post hoc tests showed a significant increase in subscale score in the placebo group between the pre- and post-drug sessions in the after cigarette condition (P=0.017). Significant decreases in subscale scores were seen in the varenicline condition between the pre- and post-drug sessions in the tobacco/alcohol cue condition (p=0.011). No significant differences between the placebo and varenicline groups were observed at any
time point. Furthermore, these results did not remain significant after Bonferroni correction (see figure 3.9).

![Graph](image)

Figure 3.9: Comparison of Alcohol Craving Questionnaire Intent to Use Alcohol subscale scores between varenicline and placebo during all four conditions. A significant cycle (p<0.001), day x cycle (p=0.012) and day x cycle x drug (p=0.003) effect were observed.

### 3.4.1.3 Anticipation of Positive Outcome subscale

A significant main effect of cycle (F(3,66)=12.442, p<0.001) and a day x cycle x drug (F(3,66)=6.518, p=0.001) interaction was observed when all four conditions were entered into a repeated measures ANOVA. When only the neutral and tobacco/alcohol conditions were examined, a similar results was observed with only cycle (F(1,22)=20.818, p<0.001) and day x cycle x drug (F(1,22)=8.549, p=0.008) interactions being significant. Post hoc tests showed a significant decrease in subscale scores between the pre- and post-drug condition in the placebo group in the after cigarette condition (p=0.040) and in the varenicline group in the tobacco/alcohol cue condition (p=0.025). No significant differences between the placebo and varenicline group were
observed at any time point. These results did not remain significant after Bonferroni correction (see figure 3.10).

Figure 3.10: Comparison of Alcohol Craving Questionnaire Anticipation of Positive Outcome subscale scores between varenicline and placebo during all four conditions. A significant cycle (p<0.001) and day x cycle x drug (p=0.001) effect were observed.

3.4.1.4 Anticipation of Relief from Withdrawal from Negative Outcomes subscale

A significant main effect of cycle (F(3,66)=6.210, p=0.001) and a day x drug (F(1,22)=6.938, p=0.015) interaction were observed when all four conditions were entered into a repeated measures ANOVA. When only the neutral and tobacco/alcohol cue conditions were examined, a significant main effect of cycle (F(1,22)=18.070, p<0.001) as well as a day x drug (F(1,22)=5.041, p=0.035) and day x cycle x drug (F(1,22)=4.286, p=0.05) interaction were observed. Post hoc tests showed a significant decrease in subscale scores in the pre- to post-drug session in the varenicline group in both the abstinent (p=0.010) and tobacco/alcohol cue (p=0.033) conditions. A statistically significant difference between the placebo and varenicline group was also
observed at the pre-drug session in the abstinent condition (p=0.037). However, these results did not remain significant after Bonferroni correction (see figure 3.11).

![Alcohol Craving Questionnaire: Anticipation of Relief from Withdrawal from Negative Outcomes](image)

Figure 3.11: Comparison of Alcohol Craving Questionnaire Anticipation of Relief from Withdrawal from Negative Outcomes subscale scores between varenicline and placebo during all four conditions. A significant effect of cycle (p=0.001) and a day x drug (p=0.015) were observed. *p=0.037

### 3.4.1.5 Lack of Control Over Use subscale

No significant main effects were observed when comparing either the 4 conditions or the neutral and tobacco/alcohol cue conditions in a repeated measures ANOVA.

### 3.4.1.6 Total Score

A significant main effect of cycle (F(3,66)=15.116, p<0.001) and a day x cycle (F(3,66)=4.287, p=0.008) and day x cycle x drug (F(3,66)=6.659, p=0.001) interactions were observed when all four conditions were examined. When only the neutral and tobacco/alcohol condition were compared, a significant main effect of cycle (F(1,22)=16.451, p=0.001) and a significant day x drug (F(1,22)=5.991, p=0.023), day x cycle (F(1,22)=8.552, p=0.008 and a day x cycle x drug (F(1,22) = 11.834, p=0.002)
interaction were observed. Post hoc tests showed a significant decrease in scores between pre- and post-drug session in the varenicline group during the tobacco/alcohol cue presentation condition (p=0.004) which remained significant even after Bonferroni correction. No differences between placebo and varenicline were observed at any time point (see figure 3.12).

![Alcohol Craving Questionnaire: Total Score](image)

Figure 3.12: Comparison of Alcohol Craving Questionnaire Total Scores between varenicline and placebo during all four conditions. A significant effect of cycle (p<0.001), day x cycle (p=0.008) and day x cycle x drug (p=0.001) were observed. Results presented in red remained significant after Bonferroni correction.

### 3.4.2 Visual Analogue Scale – Alcohol Craving

A significant main effect of day (F(1,22)=5.821, p=0.025) and cycle (F(3,66)=14.059, p<0.001) were observed when all four conditions were entered into a repeated measures ANOVA. Significant day x drug (F(1,22)=5.426, p=0.029), day x cycle (F(3,66)=4.112, p=0.010) and day x cycle x drug (F(3,66)=3.526, p=0.020) were also observed. When only the neutral and tobacco/alcohol condition were examined only a significant main effect of cycle (F(1,22)=14.486, p=0.001) was observed. Furthermore, a day x drug (F(1,22)=4.756, p=0.040), day x cycle (F(1,22)=8.843, p=0.007) and day x
cycle x drug (F(1,22)=6.141, p=0.021) interactions were observed. Post hoc tests showed a significant decrease in craving between the pre- to post-drug session in the varenicline group during the tobacco/alcohol condition (p=0.011), however this result did not remain significant after Bonferroni correction. Comparisons between the placebo and varenicline group did not show any statistically significant differences at any time point (see figure 3.13).

Figure 3.13: Comparison of Visual Analogue Scale (alcohol craving) scores were compared between varenicline and placebo during all four conditions. A significant effect of day (p=0.025), cycle (p<0.001), day x drug (p=0.029), day x cycle (p=0.010) and day x cycle x drug (p=0.020) were observed.

3.4.3 Corrected Craving

Significant decreases in corrected craving scores were observed on all subscales of the Alcohol Craving Questionnaire in the varenicline group when comparing pre- to post-drug scores with the exception of the Loss of Control of Use subscale (UADTUA: p=0.001, ITUA: p=0.005, AOPAO: 0.012, AORFWONO: p=0.048, Total: p<0.001). Only the Intent to Use Alcohol and Total scores remained significant after Bonferroni correction. Comparisons between varenicline and placebo groups found that significant
differences were present in the ITUA (p=0.020), AOPO (p=0.023), AORFWONO (p=0.047) and Total (p=0.033) scores in the pre-drug session. These results did not remain significant after Bonferroni correction.

Similarly, a significant decrease was observed in the visual analogue scale between the pre- and post-drug session in the varenicline group (p=0.008), however no significant differences were observed between placebo and varenicline groups during either the pre- or post- drug session. This result did not remain significant after Bonferroni correction.

3.5 Obsessive and Compulsive Behaviours With Respect to Alcohol Consumption:

3.5.1 Obsessive Compulsive Drinking Scale:

No significant difference in total scores, obsessive or compulsive subscale scores were observed between the varenicline and placebo groups.

3.6 Measures of Nicotine Withdrawal

3.6.1 Minnesota Nicotine Withdrawal Scale

When all 4 conditions where examined, only main effects of day (F(1,22)=20.297, p<0.001) and cycle (F(3,66)=35.825, p<0.001) were observed. No interaction terms were seen. Similarly, an ANOVA was conducted with only the neutral and tobacco/alcohol conditions these same main effects were observed (day(F(1,22)=14.471, p=0.001), cycle (F(1,22)=20.583, p<0.001)) with no interaction terms observed. Post hoc tests showed significant decreases between pre- and post-drug sessions in the varenicline group in the abstinence (p=0.017), after cigarette (p=0.028) and neutral cue (p=0.025) conditions. A significant decrease between sessions was also seen in the placebo group during the tobacco/alcohol cue (p=0.019) condition. However, these results did not remain
significant after Bonferroni correction. No statistically significant differences between placebo and varenicline groups were observed at any time point. Furthermore, no significant differences in corrected craving measures were observed (See figure 3.14).

![Figure 3.14: Comparison of Minnesota Nicotine Withdrawal Scale scores between varenicline and placebo during all four conditions. A significant effect of day ($p<0.001$) and cycle ($p<0.001$) were observed.](image)

### 3.7 Tobacco Consumption Measures

#### 3.7.1 Self-reported Tobacco Consumption

A significant effect of day ($F(2,44)=32.091, p<0.001$) was observed in this measure. No day x drug interaction terms were observed (see figure 3.15).
Figure 3.15: Self-reported tobacco consumption measures compared between varenicline and placebo during the entire study period. A significant effect of day (p<0.001) was observed.

### 3.7.2 Biochemical Measures of Tobacco Consumption

A significant effect of day was observed in cotinine (F(1,22)=6.799, p=0.016) and 3-hydroxycotinine (F(1,22)=5.101, p=0.034) measures. *Post hoc* comparisons showed a significant decrease in cotinine concentrations between the pre- and post-drug sessions in the varenicline group (p=0.032). This result did not remain significant after Bonferroni correction. No significant differences in 3-hydroxycotinine concentrations between pre- and post-drug sessions were observed. No significant differences between varenicline and placebo were observed in either the pre or post-drug session for nicotine, cotinine or 3-hydroxycotinine (see figure 3.16).
Figure 3.16: Measures of nicotine, cotinine and 3HC in the varenicline and placebo groups in the pre- and post-drug sessions.

3.8 Alcohol Consumption Measures

3.8.1 Self-reported Alcohol Consumption

No significant ANOVA terms were observed with respect to alcohol consumption (see figure 3.17).
Figure 3.17: Self-reported alcohol consumption measures compared between varenicline and placebo during the entire study period.

3.9 Cognitive Processing Measures

3.9.1 Digit Symbol Substitution Test

No significant differences in number of trial completed or correct trials were observed between the varenicline and placebo groups, suggesting that varenicline did not influence cognitive processing in this experimental paradigm.

3.10 Measures of Attentional Bias

3.10.1 Stroop Task

3.10.1.1 Incongruent Colour Words

No statistically significant differences were observed between the placebo and varenicline groups.

3.10.1.2 Congruent Colour Words

A significant main effect of day (F(1,22)=4.324, p=0.049), but no day x drug interactions were observed when mean reaction times for congruent colour words were compared between varenicline and placebo groups (see figure 3.18).
Figure 3.18: Visual representation of mean reaction times when presented with congruent colour words between varenicline and placebo groups. A significant effect of day (p=0.049) was observed.

### 3.10.1.3 Smoking Related Words

A significant main effect of day (F(1,22)=5.929, p=0.023) but no day x drug interactions were observed when mean reaction times for smoking related words were compared between varenicline and placebo groups (see figure 3.19).
Figure 3.19: Visual representation of mean reaction times when presented with smoking related words between varenicline and placebo groups. A significant effect of day (p=0.023) was observed.

3.10.1.4 Positive Smoking Effect Words

No statistically significant differences were observed between the placebo and varenicline groups.

3.10.1.5 Negative Smoking Effect Words

A significant main effect of day (F(1,22)=10.692, p=0.004) but no day x drug interactions were observed when mean reaction times for negative smoking effect words were compared between varenicline and placebo groups (see figure 3.20).
3.10.1.6 Neutral Words

No statistically significant differences were observed between the placebo and varenicline groups.

3.10.1.7 Alcohol Words

A trend level significant main effect of day (F(1,22)=3.899, p=0.061) but no day x drug interactions were observed when mean reaction times for alcohol words were compared between varenicline and placebo groups (see figure 3.21).
Figure 3.21: Visual representation of mean reaction times when presented with alcohol words between varenicline and placebo groups. A trend level significant effect of day (p=0.061) was observed.

3.11 Summary of Adverse Events

No statistically significant differences between rates of adverse events were observed between the varenicline and placebo groups. However, it should be noted that those in the varenicline group did report more vomiting (varenicline = 1, placebo = 0), nausea (varenicline = 4, placebo = 2), drowsiness (varenicline = 5, placebo =1) and heartburn (varenicline = 3, placebo = 0). No significant differences between groups were observed on Hopkins Symptom Checklist. Furthermore, no significant differences in depression symptoms presence or severity were observed throughout the course of this study.

3.11 Assessment of Compliance

According to pill counts conducted on each study day, subject randomized to varenicline reported taking 96.67% of the study medication whereas those randomized to
placebo reported taking 96.33%. No significant differences in compliance were observed between groups.
Section 4: Discussion:

This study is the first of its kind to investigate whether varenicline can attenuate both tobacco and alcohol cue-induced craving during a concurrent cue presentation paradigm. The main findings of this study were that administration of varenicline at therapeutic concentrations compared to placebo can decrease craving for tobacco, although this effect is not specific to cue-induced craving. Varenicline had no effect on alcohol cue-induced craving or consumption compared to placebo.

To date, only a single study has investigated the influence of varenicline on tobacco cue-induced craving (Niaura, Hitsman et al. 2007). However that study has only been published as an abstract and had some significant limitations, namely, changes in cue-induced craving were examined after administration of only a single dose of varenicline. As varenicline has a half-life of approximately 20 hours (Faessel, Gibbs et al. 2006), a single dose study would not be able to determine whether varenicline would have any effect on this measure at its intended therapeutic concentration. In the current study, the design was improved by administering varenicline for 2 weeks according to the dosing instructions found in the product monograph. This provided a two-fold benefit. First, the number of adverse events, due to the dose titration schedule employed during the first week, was reduced. Secondly, individuals took the medication at the full dose (1 mg bid) for 7 days. As the half-life of varenicline is approximately 1 day, this dosing schedule was sufficient to allow the examination of cue-induced craving at steady state drug concentrations. With respect to alcohol cue-induced craving, to date, no studies have investigated the effect of varenicline on this measure.
4.1 Subjective Tobacco Craving

Although not significant after Bonferroni correction, decreases in craving measures were observed between the pre- and post-drug condition in the varenicline group during the tobacco-alcohol condition on multiple measures of the QSU including the desire to smoke, anticipation of positive outcomes and intention to smoke subscales. Similarly, decreases were also observed on the Factor 1 subscale score which is a measure that primarily examines the intention and desire to smoke and the anticipation of pleasure from smoking a cigarette. Similar results were also observed on the single item visual analogue scale question which provided a global overall assessment of craving that an individual was experiencing at that particular point in time. On this measure, decreases in craving were observed in the abstinent, neutral and tobacco/alcohol condition. Furthermore these differences between placebo and varenicline were observed during the neutral and tobacco/alcohol cue conditions on the post-drug day.

The decreases in craving that were observed in this study are comparable with those seen in clinical trials of varenicline. In those studies, decreases in craving, which were investigated using the QSU-Brief, were also seen between varenicline and placebo when differences between baseline and week 7 were investigated (Gonzales, Rennard et al. 2006; Jorenby, Hays et al. 2006; Nides, Oncken et al. 2006). Although these studies reported overall decreases in urge to smoke, no subscale scores were provided making it difficult to make direct comparisons to the findings in this thesis. Furthermore, no published studies to date have indicated which specific subscales decreases in craving were measured.
Similar to the clinical trials, the results of this study also show a decrease in tobacco withdrawal as measured with the Minnesota Nicotine Withdrawal Scale; however, these results did not remain significant after Bonferroni correction. These differences were seen between the two study days in the varenicline condition during the abstinent, after cigarette, and neutral cue conditions. Although decreases in craving and withdrawal measures were observed in those in the varenicline group, no significant differences in self-reported tobacco consumption were noted during the study. These observed results correspond with those seen in an imaging study investigating brain activation during smoking cue exposure. In that study an association was observed between nicotine dependence and craving however no associations were observed between craving measures and tobacco consumption (Smolka, Buhler et al. 2006). However it should be noted that other studies have observed the converse in that they observed positive associations between tobacco consumption and total craving experienced after cue exposure (Carpenter, Saladin et al. 2009). Although self-reported consumption did not change, a decrease in cotinine, a metabolite of nicotine, was seen between pre- and post-drug condition, however no differences in nicotine, or a metabolite of cotinine, 3-hydroxycotinine, were observed. This discrepancy between self-reported consumption and cotinine values may be due to a variety of reasons. Varenicline has been shown to decrease the satisfaction or positive rewarding effects associated with smoking a cigarette (Gonzales, Rennard et al. 2006; Jorenby, Hays et al. 2006; Nides, Oncken et al. 2006; Oncken, Gonzales et al. 2006) and so it may be hypothesized that while individuals may still have a craving to smoke, and proceed to light a cigarette, the satisfaction they experience is minimal and therefore they may extinguish the cigarette.
prematurely. Another possibility, although not investigated in this study, is that varenicline may influence smoking topography. If this were the case, individuals would report smoking the same number of cigarettes however factors such as number of puffs, puff volume or duration of puffs may have changed after varenicline treatment. Although this may be a potential mechanism to explain this result, currently no studies have been published reporting the effects of varenicline on smoking topography. However, the results from studies using mecamylamine, a non-competitive nicotinic acetylcholine receptor antagonist, report either increases (Nemeth-Coslett, Henningfield et al. 1986) or no change (Pomerleau, Pomerleau et al. 1987) in smoking topography measures, suggesting that varenicline would likely not have any effect in decreasing smoking topography measures. However, the differences in the pharmacology of these drugs (i.e.: antagonist vs. partial agonist) makes it difficult to draw any conclusions regarding this effect without definitive empirical evidence of the effect of varenicline on these measures.

Although our results confirm that varenicline can decrease tobacco craving and withdrawal even with a 2 week treatment period, these results do not necessarily indicate decreases in cue-induced craving per se. When investigating the effect of cue-induced craving specifically, controlling for craving during the neutral cue presentation procedure is the most conservative approach. In this study, when this craving was accounted for and a corrected craving term was derived, no statistically significant differences were observed between the pre- and post-drug condition in the varenicline group or in the post-drug session between varenicline and placebo. Although we use this as evidence suggesting that varenicline did not have a specific effect on cue-induced craving this may
be an overly conservative approach as other published studies which report decreases in
cue-induced craving do not observe significant results when using corrected craving
values (Carpenter, Saladin et al. 2009).

Furthermore, the results showing decreases in craving and withdrawal need to be
interpreted with caution. Many of the statistically significant results observed in the
varenicline group were only observed using a within-subjects comparisons approach but
not when compared to the placebo group during each study condition. Furthermore, after
correction for multiple comparisons, significance was only observed on some measures
of the visual analogue scale, thereby precluding any definitive claim of reduction in
craving without there being an increase in a type 1 error being made.

Prior to this study, only limited evidence existed implicating the cholinergic
system in cue-induced craving. To date, only a single human study investigating the
influence of mecamylamine on cue-induced craving has been published, however this
effect was investigated using cocaine cues (Reid, Mickalian et al. 1999). Although these
investigators observed a decrease in cue-induced craving, the only other study
investigating the influence of varenicline on tobacco cue-induced craving did not observe
decreases on this measure (Niaura, Hitsman et al. 2007). Similarly, a study conducted in
rats trained to self-administer nicotine showed that varenicline did not attenuate the
reinstatement of nicotine seeking after nicotine-paired cues were presented (O'Connor,
Parker et al.). The results from these studies and those presented in this thesis provide
further evidence that the cholinergic system, specifically the α4β2 nicotinic acetylcholine
receptor, does not likely mediate a clinically significant role in establishment or
maintenance of craving after presentation of tobacco cues.
4.2 Subjective Alcohol Craving

Decreases in alcohol craving scores were observed on a variety of different measures between the pre- and post-drug condition in the varenicline group during the tobacco and alcohol cue condition. These decreases were observed in the Urge and Desire to Use Alcohol, Intention to Use Alcohol, Anticipation of Positive Outcomes, Anticipation of Relief from Withdrawal or Negative Outcomes and VAS alcohol measures. Similar results were also observed with corrected craving measures, however only the intent to use alcohol and total scores remained significant after correction for multiple comparisons.

Although these results do suggest a decrease in alcohol cue-induced craving, these decreases were more likely explained by differences between perceived alcohol availability in the varenicline vs. placebo group. In those randomized to varenicline, there was a large increase in craving during the pre-drug session after presentation of tobacco and alcohol cues. Although this craving was elevated on the pre-drug session, this craving decreased to a level that was similar to placebo in the post-drug session. A potential reason for this could be that subjects were not informed as to whether they would or would not be able to consume alcohol during the cue presentation procedure, but they were informed that the pre- and post-drug sessions would be identical. This may have led to differences in assumptions between those in the varenicline vs. placebo groups regarding alcohol availability. Studies investigating the role of perceived alcohol availability on cue-reactivity suggest that those individuals who were presented cues but believed that the substance was unavailable experienced the greatest craving (MacKillop and Lisman 2005), suggesting that if those in the varenicline group perceived alcohol as
being unavailable, then these individuals may have experienced greater alcohol cue-induced craving in the pre-drug session. In the post-drug session, both groups were aware that they would not be consuming alcohol, therefore these differences in responses were not seen.

Other factors such as genetics may have also influenced these discrepancies in craving. Studies in alcohol-dependent individuals have shown that those with the long variant of the 5-HT transporter experience greater craving than those with the short variant (Ait-Daoud, Roache et al. 2009). Although this specific alteration does not explain the findings reported in this thesis (as these craving measures would be expected to remain the same in the post-drug session and our sample was not an alcohol dependent population) it does suggest that other factors such as genetics could have influenced the results.

Although we did observe differences between the varenicline and placebo groups, they did not differ on measures of alcohol use severity, obsession and compulsions regarding alcohol use, or number of drinks consumed per week either at baseline or throughout the course of the study, suggesting that these effects were not mediated by differences in alcohol use patterns but by some other currently unidentified mechanism.

Varenicline also did not appear to have any effect on alcohol consumption. This may be due to two potential reasons. First, the participants in this study were light drinkers who typically consumed alcohol in social situations and with meals and did not meet abuse or dependence criteria. As these individuals consumed a relatively low number of drinks per week, it may have been difficult to observe a statistically significant decrease in consumption in this population. Another potential reason may lie in the
pharmacodynamics of this medication. Although studies in both animals (Kamens, Andersen et al.; Steensland, Simms et al. 2007) and humans (McKee, Harrison et al. 2009) have observed decreases in alcohol consumption with varenicline, studies in animals using DHβE, an α4β2 antagonist, either did not observe any decreases in consumption (Le, Corrigall et al. 2000) or only observed decreases at high doses (Kuzmin, Jerlhag et al. 2009). Furthermore, studies conducted using mecamylamine showed decreases in alcohol consumption in animal models (Farook, Lewis et al. 2009; Hendrickson, Zhao-Shea et al. 2009) and decreases in the euphoric and stimulant effects of alcohol in humans (Chi and de Wit 2003). While these studies suggest that the nAchR does play a role in alcohol consumption, the results presented in this thesis do not necessarily implicate the α4β2 nAchR as the main subtype modifying alcohol consumption. These discrepancies between studies suggest that further studies elucidating the function of different nAchR subtypes on alcohol consumption need to be conducted in both animal and humans.

4.3 Attentional Bias

In this study, a main effect of day on mean reaction times between varenicline and placebo for congruent colour words, smoking words and negative smoking effect words was seen. As no interaction term including drug was observed, it is likely that these observed decreases were due to a learning effect, as decreases were seen both in the varenicline and placebo group in the post-drug, compared to those observed in the pre-drug session.

To date, only a single study of the effect of varenicline on attentional bias has been published (Sofuoglu, Herman et al. 2009). The results observed in the current study
differ from those observed by Sofuoglu et al. In that study, a main effect of drug and a
decrease in reaction time to smoking related words in the varenicline but not in the
placebo group was observed. While the results of the current study and the Sofuoglu
study differ, there were similarities in sample size, allowing a comparison to be made
between these studies. It is important to note that the current study used a between-
subjects design with 24 participants and the Sofuoglu study used a within-subject cross-
over design with 12 participants, thus the Sofuoglu study in all likelihood had greater
power to detect an effect due to its design. One important difference between these two
studies was differences with respect to dosing. In the Sofuoglu study, subjects were
given varenicline for 4 days with the maximum dosing being 1 mg per day (0.5mg bid),
suggesting that subjects were administered a subtherapeutic dose. This dosing schedule
differed from that employed in the current study where varenicline was administered
according to the product monograph (maximum dose of 2 mg per day). Based on the
doses administered in the current study, it would be expected that comparable or greater
differences would be observed compared to the Sofuoglu study. At this time, the
underpinning of this discrepancy is not currently apparent, however it is possible that
differences in the Stroop paradigm itself, ie: differences in word size or other variable
may have led to these contrasting results.

4.4 Limitations

A variety of limitations exist with respect to the current study. One limitation of
the current study was the small sample size. As no previous studies investigating the
effect of varenicline on cue-induced craving existed at the time of the conception of this
study, calculation of a priori sample size was carried out using a cue-reactivity study
using bupropion. It was noted at the time that the mechanisms of action of these medications differed. Since statistically significant results were not obtained on corrected craving measures (a conservative measure of cue-induced craving), post hoc sample size calculations were conducted to determine what sample size would be required to observe a significant effect. Based on the differences observed on the QSU Factor 1 scores during the post-drug session, the effect size observed between varenicline and placebo was 0.625 with an alpha of 0.05 and power of 0.80. Based on these values, a sample size of 84 subjects, or 42 subjects per group would be required to observe a statistically significant difference between groups. In this study only 12 subjects were recruited per group, suggesting that this study was underpowered.

A further limitation was assessment of compliance during the study. Although every attempt was made to ensure compliance by providing subjects with blister packs of the study medication and collecting unused medications on a weekly basis, biochemical verification was not carried out (i.e.: spiking the medication with vitamin E or riboflavin, to assess this measure). Regardless, our observation of decreases in craving in the varenicline group provided a positive drug effect providing empirical evidence that the medication was taken by those in the varenicline group and that compliance was high.

Another limitation is the use of the Alcohol Craving Questionnaire in this light drinker population. Although the validity of this scale has been established in a heavy drinker population, it has not been validated in light drinkers. Although this is a clear limitation, this study was conducted with the intention that results obtained and presented in this thesis would be compared to those obtained using an identical paradigm conducted in heavy drinkers. As this was the case, the Alcohol Craving Questionnaire was used to
allow valid comparisons to be made across these two groups. Although this was a significant limitation, the results that we observed were similar to those seen using the visual analogue scale measures of alcohol craving suggesting that the results observed did properly identify alcohol craving in this group.

While adverse events reported during the study were minimal and no significant differences between groups were observed, the assessment of these events was only conducted after subjects began taking medication. While these differences were not significant, it may be possible that some of the reported adverse events may have been present prior to the medication and may have not been due to the medication, thus causing an over-reporting of these adverse events. However, as this was a randomized, placebo-controlled study, it would be expected that the incidence of these adverse effects would be similar between the active and placebo groups, thus not greatly influencing the adverse events attributable to varenicline.

Although individuals were asked at the pre-screening interview (conducted by telephone), whether they were seeking treatment for smoking cessation, motivation to quit smoking was not quantified using any validated measures at any time point during the study. It is possible that individuals differed in their motivation to quit and this may have influenced cue-induced craving.

The presentation of the combined tobacco and alcohol cues within a bar environment makes it impossible to examine the interaction of craving and the potential influence of alcohol cues on nicotine craving and vice versa. It is theoretically possible that the presentation of alcohol cues may have increased nicotine craving or vice versa and therefore may have obscured a potentially significant effect if these measures were
presented alone. Although this was a limitation, one of the aims of this study was to investigate the effect of varenicline in a naturalistic environment where cues to both alcohol and tobacco are commonly present.

In this study, subjects were given a 1 hour break after smoking a cigarette prior to being shown neutral cues. Although this was done to allow any acute physiological effects of tobacco to return to baseline while preventing the onset of withdrawal (Spohr, Hofmann et al. 1979; Niaura, Abrams et al. 1989), it is possible that some individuals may have been experiencing some acute withdrawal effects during the cue-presentation paradigm. This craving, if present, may have masked or obscured any cue-induced craving that may have been experienced by these subjects. Furthermore, as the scales used measured overall craving, differences between subjects associated with this craving measure may have increased the variability in these results and may have obscured any statistically significant result from being observed. Although this may have been the case, the increases observed in withdrawal measures between the neutral and tobacco/alcohol cue condition were similar between the placebo and varenicline group suggesting that this likely was not the case.

Finally, in this study, craving measures were all based upon self-report. Objective measures of craving such as skin conductance or vital signs were not included. It is possible that had these objective measures been included, they may have detected a significant effect of varenicline. It may be possible that the effect size of varenicline to alleviate cue-induced craving is small and the variability of self-report data may have prevented this effect from being detected. Objective measures, which would have allowed for physiological change to be observed, may have allowed for a more definitive
conclusion to be made regarding the effectiveness of varenicline to reduce cue-induced craving.

4.5 Conclusions

Although in this study statistically significant decreases in craving in both measures of tobacco and alcohol craving were found, the primary hypothesis that varenicline would specifically decrease cue-induced tobacco and alcohol craving compared to craving induced by neutral cues was not supported by the results observed. Furthermore, while a decrease in cotinine was observed in the varenicline group, varenicline did not decrease either cigarettes smoked per day or alcoholic drinks consumed per week, an effect that differs from results reported in the literature. Similarly, no effect of varenicline was observed on measures of attentional bias towards drug related words.

4.6 Recommendations for future studies

Although there is some evidence suggesting that the cholinergic system is involved in the process of cue-induced craving, further animal studies investigating the effect of nicotinic acetylcholine receptor antagonists or partial agonists on different nAchR subtypes is required to further elucidate the mechanism of cue-induced craving. The results obtained from such studies, if positive, could provide further evidence for the development of effective treatments to alleviate cue-induced craving and thus potentially decrease relapse.

With respect to human studies, further investigation of varenicline as a potential treatment option to reduce cue-induced craving is required. One of the strengths of the current study was that it allowed for the investigation of cue-induced craving using a
combined cue exposure paradigm that incorporated a variety of distal and proximal olfactory, tactile and visual cues. However additional studies investigating the role of varenicline on tobacco or alcohol cue-induced craving alone should be undertaken to determine these effects individually. Furthermore, studies with a similar design are required in groups such as binge drinkers who are social smokers and who typically only smoke when drinking. In this group of social smokers, alcohol and tobacco consumption are closely paired and since these individuals are not dependent smokers this removes some of the elements of dependence and withdrawal and will thus remove some of the variability associated with these factors. Such studies may provide a greater understanding of the influence of alcohol cues on tobacco craving and would be able to investigate the effect of varenicline to attenuate craving after alcohol cue presentation.

Furthermore, the effect of varenicline in attenuating cue-induced craving should also be studied in relapse-prevention paradigms. As cues have been implicated in relapse, an alternate method to investigate the effect of smoking cessation medications on cue-induced relapse may be to investigate relapse rates after reaching an abstinent state. Investigating cue reactivity after maintained abstinence would provide a model with greater face validity with respect to cue-induced relapse and may yield differing results compared to abstinence initiation trials.

As mentioned previously, the associations between alcohol and tobacco use are highly linked. Although research has shown that craving for tobacco increases after an acute alcohol drink and vice versa, the effectiveness of varenicline in attenuating this effect has never been investigated. A study conducted in regular smoker/heavy drinkers or in a population of binge drinkers/social smokers, where craving for tobacco is
measured after an acute dose of alcohol followed by the same measures being made after individuals are at a therapeutic concentration of varenicline may provide meaningful results. As it is known that alcohol consumption is associated with relapse to smoking the results of such a study would be able to determine whether varenicline can attenuate this increase in tobacco craving after alcohol consumption, and if positive results were observed this could have clinical implications in the use of varenicline in smoking relapse prevention.

Although a limited number of studies in the literature have reported decreases in alcohol consumption with varenicline, these results were not confirmed in the present study. Although these preliminary studies suggest an effect of varenicline may exist, further more comprehensive studies investigating consumption in both naturalistic environments and in alcohol dependent individuals is required to determine whether this effect is maintained under these scenarios.
Section 5: References


Canadian Pharmaceutical Association Compendium of pharmaceuticals and specialties (Canada). Toronto, Canadian Pharmaceutical Association.


paradigm with concurrently available drug and environmental reinforcers." *Psychopharmacology (Berl)* **184**(3-4): 391-400.


Section 6: List of Publications and Abstracts


APPENDIX 1

Informed Consent Form
Subject Information
And
Informed Consent

Feb 24th, 2009
(Version 4)

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.

I have read the information on this page 114
Initials: __________
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 (eg: 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 in some individuals of unusual feelings of agitation, depressed mood, hostility, changes in behaviour, or impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. 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. We also ask that you review a separate sheet attached to this consent form that outlines in more detail the neuropsychiatric symptoms some people have experienced while taking this medication.

**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.

I have read the information on this page 116

Initials: __________
Compensation:
In consideration of your participation in this study you will receive $350.00 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.
A number of patients taking varenicline (trade name: Champix) have experienced unusual feelings of agitation, depressed mood, hostility, changes in behavior or impulsive or disturbing thoughts such as thoughts of self-harm or harm to others. Tell the study investigators and study physician if you have experienced depression or other mental health problems before taking CHAMPIX as these symptoms may worsen while taking CHAMPIX.

Stop taking CHAMPIX and tell the study investigators and study physician right away if you, your family or caregiver noticed any of these symptoms, if you experienced these symptoms in a way that is not typical for you, or if you have thoughts of self-harm or harm to others.

US Food and Drug Administration (FDA) have also issued similar warning. (http://www.fda.gov/Cder/Drug/advisory/varenicline.htm)

- **Patients should tell their study investigators and study physician about any history of psychiatric illness prior to starting Champix.** Champix may cause worsening of a current psychiatric illness even if it is currently under control and may cause an old psychiatric illness to reoccur.

- **Healthcare professionals, patients, patients’ families, and caregivers should be alert to and monitor for changes in mood and behavior in patients treated with Champix.** Symptoms may include anxiety, nervousness, tension, depressed mood, unusual behaviors and thinking about or attempting suicide. **In most cases, neuropsychiatric symptoms developed during Champix treatment, but in others, symptoms developed following withdrawal of varenicline therapy.**

- **Patients taking Champix should immediately report changes in mood and behavior to the study investigators and study physician.**

- **Patients taking Champix may experience vivid, unusual, or strange dreams.**

- **Patients taking Champix may experience impairment of the ability to drive or operate heavy machinery.**

I have read the information on this page 118 Initials:__________
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 _______________________________

119
APPENDIX 2

Study Advertisements
We are currently conducting a research study on the effects of varenicline on smoking and alcohol drinking.

You will be required to take varenicline, complete questionnaires and computerized tests.

You may be eligible if:

YOU SMOKE 10 or MORE CIGARETTES / DAY and
YOU DRINK ALCOHOL (Less than 14 drinks/week [less than 9/week for women])

For more information please call: Greg at 416-535-8501 ext. 6346

ALL QUERIES ARE STRICTLY CONFIDENTIAL

Financial compensation provided.

Must be available weekdays, with no current health problems.

CAMH provides other treatment options for mental illness or addiction. For more information call CAMH at 416-535-8501.
We are currently conducting a **research study** on the effects of **varenicline** on smoking and alcohol drinking.

You may be eligible if:

**YOU SMOKE 10 or MORE CI GARETTES/ DAY**

and

**YOU DRINK ALCOHOL**

(Less than 14 drinks/ week for men or less than 9/ week for women)

For more information please call:

**Greg** at **416-535-8501 ext. 6346**

**ALL QUERIES ARE STRICTLY CONFIDENTIAL**

**Financial compensation provided.**

**Must be available weekdays**, with no current health problems.

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.
### VAT Study
CAMH

#### Telephone Pre-screening Form

<table>
<thead>
<tr>
<th>Subj. Initials:</th>
<th>Subj. #</th>
<th>Date:</th>
<th>Time:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Form Completed by: ____________________________

<table>
<thead>
<tr>
<th>Name:</th>
<th>Date:</th>
<th>Sex:</th>
<th>Age:</th>
<th>DOB:</th>
<th>Telephone:</th>
<th>May I leave a message at this number:</th>
<th>Other number:</th>
<th>How did you find out about this study:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### SMOKING SCREENING:

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
<th>Answers</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you currently smoking?</td>
<td>YES NO</td>
<td>YES</td>
<td>3</td>
</tr>
<tr>
<td>Are you currently interested in quitting smoking?</td>
<td>YES NO</td>
<td>NO</td>
<td>0</td>
</tr>
<tr>
<td>Are you interested in quitting smoking in the next 30 days?</td>
<td>YES NO</td>
<td>NO</td>
<td>0</td>
</tr>
<tr>
<td>On average, how many cigarettes do you smoke per day?</td>
<td>0-10 11-15 &gt;15</td>
<td>0-10</td>
<td>3</td>
</tr>
<tr>
<td>Are you currently in treatment for tobacco dependence?</td>
<td>YES NO</td>
<td>YES</td>
<td>1</td>
</tr>
<tr>
<td>If NO, Were you ever in treatment for tobacco dependence?</td>
<td>YES NO</td>
<td>NO</td>
<td>0</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 No</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></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 No</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>6. Do you smoke even if you are so sick that you are in bed most of the day?</td>
<td>Yes No</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**Fagerstrom test score =**

FTND <3 FTND >3

---

124 FORM 1
**Telephone Pre-screening Form**

<table>
<thead>
<tr>
<th>VAT Study</th>
<th>CAMH</th>
</tr>
</thead>
</table>

**Subj. Initials:**_____________   **Subj. #** ______________  
**Date:** ___________________   **Time:** ______________  
**Form Completed by:** ____________________________

**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>
</table>

How often do you drink alcohol?  
- □ Never  
- □ Monthly or less  
- □ 2-4 times/month  
- □ 2-3 times/week  
- □ 4 or more times/week

On those occasions that you do drink alcohol, how many drinks do you usually have?  
- □ 1-2  
- □ 3-4  
- □ 5 or more

In the past 12 months, have you ever consumed 5 or more drinks on any one occasion?  
- □ YES  
- □ NO

If **yes**, how often does that happen?  
- □ Monthly or less  
- □ 2-4 times/month  
- □ 2-3 times/week  
- □ 4 or more times/week

In total, how many drinks do you consume per week?  
- □ > 70 (male)  
- □ < 70 (male)  
- □ > 52 (female)  
- □ <52 (female)

**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>
</table>

1. Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?  
   - YES  
   - NO

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?  
   - YES  
   - NO

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

Over the past two weeks, when you felt depressed or uninterested:

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)?  
   - YES  
   - NO

2. Did you have trouble sleeping nearly every night (difficulty falling asleep, waking up in the middle of the night, early morning wakening or sleeping excessively)?  
   - YES  
   - NO
### Telephone Pre-screening Form

<table>
<thead>
<tr>
<th>VAT Study</th>
<th>CAMH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subj. Initials: __________       Subj. # __________</td>
<td></td>
</tr>
<tr>
<td>Date: __________      Time: __________</td>
<td></td>
</tr>
<tr>
<td>Form Completed by: ____________________________</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</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 difficulty 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:

<table>
<thead>
<tr>
<th>WOMEN:  Are you currently pregnant or lactating?</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<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>
<tr>
<td>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?</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>
| If YES:  
What: ____________________________________________________________________________  
How much: ____________________________________________________________________________  
How often: ____________________________________________________________________________  |

<table>
<thead>
<tr>
<th>ELIGIBLE GROUP</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD: Heavy Smoker, Heavy Drinker</td>
<td>HD</td>
<td>SD</td>
</tr>
<tr>
<td>SD: Heavy Smoker, Social Drinker</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Assessment day: Date __________      Time __________
APPENDIX 4

Example of Cue Pictures
Neutral Cues
Tobacco Cues
Alcohol Cues