Real-world Effectiveness of Bupropion versus Varenicline for Smoking Cessation: Exploring the Role of Metabolic and Personality Variables

By

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Graduate Department of Pharmacology and Toxicology
University of Toronto

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ABSTRACT

Varenicline and bupropion are efficacious, prescription-only pharmacotherapies for smoking cessation; however, their real-world impact is limited by affordability and accessibility. Using a randomized design, we evaluated the real-world effectiveness of mailed bupropion and varenicline, as well as the roles of nicotine metabolism (NMR) and personality traits, in a sample of interested smokers, utilizing web-based recruitment and follow-up. Quit rates at the end-of-treatment were significantly higher for varenicline (28.3%) compared to bupropion (16.8%). Medication compliance was a significant predictor of quit outcome. NMR was not associated with nicotine dependence, or with quit success with either bupropion or varenicline. Neuroticism (positively) and extraversion (negatively) were significantly correlated with nicotine dependence in men only. Furthermore, in males, conscientiousness and neuroticism were significant predictors of smoking abstinence. Given the low real-world quit rates, improving medication compliance and implementing personalized pharmacological and behavioral interventions are promising approaches to increase effectiveness of tobacco cessation treatments.
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1. INTRODUCTION

1.1 Tobacco Use and its Consequences

Tobacco use is the single most preventable cause of disease, disability, and death (Schroeder, 2013; WHO, 2013). Worldwide, tobacco use and smoking-related illnesses are responsible for approximately 5 million deaths every year. In other words, one out of 10 adult deaths is due to tobacco use globally. In fact, tobacco kills up to 50% of all its users (WHO, 2008). The World Health Organization (WHO) has estimated that by 2030, tobacco use will be responsible for 8 million deaths annually (WHO, 2011). Based on the most recent Canadian data, about 17% of all deaths (21% of males and 12% of women) that occurred in 2002 were attributable to tobacco use - three times more than alcohol, drugs, suicide, homicide, and car crashes combined (ONGov, 2011). In addition, tobacco use in Canada accounted for 515,607 potential years of life lost due to premature death. In 2002, smoking was also responsible for 2,210,155 days spent in hospital (Rehm J, 2006).

1.1.1 Prevalence of Tobacco Use in Canada

Smoking prevalence in Canada has declined in the recent years. However, based on the most recent survey in 2012, the percentage of Canadians who smoked remained high at about 16% of the general population aged 15 years and older (HC, 2013a). Specifically, 12% of the Canadian population smoked daily, with the remaining 4% identifying themselves as occasional smokers (HC, 2013a). Moreover, based on the survey conducted in 2012, this population of Canadian daily smokers reported smoking 15 cigarettes per day on average (HC, 2013a). In addition, more males (18%) reported smoking than females (14%); and on average, males also smoked more cigarettes per day than females (HC, 2013a). Furthermore, smoking prevalence in Canada varies by province. The lowest rate of smoking estimated was 13% in British Columbia and the highest prevalence of smoking was observed in Newfoundland and Labrador at 20% of its population. The prevalence of smoking in Ontario was estimated to be 16% (HC, 2013b).

The prevalence of smoking measured in 2012 is significantly lower than when this data was first collected back in 1999. In 1999, it was estimated that 25% of the Canadian population smoked cigarettes (HC, 2013b). Despite the significant change, the rates have plateaued in
recent years and it is more difficult to show a significant decline in rates of tobacco use (HC, 2013b). This indicates that current remaining smokers may have a harder time quitting and require effectiveness and affordable treatment made available to them.

1.1.2 Health Risks of Smoking

As mentioned, smoking is responsible for a number of diseases and chronic health conditions, including cancers and cardiovascular diseases (USDHHS, 2014). In fact, smokers inhale more than 7,000 chemicals, with at least 250 of them proven to be harmful (USDHHS, 2010). In addition, at least 70 of the chemicals found in cigarette smoke are known carcinogens (NTP, 2005). Smoking affects nearly every organ in the body and is detrimental to the overall health of the individual. Studies have shown that smoking increases the risk of stroke, ischemic heart disease, peripheral vascular disease, aortic aneurism, and type II diabetes (USDHHS, 2010, 2014). Smoking also causes the vast majority of all cases of lung cancer diagnosed. Moreover, smoking is linked to a number of other forms of cancers, such as oral, kidney, liver, stomach, colorectal, bladder, prostate, and breast (Carbone, 1992; Sasco, Secretan, & Straif, 2004; USDHHS, 2010, 2014). Furthermore, smoking is responsible for several respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, and pneumonia (Anderson, 1964; Ishii, 2013; USDHHS, 2010, 2014). Some of the other potential negative health consequences of smoking include, rheumatic arthritis immune disorder, low bone density, stomach ulcer, and erectile dysfunction (USDHHS, 2014). Smoking affects more than just the smoker. Involuntary exposure to tobacco smoke in forms of second-hand smoke and third-hand smoke have deleterious health effects on those exposed, as well (UDHHS, 2006).

1.1.3 Economic Impact of Smoking

Smoking results in substantial economic burden on the healthcare system and society. The illness related economic cost of tobacco use consists of medical costs and productivity losses (Hodgson & Meiners, 1982). Based on a paper published in 2002, it was reported that tobacco use costs the Canadian economy $17 billion; about $12.5 billion of which were due to lost in productivity. In Ontario, tobacco use costs the economy $6.1 billion in direct healthcare costs and productivity losses. In addition, tobacco use costs the Canadian economy about $5.4 billion in law enforcements (Rehm J, 2006). In other words, even if an individual avoids tobacco smoke to the best of his/her ability, he or she will suffer from the economic burden that smoking has on the society.
1.1.4 Reducing Smoking Rates and its Benefits

Reducing the prevalence of tobacco use leads to reduced exposure, improved health, and less burden on the economy. In fact, many of the health risks associated with smoking are reversed after quitting (WHO, 2007). It has been shown that quitting smoking before the age of 40 reduces the chances of dying from a tobacco-attributed disease by 90% (Jha et al., 2013). Smoking cessation in adults 45 years or older also has significant benefits as it potentially gains them 6 years of life (Jha et al., 2013). Additionally, cessation in older adult smokers reduces their risk of hospitalization due to chronic smoking-related conditions (Tran, Falster, Douglas, Blyth, & Jorm, 2015). Moreover, studies have shown that quitting has both short-term and long-term benefits. After only one year of being quit, the risk of developing coronary heart disease is halved; and by 15 years after quitting, the risk decreases to that of a non-smoker (USDHHS, 2010; WHO, 2007). The risk of lung cancer also drops to about half by 10 years after becoming smoke-free (UDHHS, 1990). Quitting smoking saves the Canadian healthcare system a considerable amount, as well. It has been estimated that for every smoker who quits, about $8,500 are saved in medical costs; and additional of $413,000 is gained through prevention of premature death (FTCS, 2011). In conclusion, smoking cessation has many advantages and is the obvious solution to one of the greatest public health concerns of the 21st century.

1.2 Statement of Problem and Study Rationale

1.2.1 Challenges of Quitting Smoking

To this point, it has been established that tobacco use harms the individual smoker and the society as a whole. It has also been recognized that the key to resolving this issue is to reduce the prevalence of tobacco use. However, quitting smoking can be challenging. This is because several factors influence tobacco dependence. These include a combination of pharmacological, psychological, biological/genetics, and environmental and social elements (N. L. Benowitz, 2010; Carpenter, Wayne, & Connolly, 2007; Grunberg, Winders, & Wewers, 1991; Rigotti, 2002). Most importantly, nicotine, the powerful psychoactive substance in cigarettes, is extremely addictive, when inhaled via cigarette smoking -(Kumar & Lader, 1981; UDHHS, 1988). In fact, nicotine reaches the brain almost immediately, binds the nicotinic acetylcholine receptor, and activates the brain reward system by releasing dopamine, which in turn
reinforces smoking behaviour (N. L. Benowitz, 1999, 2010; Dani & Heinemann, 1996; Schelling, 1992; UDHHS, 1988). Furthermore, nicotine has a short half-life and in order to maintain the pleasurable effects and to avoid withdrawal symptoms, smokers need to smoke frequently. This turns the activity into an overlearned behavior that contributes to tobacco dependence (N. L. Benowitz, 2010; Davis & Gould, 2008; Olausson, Jentsch, & Taylor, 2004). Therefore, in order for smokers to quit, they need to learn to manage both the pharmacological and the behavioural aspects of their cigarette addiction. A survey conducted in a sample of 800,000 smokers reported on the main barriers to quitting, as experienced by the smokers. Some of the top reasons were enjoyment from smoking, craving for cigarettes, stress and anxiety, weight gain, and cost of treatment (UWCTRI, 2005).

1.2.2 Clinical Interventions and Barriers

Clinical interventions are an integral part of a comprehensive tobacco control strategy (Lancaster, Stead, Silagy, & Sowden, 2000). Namely, nicotine replacement therapy (NRT), bupropion, and varenicline are efficacious first-line pharmacotherapies (D Gonzales et al., 2006; Hughes JR, 2007; Silagy, Lancaster, Stead, Mant, & Fowler, 2004). However, according to the Canadian Tobacco Use Monitoring Survey in 2007, of about 66% of all smokers who have ever made an attempt to quit, less than half have used a smoking cessation aid. More surprisingly, 90% of these smokers reported attempting to quit on their own, without getting help from available smoking cessation programs (HC, 2007). Furthermore, most of these smokers identify that lack of access to adequate and evidence-based information and cost of these smoking cessation pharmacotherapies as reasons for not using these quitting aids (HC, 2007).

In order to bypass the barriers mentioned, successful methods for mass-distribution of nicotine replacement therapy have been developed and implemented (Costello et al., 2011; Zawertailo L, 2012). However, clinical trials have shown that bupropion and varenicline are more efficacious than NRT and are expected to make a notable impact if widely distributed to smokers (Jimenez, 2008; Wu, Wilson, Dimoulas, & Mills, 2006). On the other hand, bupropion and varenicline are prescription-only medications, as such they present a unique challenge (ACS, 2014). As a result, the population-level impact of bupropion and varenicline are limited by combinations of lack of knowledge, affordability, and accessibility.

Healthcare providers are ideally suited to advise and assist with smoking cessation of their patients (Stead LF, 2013). However, a survey conducted in Canada demonstrated that the
occurrence of smoking cessation discussion between physicians and patients are not common. In fact, out of 88% of smokers who visited a primary care physician in the year prior, only half received any advice on quitting or reducing smoking (Stevenson J, 2005). Studies have shown that lack of knowledge and confidence on part of the primary healthcare provider are limiting factors (Cabana, Rand, Powe, & et al., 1999; Steinberg, Nanavati, Delnevo, & Abatemarco, 2007). In the case of bupropion and varenicline, these limitations go hand in hand with smoker’s inaccessibility to these smoking cessation aids relative to nicotine replacement products, as they are only available through prescription from a licensed practitioner. Moreover, these prescription smoking cessation medications are costly with limited coverage by both public and private insurance companies (MCDONALD, COADY, & SALTMAN, 2012-13). This presents another barrier to bupropion and varenicline use, especially among smokers with lower socioeconomic status (HC, 2013a). Efforts to address these barriers could greatly improve the use of and effectiveness of these smoking cessation medications in the real-world (Gollust, Schroeder, & Warner, 2008).

Furthermore, it is important to note that although bupropion and varenicline have been proven efficacious in clinical trials (D Gonzales et al., 2006; D. Jorenby et al., 2006; M. Nides et al., 2006), there is not adequate evidence available to establish their pragmatic real-world effectiveness. Indeed, there are a number of significant differences between clinical trials and real-world settings, which could possibly influence cessation treatment outcomes. For instance, clinical trials have strict eligibility criteria, excluding participants with certain comorbidities. Therefore, participants of these studies are in better health than the general population. In addition, treatment with medications in clinical trials is accompanied with smoking cessation behavioral counselling, which is not always the case in real-world settings (D. Jorenby et al., 2006). These factors together have the potential to restrict the external validity of the clinical trials’ findings. As a result, for the reasons stated, there is a need to assess the real-world effectiveness of these prescription medications, bupropion and varenicline, at a population-level.

1.2.3 The Issue of Relapse

Lastly, one of the biggest challenges in treating nicotine dependence is that it is a chronic relapsing disease (Japuntich, Piper, Leventhal, Bolt, & Baker, 2011). Despite noticeable progress in smoking cessation interventions in recent years, current available treatments have lower efficacy than desired and only a portion of smokers benefit from them. For instance, bupropion results in a higher quit rate than nicotine replacement therapy (NRT) at the earlier
stage of treatment. However, the portion of participants who remain abstinent at the 1-year mark drops (Gold, Rubey, & Harvey, 2002; Jorenby et al., 1999). The efficacy and relapse prevention profile for varenicline looks more promising; even though, it still results in only a 22% abstinence rate at 1-year post-treatment (D Gonzales et al., 2006; D. Jorenby et al., 2006; Ramon & Bruguera, 2009).

Due to low success rates mentioned, there is a need for optimizing the effectiveness of available treatments. Interestingly, the etiology of tobacco dependence is multifactorial and there are individual differences in how smokers respond to smoking cessation medications (Phillips et al., 2007; Scollo & Winstanley, 2012; True et al., 1997). In fact, there is considerable evidence supporting the role of genetic factors in smoking behavior and smoking cessation (C. E. Lerman, Schnoll, & Munafo, 2007; Quaak, van Schayck, Knaapen, & van Schooten, 2009). Most recently, attention has been focused on the role of the nicotine-metabolizing enzyme, cytochrome P450 2A6 (CYP2A6), in smoking cessation. Studies have demonstrated that the rate by which smokers metabolize nicotine influences their responses to smoking cessation medications (Ho et al., 2009; C. Lerman et al., 2006; Schnoll et al., 2009). Previous studies have evaluated the impact of this factor while comparing treatment with varenicline and bupropion with placebo and nicotine replacement therapy, respectively (C. Lerman et al., 2015; Patterson et al., 2008). However, it is unclear whether the rate of nicotine metabolism affects bupropion and varenicline treatment outcomes differently. Understanding the role of such inherited characteristics has the potential to help tailor tobacco cessation treatments to maximize medication’s efficacy and minimize adverse reactions. It may also help identify potential targets for new smoking cessation pharmacotherapies.

Likewise, studies have shown that there is an association between certain phenotypic characteristics and smoking behavior (Nieva et al., 2011; Rondina, Gorayeb, & Botelho, 2007; Terracciano, 2004; Zvolensky, Taha, Bono, & Goodwin, 2015). However, there is limited data on specific personality characteristics that dispose an individual to a higher risk of becoming dependent to nicotine and having a harder time quitting. Thus, recognizing these traits can potentially allow for personalization of smoking cessation interventions to improve cessation outcomes.

In conclusion, the problem is clear; smoking is a complex, recurring, chronic disease of addiction that is costly to society as a whole. As a result, there is an immediate need for effective and sustainable interventions at population-level.
1.3 Purpose of the Study and Objectives

Thus far, it has been established that current prescription-only first-line smoking cessation pharmacotherapies, bupropion and varenicline, are not widely used, despite their proven efficacy in clinical trials (HC, 2007). Consequently, there is limited data on their real-world effectiveness at the population-level. Furthermore, there is evidence that individuals vary with respect to their response to smoking cessation medications, although data on the specific factors and the nature of their effects is minimal. Therefore, the purpose of this study is to address the aforementioned gaps in knowledge. The objectives and specific aims are as follows:

**Primary Objective:** To evaluate the real-world use and effectiveness of mailed bupropion and varenicline in a sample of smokers interested in quitting in a randomized controlled trial using patient-driven web-based recruitment and follow-up.

Specific Aims:
- Measure the cessations rates associated with bupropion and varenicline in a real-world setting, outside clinical trials
- Assess the real-world medication compliance and its role in quit outcomes
- Evaluate the practicality of a patient-driven internet-based mass-distribution method for prescription-only smoking cessation medications

**Secondary Objective (exploratory):** To explore the role of rate of nicotine metabolism/CYP2A6 activity in nicotine dependence and treatment outcome

Specific Aims:
- Examine the relationship between nicotine dependence and the saliva cotinine level, the primary metabolite of nicotine
- Examine the relationship between the rate of nicotine metabolism, according to the Nicotine Metabolite Ratio (NMR) (Dempsey et al., 2004), its phenotypic marker, with nicotine dependence
- Investigate the role of nicotine metabolism in cessation and treatment outcomes

**Tertiary Objective (exploratory):** To explore the role of the Big Five personality traits in nicotine dependence and treatment outcome
Specific Aims:
- Examine the relationship between the Big Five personality traits with nicotine dependence
- Investigate the roles of personality characteristics in cessation and treatment outcomes

Note: Another overall aim of the study is to assess the real-world long-term quit rates of bupropion and varenicline at 6 and 12 months, as well as their neurogenetics. However, these data are still being collected and analyzed. As a result, they are not presented as part of this thesis.

1.4 Statement of Research Hypotheses and Rationale for Hypotheses

a) We hypothesize that treatment with varenicline will result in higher quit rates than bupropion at the end of treatment (at 12 weeks).

Previously, two clinical trials have compared the efficacies of 12 weeks of treatment with bupropion and varenicline head-to-head using randomized, double-blind, placebo-controlled, parallel-group designs. In both of these phase III clinical studies, varenicline was more efficacious than bupropion (D Gonzales et al., 2006; D. Jorenby et al., 2006). Specifically, subjects were randomly assigned to receive varenicline titrated to 1 mg twice daily, bupropion SR titrated to 150 mg twice daily, or placebo for the standard 12 weeks period of treatment. The pharmacotherapy was accompanied by brief behavioral intervention. The findings of these two studies of head-to-head comparisons of bupropion and varenicline were comparable. The 30 days continuous abstinence rates at the end of treatment (at 12 weeks) were approximately 44% in varenicline, compared to 30% in bupropion, and 17% in subjects receiving placebo. The odd ratios (OR) of the treatment groups compared to placebo were as followed: for varenicline the OR was 3.8, with a 95% confidence interval (CI) of 2.7-5.5. Bupropion was also significantly more efficacious than placebo with OR of 1.9, and 95% CI of 1.4-2.6. The 7-day point prevalence rates of abstinence (PPA), defined as not having smoked even a puff in the past 7 days, were also reported. At week 4 from the start of treatment, PPA rate for varenicline was approximately 48%, compared to 37% for bupropion treatment. At week 8, varenicline and bupropion’s PPA rates were approximately 51% and 36%, respectively. At the end of treatment, at week 12, varenicline treatment resulted in approximately 50% 7 day PPA rates, compared to
36% in subjects treated with bupropion. Therefore, we believe that the results from our pragmatic study will be consistent with the results from the clinical trials and varenicline will result in higher abstinence rate than bupropion at the end of treatment. We hypothesize that a 15% difference in the end of treatment 30 days continuous abstinence rate will be observed. However, we also hypothesize that due to differences between clinical studies and the real-world, the overall quit rates in our study will be lower than that observed in clinical trials.

b) We hypothesize that the internet-based recruitment method will be successful at reaching smokers and distributing prescription smoking cessation medications, bupropion and varenicline, in both urbanized and rural and remote areas of Ontario.

The primary investigator of this study, Dr. Laurie Zawertailo, and her group have previously conducted a feasibility study that demonstrated the practicality of the mass-distribution method for prescription smoking cessation medications (Selby P). In addition, it has been shown that this approach is extremely cost-effective (Hussain S, 2012). However, it is important to note that in the feasibility study, the participants were not randomly assigned to the medication and there was no biochemical confirmation of self-reported abstinence. Nevertheless, we expect this method to be practical and effective.

c) In addition, it is hypothesized that smokers’ rate of nicotine metabolism will not be correlated with nicotine dependence as measured by the FTND score, but it may be a predictor of smoking cessation with bupropion and varenicline treatment. We hypothesize that with both bupropion and varenicline treatments, normal and slow metabolizers will have similar quit rates at the end of treatment.

One past study looked at the relationship between NMR, measured in urine, and the FTND score in a sample of 73 smokers (N. L. Benowitz, Pomerleau, Pomerleau, & Jacob, 2003). Another study looked at this relationship in 833 smokers undergoing assessment at a smoking clinic (Schnoll et al., 2014). Neither of the past studies found an association between NMR and the FTND score. Therefore, we hypothesize that NMR will not be associated with nicotine dependence in our sample. In addition, one past study has looked at the relationship between NMR and treatment outcome with bupropion, retrospectively. In this study, similar quit rates were observed across different metabolizer groups in smokers being treated with bupropion (Patterson et al., 2008). In another study, this relationship was investigated in those treated with varenicline. In particular, participants were stratified based on their metabolizer category and randomized to treatment. Similarly, observed quit rates
were similar in normal and slow metabolizers in those treated with varenicline (C. Lerman et al., 2015). As a result, we hypothesize that in our sample, NMR will not be a significant predictor of smoking cessation with bupropion or varenicline in our sample of smokers categorized into slow and normal metabolizers.

d) We hypothesize that the personality trait labelled neuroticism from the Big Five model of personality will be positively associated with nicotine dependence, as measured by the FTND score. We hypothesize that neuroticism will also negatively predict smoking cessation.

Past studies on the role of personality traits in smoking behavior and cessation are inconsistent. This is because there is high variability in the models of personality, nicotine dependence assessments, treatment, and outcome measures used. Nevertheless, most studies report on a positive association between neuroticism and nicotine dependence, measured by the FTND score. Specifically, one study using the Eysenck Personality Questionnaire (McChargue, Cohen, & Cook, 2004), and another using the Big Five model (Hooten et al., 2005), have reported on this relationship. Moreover, the trait neuroticism is defined by a set of characteristics, such as higher tendency to feel negative affect (Kassel, Stroud, & Paronis, 2003), that are consistently shown to be related to smoking (Terracciano, 2004). Therefore, we believe that neuroticism will be positively associated with nicotine dependence in our sample. However, there is mixed evidence in the literature on the role of other Big Five personality traits. Therefore, we aim to explore this research problem. Moreover, a limited number of studies have examined the role of personality traits in smoking cessation. One observational study of the US population, using the Big Five model, found that neuroticism was associated with persistence of smoking. In fact, regardless of the model of personality used, studies have reported on the negative relationship between neuroticism and quitting smoking (Cosci et al., 2009; Hooten et al., 2005). The role of other traits, such as conscientiousness and agreeableness are less consistently identified (Hooten et al., 2005; Nieva et al., 2011; Zvolensky et al., 2015). Therefore, we hypothesize that neuroticism will also be a negative predictor of quitting in our sample. The roles of other Big Five personality traits in treatment with bupropion and varenicline will be explored. In fact, we hope our findings will be hypothesis generating for future studies to be conducted.
1.5 Review of the Literature

1.5.1 Neuropsychopharmacology of Tobacco Addiction

1.5.1.1 Cigarette Design and Nicotine Content

It is important to understand a condition, its etiology, and mechanism before attempting to treat it. Tobacco addiction is a complex multifactorial chronic disorder affecting the brain. Nicotine has been identified as the main psychoactive substance in cigarettes (Dani & De Biasi, 2001; Dani & Heinemann, 1996; UDHHS, 1998). Conventional manufactured cigarettes are well-designed to maximize the efficiency of nicotine delivery. Once an individual puffs on a cigarette, nicotine is distilled and inhaled through the lungs along with other particles found in mainstream smoke. Nicotine is then absorbed through the lungs and travels through the bloodstream, reaching the brain in less than 10 seconds (Hukkanen, Jacob, & Benowitz, 2005; Maisto SA, 2004). Lungs provide a large surface area for rapid absorption of inhaled drugs. In addition, because inhaled nicotine does not pass through the systematic circulation before reaching the brain, it does not undergo first-pass metabolism and a significant amount of it reaches the brain unchanged. Altogether, inhalation as the route of administration leads to a rapid rise in blood concentration of nicotine, which contributes to the addictive properties of smoking (N. L. Benowitz, 1990). A cigarette has about 1 gram of tobacco and on average takes about 10 puffs and 5 minutes to smoke. Approximately one tenth of a cigarette’s weight consists of nicotine. However, a typical smoker only absorbs 0.5-3 milligrams of the nicotine (NIDA, 2001; RCP, 2007). Another important property of nicotine is its short half-life; it takes 2-3 hours for half of the absorbed nicotine to be eliminated (cocorse, 2012). This means that smokers need to smoke frequently in order to maintain a constant nicotine blood concentration.

1.5.1.2 Nicotine Receptors and Release of Neurotransmitter

Nicotine is a nitrogen-containing chemical, an alkaloid, which is derived from the tobacco plant (Schmeltz & Hoffmann, 1977). The mechanism by which nicotine causes dependence is very complex. At cellular level, nicotine exerts its pharmacological effects as a full agonist by binding to the nicotinic acetylcholine receptors (nAChRs). These receptors are abundantly found in both peripheral and central nervous systems. The most abundant nAChRs in the brain are the homomeric α7 and the heteromeric α4β2. However, it is important to note that the α4β2 receptor is believed to be the predominant receptor modulating the addictive properties of
nicotine in the human brain (Neal L. Benowitz, 2009; Picciotto et al., 1998). Thus, the binding of nicotine to the presynaptic nAChR results in dose-dependent release of neurotransmitters, such as dopamine, noradrenaline, acetylcholine, glutamate, GABA, serotonin, opioid peptides, and endocannabinoids (Clarke & Reuben, 1996; Conti et al., 2008; McGehee, Heath, Gelber, Devay, & Role, 1995; Pontieri, Tanda, Orzi, & Di Chiara, 1996; Watkins, Koob, & Markou, 2000; Wilkie, Hutson, Stephens, Whiting, & Wonnacott, 1993; Yang, Criswell, & Breese, 1996). Consequently, nicotine influences several physiological and psychological processes in the brain. These can include cerebral blood circulation, locomotion, pain perception, anxiety, attention, learning and memory, decreased fatigue, relaxation, mood alterations, increased arousal, feeling of pleasure, and a mild euphoria, (Decker, Brioni, Bannon, & Arneric, 1995; Henningfield, Miyasato, & Jasinski, 1985).

1.5.1.3 The Brain Reward Pathway

Of all neurotransmitters affected by nicotine, dopamine has gained the most attention due to its role in addiction. This is due to the fact that dopamine is crucial to the brain’s reward pathway. The brain’s reward system has fundamental roles in motivation and repetition of a reinforcing behavior (Nestler, 2005). Specifically, nicotine leads to release of dopamine in the mesolimbic dopaminergic system. This system includes the projection of dopaminergic neurons from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens (NAc) in the limbic forebrain and the prefrontal cortex. This pathway is the key to the rewarding effects of the drug of abuse and promotes the initial drug-seeking behavior (Nestler, 2005; Pontieri et al., 1996).

As mentioned previously, nicotine has a short half-life and in order to maintain its acute pleasurable effects, the individual needs to smoke regularly. With repeated chronic exposure to nicotine, neuroadaptation occurs in the brain reward pathways and tolerance to nicotine is developed (H. Wang & Sun, 2005). These changes can act as a barrier to abstinence and trigger relapse. In addition to neuroadaptation, the nAChRs binding sites are upregulated in the brain. This could be due to desensitization of the receptors by chronic use of nicotine. As a result, the level of dopamine drops in the absence of nicotine. It is suggested that this process plays a role in manifestation of craving and withdrawal symptoms (Dani & Heinemann, 1996). Withdrawal and craving symptoms consist of physical and emotional effects that basically oppose those experienced in the presence of nicotine. In fact, newly abstinent smokers can feel depressed, anxious, restlessness, irritable and may have difficulty concentrating, sleeping, or suppressing their appetite (Conti et al., 2008; Hughes, Gust, Skoog, Keenan, & Fenwick, 1991).
1.5.1.4 Behavioral Component of Tobacco Addiction

Nicotine dependence is established through a combination of both positive and negative reinforcements. Positive reinforcement refers to the initial pleasurable effects that are experienced in response to acute nicotine exposure. In contrast, negative reinforcement refers to relief from avoidance of negative withdrawal and craving symptoms that develop with repeated exposure to nicotine. In addition to these pharmacological mechanisms, there is a behavioral component to nicotine addiction, which is a consequence of conditioning (Neal L. Benowitz, 2009).

Behavioral conditioning occurs as a result of prolonged intake of nicotine, which forms the basis for learning of the drug-seeking behavior (Gantt, 1927). In the case of smoking, the individual develops association between certain environmental, situational, visual, or mood factors and the rewarding effects experienced from nicotine. As a result, certain cues lead to anticipation of pleasurable drug effects, which urge the individual to smoke (Rose, Behm, & Levin, 1993; Rose, Behm, Westman, & Johnson, 2000). Thus, in addition to its direct effects, smoking is in part maintained by its conditioned reinforcers (Balfour, 2004).

1.5.1.5 Other Modulators of Tobacco Addiction

It is important to note that dopamine is not the only neurotransmitter implicated in tobacco addiction. For instance, GABA and glutamate can control the brain reward pathway via their inhibitory and excitatory inputs at the level of both VTA and NAc (Mansvelder, Keath, & McGehee, 2002; Watkins et al., 2000). Data suggests that norepinephrine and serotonin may also play roles in neurobiology of nicotine dependence, however, the exact mechanisms are not known (Fletcher, Lê, & Higgins, 2008; Muller & Homberg, 2015; USDHHS, 2010). In addition, there can be targets, other than the brain reward pathway, that are involved in the additive properties of nicotine. For instance, nicotine may exert its effects by altering expression of certain genes (Dunckley & Lukas, 2003; Flatscher-Bader & Wilce, 2009).

Furthermore, beside nicotine, there are many other compounds found in tobacco and cigarette smoke, such as harman, that could contribute to tobacco addiction (Bacher et al., 2011; Hall et al., 2014; USDHHS, 2010). What these imply is that addiction is a complex disorder and not fully understood. The factors underlying the disorder likely surpass what is currently known about nicotine and its effects on the brain reward pathways.
1.5.2 Clinical Aspects of Tobacco Addiction

1.5.2.1 Clinical Diagnosis

Clinically, drug dependence is recognized as a complex disorder of the brain. Drug dependence is characterized by compulsive and repetitive drug-seeking behavior (USDHHS, 2010). There are certain criteria that need to be met for a substance use disorder to be diagnosed. These criteria have been defined by the World Health Organization in the International Classification of Diseases, tenth Revision (ICD-10) (WHO, 1992) and the American Psychiatric Association in the Diagnostic and Statistical Manual, revision five (DSM-5) (APA, 2013). The list of criteria issued in the most recent DSM-5 is listed below. According to DSM-5, tobacco use disorder is diagnosed by a cluster of at least two of the following symptoms experienced by the individual within a 1-year span (APA, 2013).

1. Increased or prolonged intake of the drug
2. Lack of control over use of the drug
3. Extensive time spent on obtaining the drug or using it
4. Craving for the drug
5. Impaired management of important tasks at work, school, or home because of substance use
6. Continued use of the drug in spite of its negative impact on relationships
7. Substitution of important activities for substance use
8. Persistent desire to administer the drug even when it puts the individual in danger
9. Continued use of the substance despite knowledge of harmful effects
10. Development of tolerance manifested by decreased effect from previously pleasurable dose or increased dose to obtain same effect
11. Experience of withdrawal symptoms in the absence of the drug, which are relieved by its use

DSM-5 allows for diagnosis on a continuum from mild to severe. However, substance use disorder is a complex condition and this list may not reflect on all the factors involved in addiction (Hasin et al., 2013).

The most widely used scale for measure of nicotine dependence is the Fagerström Test for Nicotine Dependence (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991b). This model primarily measures the level of physical dependence to nicotine (Piper, 2006). It is a
brief six-item questionnaire consisting of six multiple-choice questions. This allows for FTND to be easily administered. The total FTND score can range on a continuum from 0 to 10 with higher score indicating greater dependence to nicotine (Heatherton et al., 1991b). FTND has adequate internal consistency. It also has acceptable construct validity, meaning it can accurately measure dependence (C. S. Pomerleau, Carton, Lutzke, Flessland, & Pomerleau, 1994). In fact, many studies have used this test and have demonstrated that FTND can successfully predicts quitting and relapse (Piper, 2006).

1.5.2.1 Susceptibility to Tobacco Use Disorder

For the vast majority of people, smoking a single cigarette does not lead to the subsequent development of a tobacco use disorder. Smoking develops in three stages: initiation, maintenance, and relapse. It is reported that the majority of tobacco users smoke their first cigarette before the age of 18 (UDHHS, 2004). In fact, about 50% of the population tries a cigarette at least once in their adolescence years. However, only about 20-25% of them progress to become daily dependent smokers (CDC, 2011). There are many factors modulating the initial tobacco exposure and its progression to dependence. There are also gender differences in susceptibility to tobacco addiction. In fact, evidence indicates that men and women may smoke for different reasons (Grunberg et al., 1991). In addition to gender influences, the initiation and transition to daily dependence to nicotine is modulated by a complex interplay of biological, personal and psychological, socio-environmental, and other factors (UDHHS, 2000; WHO, 2010).

Studies have identified a number of potential biological and genetic factors involved in nicotine sensitivity and response, which may predispose an individual to develop nicotine dependence (Quaak et al., 2009). These can be categorized into either pharmacodynamics or pharmacokinetic features of nicotine dependence. For example, variations with respect to nicotine drug target, such as nAChRs, may determine its binding affinity for nicotine, mediating its pharmacological effects in the brain reward system (Al Koudsi & Tyndale, 2005; Thorgeirsson et al., 2010). Secondly, factors influencing nicotine metabolism can affect the half-life of nicotine in the body and its duration of effects (Caporaso et al., 2001; Tyndale & Sellers, 2001). This relationship is further explained in section 1.5.4.

Personal and psychological factors can also mediate smoking initiation and dependence. There is evidence that certain personality characteristics, such as impulsivity and stimulus-seeking can predict smoking initiation (T. B. Baker, Brandon, & Chassin, 2004; Wills, DuHamel, &
The relationship between personality characteristics and smoking is described in details in section 1.5.5. In addition, sociodemographic characteristics, socioeconomic status, knowledge, attitudes, and beliefs, as well as a person’s self-image and self-esteem have been implicated in the vulnerability to substance use disorder. Specifically, male individuals, who are in their late adolescence to early adulthood, of Caucasian or Hispanic decent, come from a low income family, and who do not live in an intact two-parent family structure are more prone to smoking (Robinson & Klesges, 1997; Soteriades & DiFranza, 2003; WHO, 2010). In addition, lack of knowledge on the health risks or expectation of positive outcomes, such as weight control associated with smoking may influence smoking initiation or its persistence (Cohn, Macfarlane, Yanez, & Imai, 1995). Also, there are reports on the relationship between low self-esteem and smoking initiation. An individual may initiate smoking due to the misperception that smoking will improve his or her self-image by making him/her to be perceived as more mature (Chassin, Presson, Rose, & Sherman, 1996). Individuals experiencing negative affect, such as stress, anxiety, and depression may also seek smoking as a way to self-heal (CDC, 2014; Kassel et al., 2003).

Lastly, socio-environmental factors may also play a role in an individual’s smoking behavior in that individuals are more likely to smoke if it is perceived as acceptable and normative in their social circle. The norm may be portrayed through direct tobacco advertising or indirectly through movies, where a powerful character is a smoker (DiFranza et al., 2006; Evans, Farkas, Gilpin, Berry, & Pierce, 1995; Titus-Ernstoff, Dalton, Adachi-Meijia, Longacre, & Beach, 2008). In addition, parental smoking can serve as a model for teenagers to smoke. This effect may be gender specific. Nevertheless, it is a significant influence, especially if the behavior is accepted or encouraged by the parents (Chassin et al., 1996; Gottlieb, 1982). Similarly, peer tobacco use is strongly correlated with smoking initiation and persistence (Biglan, Duncan, Ary, & Smolkowski, 1995). This could be explained by the fact that smoking may be picked up by an individual as means of social-bonding (Krohn, Massey, Skinner, & Lauer, 1983). Furthermore, accessibility and availability to cigarettes at a low price promotes their use (Robinson, Klesges, Zbikowski, & Glaser, 1997).

There are also various factors that contribute to maintenance of smoking behavior. Evidently, the physiological dependence associated with tobacco use disorder results in withdrawal and craving symptoms in the absence of the drug. These symptoms act as barriers to quitting and lead to relapse (IM, 2007; Roche et al., 2014). In fact, studies have shown that higher level of nicotine dependence, as measured by FTND, increases risk of relapse (Cosci et al., 2009). The FTND score also influences different stages of readiness to quit smoking (McChargue et al.,
Psychological factors play significant roles as inducers of continued smoking. Namely, studies suggest that many individuals maintain smoking in response to stress, depression, and to control their body weight and women are more likely than men to continue smoking for these reasons (Leventhal et al., 2007; O. F. Pomerleau et al., 2005; WHO, 2010). Interestingly, compared to men, women have lower success rates in smoking cessation studies (Schnoll, Patterson, & Lerman, 2007). This in part may be due to findings that women are more sensitive to non-nicotine psychological aspects of smoking, such as social cues; whereas men are more sensitive to the reinforcing effects and physical dependence associated with nicotine intake (Field & Duka, 2004; Pauly, 2008). Moreover, quitting success is not only influenced by these factors, but also by the smoker’s intention, motivation, and confidence to quit (Caponnetto & Polosa, 2008; Osler & Prescott, 1998; Smit, Hoving, Schelleman-Offermans, West, & de Vries, 2014). In summary, there are numerous variables influencing initiation, maintenance, and relapse of smoking behavior and these factors may affect men and women differently and suggests that in smoking treatment methods, a single approach may not be effective for all.

1.5.2.2 Biomarkers of Smoking

There is often a need to characterize an individual's smoking status in clinical practice, or research and epidemiological studies. Self-report measures, such as number of cigarettes smoked per day (CPD), are commonly employed. However, there is likely subject bias associated with self-report assessments (Caraballo, Giovino, Pechacek, & Mowery, 2001; Etter & Perneger, 2001). Additionally, CPD may not be an accurate representation of exposure to cigarette content. That is because smokers vary with respect to smoking topography characteristics, such as number of puffs taken per cigarette and puff volume (E. M. Lee, Malson, Waters, Moolchan, & Pickworth, 2003; UDHHS, 1988). For these reasons, objective biochemical measures are used as alternatives. Two commonly used methods are exhaled carbon monoxide (CO) and cotinine analysis.

CO is a low molecular weight gas that is a byproduct of tobacco combustion (Ryter & Choi, 2013). CO levels can be easily measured using portable meters (Irving, Clark, Crombie, & Smith, 1988). CO is also endogenously produced in the body. Individuals can be exposed to CO from environmental sources, such as coal and gas burning, as well (Q. Zhang et al., 2013). Therefore, depending on the population, an appropriate cutoff point needs to be determined in order to distinguish a smoker from non-smoker on the basis of CO levels. Generally, a cut-off point of 5-6 ppm have been accepted (Sandberg, Sköld, Grunewald, Eklund, & Wheelock, 2011). Other advantages of using the expired CO measure include its low cost, non-invasive
sample collection method, and immediate result (Jarvis, Russell, & Saloojee, 1980). However, its use is limited by carbon monoxide’s short half-life of about 4 hours (Sandberg et al., 2011).

Other biomarkers, such as cotinine may be more appropriate depending on the setting, where they are used. Cotinine is the primary metabolite of nicotine. It is very stable with a half-life of 16-19 hours on average. In addition, its concentration is consistent for an individual regular smoker over time (N. L. Benowitz, Jacob, Fong, & Gupta, 1994). Cotinine concentration can be measured in plasma, urine, or saliva (Etzel, 1990). Studies have shown that it is a sensitive measure of cigarette smoking (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987).

It is also an appropriate method for assessment of smoking status using mailed saliva samples (Etter, Neidhart, Bertrand, Malafosse, & Bertrand, 2005). It is worth noting that there are inter-individual differences with respect to cotinine production, which depend on the rate of nicotine metabolism, mainly affected by genes, gender, and race (N. L. Benowitz, Bernert, Caraballo, Holiday, & Wang, 2009). Nevertheless, studies have been conducted to determine an optimal cutoff point for cotinine assessment. It has been shown that a concentration of 7 ng/ml measured in saliva has high sensitivity and specificity to discriminate between smokers and non-smokers (Etter, Vu Duc, & Perneger, 2000). In conclusion, biochemical validations are reliable measures of smoking status and the choice depends on the setting and the population.

1.5.3 Smoking Cessation and Interventions

1.5.3.1 Challenges

To this point, it has been established that smoking is a chronic relapsing disorder. Tobacco dependence is multidimensional with both physical and psychological components. In fact, nicotine dependence is one of the hardest addictions to quit. Studies have shown that the success rate is very low in self-quitters. About 80% of smokers, who make an attempt to quit, relapse within the first months, with only 3-5% of them remaining abstinent at 6 month following their quit date (Hughes, 2007). In fact, on average, it takes 5 to 7 quit attempts before one can succeed at permanently quitting smoking (Hughes, 2000). Nevertheless, it is suggested that the chance of long-term quitting increases by 50% if a smoker remains abstinent for at least 3 to less than 6 months (Gilpin, Pierce, & Farkas, 1997).

Some barriers to quitting, such as perceived benefits of smoking in handling stress and depression and fear of weight gain, have been described in section 1.5.2.2 (WHO, 2010). Most important of all is the long lasting withdrawal and craving symptoms that appear when one quits
smoking (Hughes, 1992). Another factor contributing to the addiction is the strong reinforcing properties of nicotine, especially when administered by inhalation through smoking cigarettes (N. L. Benowitz, 1990). In addition, the short half-life of nicotine induces regular uptake of cigarettes, contributing to the behavioral part of the addiction (cocorse, 2012). Moreover, unlike other addictive drugs, nicotine is not intoxicating. In fact, smokers are able to self-titrate their nicotine uptake by altering the number and duration of puffs taken from a cigarette and the puff volumes. This will allow smokers to reach an optimal level of nicotine that alleviates their withdrawal and craving, but does not result in any adverse effects, such as nausea (Ashton, Stepney, & Thompson, 1979; Strasser, Lerman, Sanborn, Pickworth, & Feldman, 2007).

In summary, there are many factors contributing to the strong addictive properties of smoking. Therefore, a number of interventions have been proposed and practiced over the years to address these issues and help smokers manage the barriers they face in quitting. Although these approaches are helpful, their efficacy is limited. As mentioned, tobacco addiction is comprised of both physical and psychological dependence. As a result, these approaches include both non-pharmacological, such as behavioral interventions, and pharmacological treatments.

1.5.3.2 Behavioral Interventions

Behavioral interventions are commonly employed to treat smoking. Behavioral interventions refer to verbal instructions to modify a health-related behavior. The goal of behavioral therapy is to provide information on the mechanism of addiction, health consequences of smoking, benefits of cessation, and strategies on how to cope with craving and to successfully quit. They may also involve cognitive therapy, which includes changing the way smokers think about quitting and identifying socio-environmental cues that trigger the behavior (Kober, Kross, Mischel, Hart, & Ochsner, 2010; Mallin, 2002). Behavioral interventions can be minimal as in advice to quit from a clinician. They can also be offered as intensive clinical interventions, including individual, group, or phone counselling.

Minimal interventions have shown to have small effects in self-quitting rate. However, they can prompt the individual to seek smoking cessation aids to help them quit smoking (Stead LF, 2013). On the other hand, evidence suggests that intensive behavioral interventions can increase quitting rates substantially (Lancaster & Stead, 2005; Mottillo et al., 2009). In fact, a meta-analysis reported significant results for their effect on long-term quit rates. The highest odd ratio (OR) was attributed to group counseling methods with OR of 1.75 and a 95%
confidence interval (CI) of 1.11-2.93 (Mottillo et al., 2009). Moreover, these behavioral interventions can be used alone or in combination with pharmacotherapies (Stead & Lancaster, 2012a, 2012b). A meta-analysis of studies combining behavioral with pharmacological treatments resulted in a risk ratio (RR) of 1.92, with a 95% CI of 1.66-2.00 (Hartmann-Boyce, Stead, Cahill, & Lancaster, 2013). In fact, it has been shown that success rates are improved by 10-25% when four sessions of behavioral support are provided compared to use of pharmacotherapies alone (Stead & Lancaster, 2012a). Extended behavioral therapy can also aid with maintaining abstinence after successfully quitting (Killen et al., 2008). Furthermore, behavioral therapies are especially useful to treat pregnant women, as pharmacotherapies may not always be safe during pregnancy (Cressman, Pupco, Kim, Koren, & Bozzo, 2012).

1.5.3.3 Nicotine Replacement Therapy

For many smokers, behavioral interventions are not sufficient to aid with quitting. They may need pharmacological treatment to assist with the physiological and psychological symptoms of nicotine withdrawal. The most commonly used pharmacotherapy for smoking cessation is nicotine replacement therapy (NRT). Nicotine replacement therapies are first-line non-prescription over the counter smoking cessation medications. The main goal of this treatment is to deliver low doses of nicotine to replace the nicotine smokers derive from tobacco use (Gourlay & McNeil, 1990; Henningfield, 1995). It basically mimics the nicotine from smoking and binds to the nAchR’s to relieve withdrawal and craving symptoms. In addition, if the NRT dose is high enough to saturate the nAchR’s, it makes smoking less satisfying by desensitizing nAchR’s. In other words, if a person smokes while on NRT, the behavior will be less rewarding (Neal L. Benowitz, 2009).

NRTs come in different forms. Nicotine gums were the first type of NRT introduced into the market. They are formulated in two doses (2 and 4 mg) and designed to deliver nicotine through the buccal mucosa in the mouth. Nicotine is then systematically absorbed and reaches the brain to exert its therapeutic actions (Russell, Feyerabend, & Cole, 1976). Transdermal patches are another type of NRT that are widely used. They are available in doses of 7, 14, and 21 mg and most are designed to be applied over a period of 24 hours (Fiore, Jorenby, Baker, & Kenford, 1992). The suggested duration of treatment with transdermal patches is about 10 weeks; although, adherence is low in most smokers (B. Zhang, Cohen, Bondy, & Selby, 2015). Other forms of NRT include lozenge, tablet, nasal spray, and inhaler. Overall, NRTs have been proven efficacious. Studies have shown that they increase the chances of successfully quitting by about 2 times compared to placebo with an OR of 1.77, 95% CI: 1.66-
One of the advantages of use of NRTs is that they are safe and severe side effects in response to NRT are uncommon (Tonstad, Gustavsson, Kruse, Walmsley, & Westin, 2014). However, side effects, such as nausea and sleep disturbance can be experienced. Also, some individuals may develop skin irritation and rash at the site of patch application (HC, 2011).

1.5.3.4 Bupropion

Bupropion hydrochloride (HCl) sustained release (SR), marketed under the brand name Zyban® (manufactured by Valeant Canada LP), is the first non-nicotine first-line prescription-only smoking cessation medication, which was approved in 1997 (CW, 2015). Bupropion was discovered by chance observations in clinical practice, where smokers who were receiving treatment for depression were reporting less desire to smoke and were spontaneously quitting (Aveyard, Parsons, & Begh, 2010). The generic bupropion SR is identical to Wellbutrin® and Zyban® with respect to dosage, pharmacokinetics, and bioavailability. As a result, it has been proven bioequivalent to the brand names, but has an approved indication for depression only (Moreira et al., 2009).

1.5.3.4.1 Mechanism of Action of Bupropion

Bupropion’s exact mechanism of action in smoking cessation is not understood. However, it is proposed that bupropion, possibly through actions of its metabolites, is a dual inhibitor of dopamine and noradrenaline, and to a weaker extent, serotonin reuptake (Stahl et al., 2004; Wilkes, 2008). Its action on dopamine reuptake in the nucleus accumbens is highly implicated in its properties as a smoking cessation aid. This is because bupropion prolongs the duration of dopamine in the synapse, thereby preventing the manifestation of withdrawal and craving symptoms that occur in nicotine’s absence. In addition, inhibiting dopamine’s reuptake moderates the burst of dopamine that results in response to nicotine. Therefore, smoking may not be as reinforcing and pleasurable, while the individual is on bupropion (Warner & Shoaib, 2005). The exact role of noradrenaline in addiction is not clear. However, the release of noradrenaline in hippocampus may be playing a role in withdrawal (Done, Silverstone, & Sharp, 1992). As a result, bupropion might further help reduce withdrawal symptoms by its influence on the noradrenaline system. Serotonin’s role in nicotine dependence is being investigated and it is unclear whether bupropion’s actions are mediated by its effect on serotonin reuptake. Furthermore, it has been demonstrated that bupropion is a weak nAchR antagonist. Due to its anticholinergic feature, bupropion may interfere with nicotine binding and further help in
reducing the rewarding effects of smoking (Slemmer, Martin, & Damaj, 2000; Warner & Shoaib, 2005).

1.5.3.4.2 Clinical Studies on Bupropion

Since the discovery of bupropion's beneficial effects in smoking cessation, several clinical studies have been conducted to evaluate its efficacy. The first large-scale randomized placebo-controlled clinical trial was conducted in 1997. In this study, participants were given 7 weeks of treatment, randomly assigned to 100, 150, or 300 mg/day of bupropion, or placebo. At the end of treatment, the highest quit rate was observed for subjects treated with 300 mg of bupropion per day. The 7 day point prevalence of abstinence at the end of treatment in this group was 44%, versus 19% in placebo (Hurt et al., 1997). In this study, bupropion at the dose of 300 mg/day was effective at relieving subjective withdrawal symptoms (Hurt et al., 1997). Since then, many other studies have reported on the efficacy of bupropion in clinical trials. A recent meta-analysis of available data confirmed the superior clinical efficacy of bupropion compared to placebo, with an OR of 1.82, and CI 1.60-2.06. Also, a head-to-head comparison of bupropion with NRT revealed equal efficacy (OR: 0.99, CI: 0.86-1.13) (Cahill, Stevens, Perera, & Lancaster, 2013).

Nevertheless, data on the real-world effectiveness of bupropion is limited. A review of a number of small intervention studies demonstrated that similar quit rates were achieved with bupropion in the real-world, although these studies lacked biochemical confirmation of smoking status (Holmes et al., 2004). A recent cross-sectional study of multi-national population indicated that use of bupropion improved quit outcomes compared to no use of any cessation aids (Kasza et al., 2013). With this being said, a pragmatic randomized clinical study of bupropion has not been conducted. Such a study could point out to the real-world setting utility of bupropion. Furthermore, studies have indicated that bupropion may be more efficacious or better tolerated in subpopulation of smokers with comorbidities or certain genetic polymorphisms (David et al., 2007; Tonstad, 2002).

1.5.3.4.3 Pharmacokinetics of Bupropion

Based on the findings of several clinical studies, the approved dosing regimen of bupropion for smoking cessation in clinical practice is titrated 150 mg twice daily. This medication is recommended for those, who smoke 10 cigarettes per day or more. The smokers are advised to start the medication about 7-14 day before their target quit date and continue the treatment
for 10-11 weeks after, for a total treatment period of 12 weeks (Patel, Feucht, Reid, & Patel, 2010; West, 2003). A single dose of bupropion 150 mg results in a $C_{max}$ of 100 ng/ml in approximately 3 hours. However, the purpose of titration and pre-quitting periods are to allow for the body to adapt to the medication and for stable brain concentrations of bupropion to be achieved (West, 2003). The orally administered bupropion is absorbed through the guts, expansively metabolized, and excreted through the kidneys. The elimination half-life of bupropion is about 21 hours. Bupropion is extensively metabolized in the liver into three active metabolites, hydroxybupropion, threohydrobupropion and erythrobupropion. In particular, the hepatic cytochrome P450 2B6 (CYP2B6) is responsible for the conversion of bupropion to its primary active metabolite, hydroxybupropion (Jefferson, Pradko, & Muir, 2005). It is proposed that the pharmacological effects of bupropion are mainly exerted via its three metabolites (Warner & Shoab, 2005). It is worth noting that CYP2B6 is a polymorphic enzyme and this can potentially result in variability in response to bupropion (A. M. Lee et al., 2007). In fact, one study has shown that CYP2B6- mediated formation of hydroxybupropion is associated with differential response to bupropion treatment (Zhu et al., 2012). Bupropion is also a potent inhibitor of the highly polymorphic CYP2D6 enzyme (Kotlyar et al., 2005). This characteristic of bupropion can result in drug-drug interactions with compounds that are metabolized by this enzyme. As a result, some antidepressants, antiarrhythmic and antipsychotics have been contraindicated for concurrent use with bupropion (J. S. Wang et al., 2006; Wilkes, 2008).

1.5.3.4.4 Safety of Bupropion

Bupropion is safe and well-tolerated in the general population at its approved doses. However, due to its diverse pharmacological actions, side effects may be experienced. In fact, adverse reactions are experienced by half of the patients in the first two weeks of taking bupropion. However, this rate drops to 6% by 3 months (Barrueco et al., 2005). Most of the adverse effects are mild and resolve on their own without clinical interventions. Some common ones include insomnia (24-42%), dry mouth (6-28%), nausea/vomiting (9-13%), dizziness (2-11%), headache (4-33%), and anxiety (5-9%). Seizures are rare, but have been reported. Allergic reaction or hypersensitivity, though infrequently, has also been reported (Boshier, Wilton, & Shakir, 2003; Johnston et al., 2001; West, 2003; Wilkes, 2008). It is important to note that many of the side effects experienced are similar to that of nicotine withdrawal symptoms, making them hard to distinguish (Hurt et al., 1997). Moreover, FDA has issued a black box warning for bupropion cautioning patients and practitioner of serious neuropsychiatric and suicidality events that may occur while on bupropion (FDA).
1.5.3.4.5 Compliance with Bupropion Treatment

One limitation of bupropion treatment is its low compliance rate. This is in part attributed to its side effects profile. Generally, it has been shown that the compliance drops to 75% by the third week of treatment. It further drops to 40% by week 7, and 28% by week 10 of treatment (Kohlenberg, Antonuccio, Hayes, Gifford, & Piasecki, 2004). Another study showed that overall, 9% of patients discontinue use of bupropion at some point prior to its 12 weeks long course of treatment and another 13% briefly pause the treatment (Barrueco et al., 2005). Fortunately, in research settings, compliance to bupropion can be validated by self-report measures or biochemically. Nevertheless, this emphasizes that although clinically efficacious, the read-world effectiveness of bupropion may be restricted by poor adherence to the treatment regimen.

1.5.3.5 Varenicline

Varenicline tartrate is the second prescription-only medication, approved for first-line treatment of smoking cessation in Canada. It is sold under the brand name Champix, manufactured by Pfizer Inc. Varenicline was first synthesized and identified by Jotham Coe, PhD and Brian O’Neill, PhD, a team of chemists at Pfizer, as a novel smoking cessation agent (Coe et al., 2005). After further evaluations, it has been approved for use since 2007 (Lam & Patel, 2007).

1.5.3.5.1 Mechanism of Action of Varenicline

Varenicline is a selective partial agonist of the α4β2 nAchR and binds the receptor with high affinity (Hays, Ebbert, & Sood, 2008; C. Jimenez-Ruiz, Berlin, & Hering, 2009). It has been proposed that varenicline aids with smoking cessation in two ways. Firstly, by binding to the α4β2 receptor, it leads to the release of dopamine in the brain reward pathway. Therefore, varenicline’s dopaminergic activity alleviates the withdrawal and craving symptoms that arise in the absence of dopamine in these brain regions. Because varenicline is a partial agonist, it does not elicit a substantial increase in the extracellular dopamine levels. In fact, studies in rats have shown that at the maximum dose of 1mg/kg, the dopamine release by varenicline in the nucleus accumbens is only approximately 60% of what is maximally induced by nicotine. Thus, varenicline is not expected to possess an abuse liability potential (Coe et al., 2005; Rollema et al., 2007). Secondly, it has been demonstrated that the affinity of varenicline for the α4β2 receptor is 16 times higher than nicotine. As a result, varenicline competes with nicotine for the binding site and antagonize its activity. So, if a smoker smokes in the presence of varenicline, the nicotine-inducing reinforcing effects of smoking will be blocked (Coe et al., 2005).
Furthermore, varenicline has shown moderate affinity for the serotonin 5-HT<sub>3</sub> receptor; but, this characteristic of varenicline is not believed to be implicated in smoking cessation (C. Jimenez-Ruiz et al., 2009). Moreover, although varenicline is selective for the α4β2 receptor, it has been shown to also act as a weak partial agonist at a number of other nAchRs, such as α3β2 and α6-containing receptors. Additionally, varenicline is a full agonist at the homomeric α7 nAchR (Mihalak, Carroll, & Luetje, 2006). It is unclear whether its actions on these receptors play a role in its mechanism of action as a smoking cessation aid.

1.5.3.5.2 Clinical Studies on Varenicline

Several clinical trials have reported on varenicline’s superior efficacy compared to other available pharmacotherapies, bupropion and NTR (Xi, 2010). In a pooled-analysis of two Phase III trials by Gonzales et al (D. Gonzales et al., 2006) and Jorenby et al (D. E. Jorenby et al., 2006), treatment with 1mg of varenicline, taken twice daily, led to significantly higher quit rates than both bupropion and placebo. Specifically, the continuous abstinence rates at the end of treatment were 44.0% in subjects being treated with varenicline, versus 29.7% and 17.7% in bupropion and placebo groups, respectively (Nides et al., 2008). In these two studies, smoking satisfaction and psychological rewards were significantly reduced, while the subjects were on varenicline. Varenicline also relieved craving once the subject stopped smoking.

Moreover, a more recent meta-analysis of available studies in smoking cessation, varenicline was shown to be more efficacious than placebo with an OR of 2.88, and a 95% CI of 2.40-3.47. Varenicline also increased the odds of quitting compared to bupropion (OR: 1.59; 95% CI: 1.29-1.96) and single forms of NRT (OR: 1.57; 95% CI: 1.29-1.91) (Cahill et al., 2013). Another meta-analysis of 19 randomized clinical trials of varenicline was conducted very recently. This analysis indicated that the quit rates for varenicline were 49% and 22% at weeks 9-12 and at week 52 from the start of treatment, respectively. The relapse rate in the varenicline group (55%) was similar to the group of subjects receiving placebo (53%), which had abstinences rates of 17% and 8% at weeks 9-12 and at week 52, respectively. Nevertheless, overall, a significantly higher percentage of subjects treated with varenicline were able to be quit at one year after the start of treatment (Agboola, Coleman, McNeill, & Leonardi-Bee, 2015).

In spite of its proven efficacy in clinical trials, data on effectiveness of varenicline in real-world settings is limited. One prospective pragmatic interventional study reported a continuous quit rate of 58.3% at the end of treatment in subject being treated with varenicline combined with
cognitive behavioral therapy. The quit rates reported were biochemically confirmed (Ramon & Bruguera, 2009). Another group of researchers performed a retrospective chart review of patients with or without psychiatric comorbidities in an attempt to measure the real-world effectiveness of varenicline. The quit rates at the end of treatment with varenicline (33.7%) was almost doubled compared to NRT (18.4%) (RR: 1.83; 95% CI: 1.22-3.03). The results remained significant after adjustment for a number of baseline and demographic characteristics (Kaduri et al., 2015). The knowledge on the real-world effectiveness of varenicline is restricted to analysis of observational studies. Therefore, a randomized pragmatic study can provide additional certainty on how varenicline successes outside clinical trials.

1.5.3.5.3 Pharmacokinetics of Varenicline

In clinical practice, varenicline is recommended for use by smokers, who smoke 10 cigarettes per day or more. Patients are advised to start varenicline one week prior to their quit date. The standard dose for varenicline is 1mg taken twice per day. The dose needs to be titrated in order to give the body time to adjust and to minimize side effects, such as nausea (Lam & Patel, 2007). One significant pharmacokinetic characteristics of varenicline is that when orally administered, it is highly bioavailable and unaffected by the time of intake and presence of food.

A single 1 mg dose of varenicline administrated in healthy smokers results in a maximum plasma concentration of about 5 ng/ml in approximately 3-4 hours (Faessel, Smith, et al., 2006). Varenicline undergoes very minimal biotransformation. In fact, more than 90% of varenicline is excreted in its unchanged form. A small percentage of ingested varenicline undergoes N-carbamoyl glucuronidation and oxidation and produces varenicline N-carbamoylglucuronide and N-glucosylvarenicline (Obach et al., 2006). The elimination half-life of varenicline is about 24 hours and it is primarily cleared in the urine by the kidneys (Faessel, Gibbs, et al., 2006). Varenicline is in part cleared by active tubular secretion through the organic cation transport OCT2. As a result, polymorphic variations in OCT2 or impaired kidney function may affect varenicline’s elimination and consequently, its efficacy and safety (Bergen et al., 2014; Feng et al., 2008). In addition, studies have shown that varenicline does not inhibit or induce any major cytochrome P450 enzymes. Because varenicline, for the most part is not metabolized by cytochrome P450s, nor does it affect their activity, there is very little potential for an interaction between varenicline and other drugs that go through these enzymes (Faessel et al., 2010). As a result, it may be a suitable choice for smokers with comorbidities, who may be administering multiple medications for treatment of other conditions. However, caution should be made about pharmacodynamic drug-drug interactions with other medications that act on nAchRs.
1.5.3.5.4 Safety of Varenicline

Varenicline is generally well-tolerated. In most cases, the frequency of adverse effects experienced in patients treated with varenicline can be similar to that of bupropion and placebo. This is because stopping smoking leads to similar symptoms and it is difficult to distinguish between treatment-emergent adverse effect and indications associated with cessation (C. Jimenez-Ruiz et al., 2009). The most common side effects associated with varenicline pharmacotherapy are nausea (30%), insomnia (18%), headache (15%), abnormal dreams (13%), constipation (8%), and abdominal pain (7%). Sleep disturbance, dizziness, dry mouth, increased appetite, and weight gain have also been reported (Garrison & Dugan, 2009; Lam & Patel, 2007). These side effects are not serious and they are only temporarily experienced in the first few weeks of treatment. In fact, the rate of discontinuation due to side effect is very low and occurs in less than 2% of patients (Xi, 2010). On the other hand, during the post-marketing surveillance of varenicline, concerns on the neuropsychiatric side effect have risen. For this reason, FDA has issued a black box warning to caution patients and practitioners (FDA).

1.5.3.5.5 Compliance with Varenicline Treatment

One drawback common to all smoking cessation treatments is that compliance is generally low; and varenicline is no exception. In fact, studies have demonstrated a positive correlation between treatment compliance and quit outcome. Varenicline use can be biochemically validated if required. In an attempt to measure the real-world compliance rates associated with varenicline treatment, one study examined varenicline use in a large sample of patients from primary care setting. This study found that about 55.7% never initiated the treatment. Of those who started the medication, only 54.9% of them finished the full 12 weeks course of treatment. The abstinence rates were also measured. In the fully adherent group, 50.7% were able to successfully quit; whereas only about 30% of the non-adherent and partially adherent became abstinent (Liberman et al., 2013). It is important to note that the results of this study could have been confounded by factors such as motivation to quit. In other words, those smokers who remained fully compliant with the treatment could have been more motivated to quit. Overall, varenicline is an effective pharmacotherapy for smoking cessation. In clinical settings, treatment can be adjusted to meet the needs of individuals. For instance, the dose can be reduced in patients experiencing persistent side effects. Varenicline can also be used long-term to maintain abstinence and to prevent relapse (Ebbert, Wyatt, Hays, Klee, & Hurt, 2010). Varenicline can even be administered for an extended duration in the pre-quit period to help
smokers reduce before they fully quit smoking (Ebbert et al., 2015). In summary, varenicline is an efficacious smoking pharmacotherapy and it is customizable to further improve outcomes.

1.5.3.6 Technology-Based Interventions

Innovative approaches are needed to attract smokers, who do not respond well to traditional smoking programs. Mobile phones and the internet have become an integral part of daily lives of many people. They are widely used and instantly accessible (PBLOG, 2012; Pew, 2014). Therefore, interventions that are delivered through the internet and mobile devices are expected to make a significant impact on behavioral changes, such as smoking. In fact, there are cessation aids offered through text messaging services and mobile applications. Most of these tools can be personalized, which makes them more appealing to the users. Some mobile applications remind smokers of how far they have come and help them set reachable goals. Recent studies have shown that these self-help online and mobile-based smoking interventions are in fact effective at increasing quitting success rates compared to no treatment. They can also assist with maintenance of abstinence (Civiljak, Stead, Hartmann-Boyce, Sheikh, & Car, 2013; Hartmann-Boyce et al., 2013; Whittaker et al., 2012).

1.5.4 Nicotine Metabolism and Cigarette Smoking

1.5.4.1 Metabolism of Nicotine

There are several factors that play a role in the level of nicotine dependence and one’s ability to quit smoking. One factor that has gained recent attention is the rate of nicotine metabolism. Nicotine is extensively metabolized by the liver (Hukkanen et al., 2005). This primarily occurs by the enzyme cytochrome P450 2A6 (CYP2A6). In fact, about 80% of nicotine is metabolically inactivated by CYP2A6 to its major metabolite, cotinine (COT), which has a half-life of 16-18 hours (N. L. Benowitz & Jacob, 1994). Similarly, cotinine undergoes further biotransformation to produce 3'-hydroxycotinine (3HC). The biotransformation of cotinine to 3HC is almost entirely carried out by the same enzyme, CYP2A6 (Messina, Tyndale, & Sellers, 1997). A schematic diagram of nicotine metabolism is shown in Figure1. 3HC has a shorter half-life and is eliminated by 50% in about 5 hours. Studies have shown that there is high inter-individual variability in the intrinsic hepatic clearance of nicotine (Raunio, Rautio, Gullsten, & Pelkonen, 2001). Twin studies have demonstrated that most of this variation, about 60%, is attributed to genetic factors (Swan et al., 2005). In addition to genetic sources of variability, demographic characteristics, such as age, gender, and ethnicity can alter enzyme activity. Moreover,
CYP2A6 is influenced by environmental factors including presence of inhibitors and inducers (e.g. estrogen) of the enzyme (Chenoweth et al., 2014).

Figure 1. Nicotine Metabolism by the enzyme cytochrome P450 2A6 (CYP2A6)

1.5.4.2 Nicotine Metabolite Ratio (NMR)

One approach to quantify an individual's CYP2A6 enzyme activity is genotyping. However, genotyping can be expensive and it does not provide an accurate measure of actual nicotine metabolism. In order to take into consideration all sources of variability and get a more representative measure, a novel biomarker has been identified, called the nicotine metabolite ratio or NMR. Specifically, NMR is the ratio of 3'hydroxy cotinine (3HC) over cotinine (COT) concentration. NMR is a validated non-invasive phenotypic marker of CYP2A6 activity, measured in plasma, urine, or saliva (Dempsey et al., 2004). This ratio has been recognized as a marker of CYP2A6 activity on the basis that the biotransformation of cotinine to 3HC is a function of CYP2A6 activity. Although 3HC has a shorter half-life compared to COT, its elimination is limited by its formation from COT. Therefore, 3HC's concentration in biological fluids is proportional to its rate of formation. As a result, the ratio of 3HC to COT remains constant (N. L. Benowitz & Jacob, 2001). Furthermore, there is evidence that there is little within subject variability of this ratio. In fact, it has been shown that NMR is not affected by the time of sampling and remains relatively constant from day to day in a smoker with regular smoking habits. As a result, a single sample can provide a true measure of the individual's NMR value (Lea, Dickson, & Benowitz, 2006).

1.5.4.3 NMR and Smoking Behavior

A number of studies have utilized NMR as a marker to study the relationship between nicotine metabolism and smoking-related characteristics. In fact, one study found that faster
metabolizers, categorized on the basis of NMR measures, take deeper puffs on their cigarettes (Strasser et al., 2011). Moreover, several studies have shown that NMR is positively correlated with the number of cigarettes smoked per day. In other words, rapid metabolizers smoke more cigarettes (N. L. Benowitz et al., 2003). This is expected as they clear nicotine faster and need to smoke more frequently in order to maintain steady-levels of nicotine in their body. However, one study investigating this relationship in a sample of African American light smokers reported no correlation between NMR and CPD (Ho et al., 2009). Moreover, most studies have not found an association between NMR and nicotine dependence (N. L. Benowitz et al., 2003; Falcone et al., 2011; Schnoll et al., 2014). This indicates that nicotine dependence is a multifactorial trait and is influenced by more than nicotine metabolism. Consistent with the above findings, one study also reported that NMR can predict early onset of withdrawal symptoms in the absence of cigarettes (Hendricks, Delucchi, Benowitz, & Hall, 2014).

1.5.4.4 NMR and Smoking Treatment Outcome

In an effort to improve treatment efficacy, a number of studies have utilized the nicotine metabolism biomarker to identify smokers, who better respond to certain treatments. One study found that NMR predicted treatment outcome in a sample of smokers being treated with 8 weeks of open-label transdermal nicotine patch. In particular, smokers were categorized into 4 quartiles on the basis of their pre-treatment 3HC/COT ratio measures. The odds of quitting differed by about 70% between slowest and fastest metabolizers. These results were adjusted for nicotine dependence level, body mass index, ethnicity, and gender. In contrast, NMR levels were not associated with abstinence rates in smokers treated with nicotine nasal spray (C. Lerman et al., 2006). A similar study, controlling for variables, such as age, gender, ethnicity, and nicotine dependence, was able to validate these findings (Schnoll et al., 2009). Furthermore, a study of the African American light smokers demonstrated a significant association between quitting smoking and CYP2A6 activity, measured by either NMR or genotyping. This association was more pronounced in females (Ho et al., 2009).

CYP2A6 activity has also been shown to correlate with response to non-nicotine pharmacotherapies. In fact, the relationship between NMR and bupropion treatment outcome combined with counseling has also been investigated. Similar to previous studies, smokers were categorized into 4 quartiles based on their NMR value. Abstinence rates were measured at the end of the 10-week treatment. Interestingly, slow metabolizers in the first NMR quartile treated with bupropion or placebo had similar quit rates (32%). On the other hand, quit rates were very low in fast metabolizers (4th NMR quartile) receiving placebo (10%). The rate was
significantly improved in the group of fast metabolizers, who were treated with bupropion (34%) (Patterson et al., 2008). This suggests that bupropion does not provide any additional benefit to slow metabolizer smokers; but, it is greatly beneficial to fast metabolizers. Therefore, NMR can be a promising tool to aid with prescribing bupropion to those who will benefit. In addition, this can help avoid unnecessary exposure to those who do not benefit from bupropion treatment, but may suffer from possible side effects.

Moreover, a recent study examined the role of NMR in varenicline treatment, compared to treatment with nicotine patch. Specifically, in an NMR stratified (cutoff of 0.31), randomized, placebo-controlled clinical trial, treatment seeking smokers were assigned to placebo, patch, or varenicline. End of treatment 7-day point prevalence abstinence rates were assessed. In normal metabolizers, varenicline was more efficacious (38.5%) compared to nicotine patch (22.5%). On the other hand, in slow metabolizers, varenicline (30.4%) and nicotine patch (27.7%) resulted in similar abstinent rates. However, slow metabolizers receiving varenicline reported more severe side effects compared to fast metabolizers (C. Lerman et al., 2015). This demonstrates that not only varenicline does not provide additional benefit to slow metabolizers, it also places them at a higher risk of adverse reactions. To date, studies have focused on NMR’s role in treatment response to NRT or placebo versus a non-nicotine pharmacotherapy. However, no study has compared the two non-nicotine therapies, varenicline and bupropion, to evaluate if CYP2A6 activity differentially affects treatment outcome with these two medications. On the path to personalized medicine, NMR has the potential to help improve treatment outcomes and minimize side effects.

1.5.5. Personality and Cigarette Smoking

1.5.5.1 Personality Traits of Smokers

Evidence suggests a relationship between phenotypic personality characteristics and smoking behavior. A number of personality assessment procedures have been employed. But, comparable conclusions were reached. Several studies investigating this relationship utilized the theoretical model proposed in 1967 (H. Eysenck, 1967). The Eysenck Personality Questionnaire (EPQ) is distinct in that it describes the underlying genetics determinants controlling the personality traits (H. Eysenck, 1967; H. J. Eysenck, 1990). Based on this model of personality, there are three major dimensions of personality: extroversion, neuroticism, psychoticism (H. Eysenck, 1967). Although controversial, smokers generally tend to be extroverts, described as being sociable, assertive, enthusiastic, and talkative. In addition,
compared to non-smokers, smokers tend to score high on the neuroticism dimension, which comprises traits such as anxiety, anger, envy, guilt; and is generally related to anxiety and depression disorders (Arai, Hosokawa, Fukao, Izumi, & Hisamichi, 1997; Cherry & Kiernan, 1976; Munafó & Black, 2007). These associations remain debatable as studies have shown contrary results (McManus & Weeks, 1982; Rondina et al., 2007; Sijuwola, 1989; Wakefield Jr, 1989). On the other hand, the relationship between being a smoker and psychoticism dimension of personality has been proven consistently. Psychoticism is characterized by aggressiveness and interpersonal hostility (Arai et al., 1997; Cherry & Kiernan, 1976; McManus & Weeks, 1982; Munafó & Black, 2007; Sijuwola, 1989; Wakefield Jr, 1989). Other traits that are commonly reported to be significantly greater in smokers are impulsivity and sensation-seeking (Glicksohn & Nahari, 2007; Granö, Virtanen, Vahtera, Eloainio, & Kivimäki, 2004; Gurpegui et al., 2007).

1.5.5.2 The Big Five Personality Traits of Smokers

The most widely used model of personality, the Big Five Model or the Five Factor Model (FFM), has also been employed to study the relationship between personality characteristics and smoking habit, although to a lesser extent (John, 1992; Rondina et al., 2007). Costa and McCrae were one of the set of researchers, who independently worked on developing the FFM in 1985. The FFM is comprised of the following five traits: extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience (P. Costa & McCrae, 1985; John, 1992). These traits are about 50% genetically determined and remain relatively constant during the life-time of an individual (R. McCrae & Costa Jr., 1997). One study, based on this model, found distinct differences in personalities of current-smokers, former-smokers, and never-smokers. In this study, current-smokers scored significantly higher on neuroticism and significantly lower on agreeableness and conscientiousness, in comparison to never-smokers. On the other hand, former-smokers scored intermediate on the above factors. The relationship between neuroticism and smoking was especially observed in individuals with low conscientiousness, demonstrating an interaction between the two traits. Lastly, this study did not find any significant differences in extraversion and openness to experience among the different groups (Terracciano, 2004).

One recent study investigated the correlation between FFM with lifetime cigarette use, smoking progression, and smoking persistence is US adults over a 10 year time span. Their data were adjusted for demographic characteristics, depression, anxiety disorder, and substance use problem. Most interestingly, it was found that neuroticism and openness to experience were
significantly associated with any lifetime cigarette use. In contrast, they observed a significant negative correlation between lifetime cigarette smoking and conscientiousness. The only trait that predicted likelihood of progression from smoking initiation to daily dependent smoker was neuroticism. However, this relationship did not hold after adjusting for demographics, depression, and anxiety disorder (Zvolensky et al., 2015).

1.5.5.3 Personality and Nicotine Dependence

To date, most of the research in this field has focused on the trait differences between smokers and non-smokers. Some have distinguished light and heavy smokers. Others have looked at the effect of personality characteristics on cigarette consumption. For instance, one study demonstrated that within a group of smokers, high impulsivity predicted a greater number of cigarettes smoked per day in women. Interestingly, this correlation was not observed in male smokers (Granö et al., 2004). Nevertheless, only a few studies have examined these traits within a sample of smokers in order to compare personality to dependence level on a continuum scale. One study utilized the EPQ to investigate this relationship in male college students and found a relationship between neuroticism and dependence, as measured by the FTND (McChargue et al., 2004). Of particular interest, one study by Nieva and colleagues used the Alternative Big Five Factor Model (AFFM) to study this relationship (Nieva et al., 2011). The AFFM was proposed based on a psychological approach and is expected to provide more comprehensive and detailed factors. The traits identified in this model are: Neuroticism–Anxiety (N-Anx), Aggression–Hostility (Agg-Host), Impulsivity–Sensation Seeking (Imp-SS), Sociability (Sy), and Activity (Act) (Zuckerman, Kuhlman, Joireman, Teta, & Kraft, 1993). Interestingly, the findings of this study also varied according to gender. Sociability was negatively correlated with nicotine dependence (measured by FTND) and CPD in male smokers. In addition, in males, higher smoking rates were associated with low sensation-seeking and high impulsivity. In contrast, none of the personality traits were associated with nicotine dependence in female smokers. However, CPD was partially explained by high impulsivity-sensation seeking and general activity in women (Nieva et al., 2011).

1.5.5.4 Personality and Smoking Treatment Outcome

Similarly, personality traits are expected to affect quit outcomes and relapse. In fact, using the FFM, one observational study of the US population showed that neuroticism was the only personality trait that was significantly positively associated with persistence of smoking behavior. On the other hand, higher scores on conscientiousness decreased the likelihood of
persistent smoking. This association, however, was not significant after controlling for demographic characteristics (Zvolensky et al., 2015). Nieva and colleagues also looked at cessation outcomes in response to 12 months of combined treatment with cognitive-behavioral therapy and medication. Gender differences were observed with respect to treatment outcome, as well. Specifically, after adjusting for nicotine dependence level, a higher rate of relapse was observed in men with high scores on impulsivity. On the other hand, women were more likely to relapse if they scored higher on sociability (Nieva et al., 2011). These findings emphasize on the fact that one treatment does not help all. Gaining understanding on the factors that influence quit outcomes can help improve effectiveness. With this being said, no studies have evaluated whether personality traits differentially affect outcomes to one treatment compared to the others. In fact, if such effects are observed, personality tests can become a useful method to tailor treatments to the individuals’ needs.

1.5.6 Summary and Restatement of Objectives

To this end, it has been demonstrated that tobacco use disorder is a chronic, relapsing, and multidimensional condition. Tobacco use is the single most preventable cause of disease, disability, and death worldwide. Many of the health risks associated with smoking are reversed after quitting. As a result, reducing prevalence of smoking can save lives and reduce the burden it has on our healthcare system. There are currently two first line prescription-only pharmacotherapies, bupropion and varenicline, that have been approved for use in Canada. These medications have been proven efficacious in clinical trials. Clinical trials assess efficacy of medications in ideal conditions, which may not apply to real-world settings. Therefore, the effectiveness of these smoking cessation aids needs to be evaluated in real-world settings. However, data on the real-world effectiveness of bupropion and varenicline are limited. In fact, factors, such as knowledge, accessibility, and affordability limit the use of these medications to less than half of smokers, who intend to quit smoking. This highlights the need for methods that address these barriers to increase the use of these efficacious medications. Moreover, even though these medications have been shown to double the chances of successfully quitting smoking, the efficacies of smoking cessation treatments are far from optimal and relapse to smoking is common. There is a substantial body of literature reporting on individual differences in tobacco dependence susceptibility and differential responses to treatment. Two of these factors include nicotine metabolism and personality. However, data on whether these factors affect bupropion and varenicline treatment outcomes is limited. Taken together, there is a need to assess the real-world effectiveness of bupropion and varenicline using an innovate approach bypassing barriers. Additionally, it is crucial to explore how individual characteristics affect
nicotine dependence and quit outcomes with treatment with these medications. Understanding the roles of such inherited characteristics can help tailor tobacco cessation treatments to maximize medication's efficacy and minimize adverse reactions. It may also help identify potential targets for new smoking cessation pharmacotherapies.
2. METHODS

2.1 Study Design and Overview

Data presented in this thesis are an interim analysis of the MATCH Study. I was the primary study personnel and coordinator for the MATCH Study and the set-up of study, study procedures, and data analysis were performed by me, unless otherwise stated.

To pursue the aforementioned objectives, the MATCH Study was designed by the scientists at the Nicotine Dependence Service at the Centre for Addiction and Mental Health (CAMH). MATCH stands for Medication Aids for Tobacco Cessation and Health. MATCH was an open label study, where participants were randomized to receive one of the two study medications, bupropion (Zyban®) or varenicline (Champix®). Eligible participants received 12 weeks of pharmacotherapy by mail. During the 12-weeks of treatment period, participants also received weekly motivational emails. Participants were also given the option to participate in a sub-study, where consenting individuals completed a personality trait assessment online and provided saliva sample by mail for DNA analysis.

MATCH Study was designed in a way that it was patient-driven. In other words, participants were not approached by study personnel to be recruited into the study. In contrast, treatment seeking smokers, who had found out about the study by contacting a Public Health Unit, Smoker’s Helpline, or by word of mouth, visited the study website and self-registered into the study. Enrollment and all follow-up data collections were conducted via internet, as well.

A schematic overview of the study procedures is provided in Figure 2. Specifically, interested participants were directed to the study website at www.matchstudy.ca (Appendix 1). After reading about the study, they were then instructed to click on a link, which took them to the study information and consent form, which was followed by the enrollment survey on the study’s Online Portal and Data Collection Platform (Appendix 2). At this point, interested individuals were instructed to read through the Study Information and Consent Form (Appendix 3) and provide their consent by choosing “yes” on the online form. Once consent was provided, they answered a series of questions to assess for their eligibility (Appendix 4). If eligible, individuals were then given the choice to participate in the optional sub-study. If interested, participants were directed to read through the Substudy Information and Consent Form.
Consenting individuals completed the BFAS personality test (Appendix 6), which assessed for the big five personality traits (DeYoung, Quilty, & Peterson, 2007). This personality test is a public domain test with demonstrated reliability and validity, which consists of 100 questions answered on a five point scale ranging from “strongly disagree” to “strongly agree” (DeYoung et al., 2007). Once the questionnaires were submitted, the participants received an on-screen message notifying them of their eligibility status. Concurrently, eligible participants were randomized by the computerized system to one of the two treatment arms and an enrollment confirmation email (Appendix 7) was automatically sent by the system to notify them of their medication group assignment. This email contained important documents, namely the Letter to the Doctor (Appendix 8) and the Standard Script (Appendix 9.a and 9.b) for the medication they were randomly selected for. Additionally, the email included a copy of the Study Information and Consent Form and detailed instructions on what to do next. Those who consented to the MATCH Sub-Study received a second email with the Sub-Study Information and Consent Form and information on what to expect next.

Participants were given 5 weeks to visit their family physician or a licensed practitioner, taking with them the Letter to the Doctor and the Standard Script. At this point, the participants had the opportunity to discuss with the practitioner if the medication that they had been randomized to was appropriate for them to take as a smoking cessation aid. Even if the practitioner did not prescribe the assigned medication, the participants were still sent weekly motivational emails and were also followed up at all time-points as a no medication control group. However, these data were not included in the main analysis. For others, signed prescriptions were faxed to the study contract mail-order pharmacy from the practitioner’s office. Then, the pharmacist completed a brief phone counselling, confirmed eligibility, and couriered 12 weeks’ worth of medication to the participants. The pharmacy information was logged in the Pharmacy Online Portal (Appendix 10) and the participants were activated in the system once the medication was dispensed. The activation function triggered scheduling of the follow-up surveys. The participants chose their preferred quit dates within 30 days of receiving the study medication, but were advised to start the medication 7-14 days prior to their chosen quit date. The participants also received weekly motivational emails (Appendix 11) for the 12 weeks of the treatment period, which included tips and recommendations on a number of behavioral strategies to help participants quit smoking.

All participants were followed up for 12 weeks from the start of treatment. Follow-ups (Appendix 12-14) were conducted online at 4, 8, and 12 weeks from the start of treatment to collect data related to smoking cessation outcome measures, medication compliance, and adverse effects.
Long-term abstinence was assessed at 6 and 12 months from the start of treatment. Participants were notified of their follow-up due dates via email, which also included a direct link to the survey. Biological samples (saliva) were also collected. These were collected by mail at baseline and mid-treatment. The samples were used for assessment of NMR, validation of self-reported smoking status, as well as medication compliance.

**Figure 2. Study Flow Chart.**
2.2 Ethics and Study Registration

The study methods and protocol were approved by the standing Research Ethics Board (REB) at the Centre for Addiction and Mental Health, with the REB Protocol Number 200/2012. Study approval was renewed annually.

MATCH was registered on clinicaltrials.gov under the following identifier: NCT02146911.

All study personnel completed the following trainings:
- Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans Course on Research Ethic (TCP S)
- Good Clinical Practice (GCP)
- Privacy Fundamentals
- Privacy in Research
- Standard Operating Procedure (SOP)
- Responsible Conduct of Research (RCR)

The MATCH study was conducted according to the GCP guidelines and was compliant with TCPS and the Declaration of Helsinki.

2.3 Participants: Inclusion and Exclusion Criteria

The participants were daily smokers, who smoked 10 cigarettes or more per day, aged 19 years or older, from across Ontario, who wished to quit smoking within 30 days of receiving the assigned medication, did not have any contraindications for bupropion or varenicline; and were not pregnant or breast-feeding.

The Inclusion Criteria were chosen to align with the study objectives and treatment recommendations. In particular, this study aimed to evaluate the feasibility of this medication distribution method within Ontario. In addition, bupropion and varenicline are recommended for use by daily dependent smokers, who smoke 10 cigarettes or more per day (Lam & Patel, 2007; Patel et al., 2010; West, 2003). Moreover, participants were required to indicate that they had an intention to quit within 30 days of receiving the study medication. This was decided because 30 days is the validated standard for being in the preparation stage for a behavioral
change, such as smoking, according to the Prochaska Stages of Change Model (Prochaska & DiClemente, 1983). Specifically, the following criteria were met in order for an individual to be eligible and randomized to one of the two medication groups:

1) Ontario resident
2) Having a valid email address
3) 19 years or older
4) Current daily smoker
5) Smoking 10 or more cigarettes per day
6) Daily smoker for the past year
7) Intention to quit smoking within 30 days of receiving the medication

The Exclusion Criteria were primarily selected based on the contraindications stated for the study medications (Pfizer, 2011; Valeant, 2012). Because the participants were randomized to medication groups, contraindication with either of the study drugs resulted in exclusion from the study. Specifically, individuals were excluded from study participation if they endorsed any of the following:

1) Pregnant or breast-feeding
2) Current/history of eating disorder
3) Current/history of psychotic disorders (schizophrenia or bipolar disorder)
4) Brain injury
5) Seizure disorder
6) Allergy or sensitivity to bupropion/ Zyban®, Wellbutrin® or varenicline/ Champix®
7) Currently on varenicline/ Champix®, bupropion/ Zyban®, Wellbutrin®, monoamine oxidase inhibitors, thioridazine, anti-depressants, or other medications containing bupropion hydrochloride

2.4 Interventions

Participants received pharmacological and behavioral interventions. Specifically, participants received open-label bupropion or varenicline according to their randomization; or neither if the practitioner chose not to prescribe the assigned medication. All participants received weekly
motivational emails regardless of their mediation assignment or whether or not the prescription was filled.

2.4.1 Pharmacological: Smoking Cessation Medication

- Bupropion hydrochloride SR (generic), Sandoz Canada, Jules-Léger, Quebec. Dispensed for 12 weeks. One tablet (150mg) once daily for first three days, then twice daily for the remainder of 12 weeks.

  Generic bupropion hydrochloride SR has been shown to be bioequivalent to Zyban® (Moreira et al., 2009). Therefore, we were given approval from Health Canada to use the generic form in this study. Bupropion was purchased from the drug company through the CAMH pharmacy.

- Varenicline tartrate (Champix®), Pfizer Canada Inc., Kirkland, Quebec. Dispensed for 12 weeks. One tablet (0.5mg) once daily for first three days, then one tablet (0.5 mg) twice daily for next four days, then 1 mg (one 1mg tablet or two 0.5mg tablets) twice daily for the remainder of 12 weeks.

  Champix® was supplied by Pfizer Canada Inc. at no cost (as investigational product) as part of the research grant funding agreement.

2.4.2 Behavioral: Motivational Emails

All eligible participants, regardless of their medication assignment, received weekly motivational emails. Weekly motivational emails were sent automatically via the study Online Portal. The first email was sent at the start of the treatment period. The motivational emails were sent out on a weekly basis throughout the treatment phase of the study. Therefore, a total of 12 weekly motivational emails were sent out. The emails included tips and recommendations on a number of behavioral strategies that the participants could employ in order to increase their chances of becoming smoke-free. They provided tips on ways to create an atmosphere that promoted quitting and remaining abstinent. They also included recommendations on how to address issues with withdrawal symptoms and cravings. In addition, they provided positive motivational messages by stating facts on benefits of quitting smoking. These emails were also sent to those eligible participants who did not receive medication. To those participants, the first email was automatically sent after their time to visit a licensed prescriber was up. The content of emails varied from week to week and can be found in Appendix 11.
Subject recruitment for the study started on June 6th, 2014. The primary method of recruitment for this study was through word of mouth. In particular, the investigators of MATCH Study have also conducted the STOP Study (Costello et al., 2011; Zawertailo L, 2012), where they have connected with a collaborative network of health care providers from Public Health Units (PHUs), Community Health Centers (CHCs), and Family Health Teams (FHTs). These agencies are an effective medium to communicate new treatment opportunities to interested individuals. Prior to launching the MATCH Study, an email was sent out to this network of providers to inform them about the new opportunity. They were provided with a brief description of MATCH, treatments provided, and information on how to refer interested individuals. As a result, individuals, who expressed an interest in quitting smoking, self-identified, and inquired about treatment options were directed to the MATCH study website. Some of the agencies promoted MATCH through their website or social media accounts. MATCH was also picked up by a local news broadcaster through one of the Public Health Units and an article was published about MATCH by CBC News Windsor (CBC, June 24th, 2014).

Moreover, the STOP program, which is an Ontario-wide program that mass-distributes NRT to interested smokers, has a research component that is also co-investigated by the primary investigator of the MATCH Study, Dr. Laurie Zawertailo (Zawertailo L, 2012). As part of the consenting procedure for those who participate in the STOP Program, individuals are asked if they would like to be contacted about new research opportunities by CAMH. Those who choose ‘yes’ are then included in a database forming a smoker’s registry that can be contacted in case new research opportunities come up. As a result, STOP ex-participants, who were no longer enrolled in the program and had provided a valid email address, were notified about the MATCH Study via email. The email content included a brief description of MATCH and information on how to enroll. Therefore, interested individuals were able to access the study website and self-register. In addition to above methods, the public was informed about the study via CAMH social media accounts and Smoker’s Helpline. Participants could also be referred by word of mouth through family and friends.
2.6 Enrollment

Study enrollment was web-based. Participants self-registered into the MATCH Study by visiting the study website at matchstudy.ca. Upon provision of Informed Consent, subjects were assigned a unique subject identifier by the system and were referred to by their ID’s for confidentiality reasons.

2.6.1 Study Website: matchstudy.ca

The first step in enrollment was for participants to visit the study website, regardless of how they had heard about the MATCH Study. The website included a brief description of the MATCH Study, affiliated institution (CAMH), study purpose, and treatments provided. It also provided the visitor with an overview of the study procedures. Moreover, participants had the opportunity to access a list of Frequently Asked Questions (FAQs) regarding the study. Study contact information in forms of a telephone number and an email address were also provided on the study website in case an individual had questions or concerns that needed further clarification by the study personnel. Participants were also able to contact the study personnel during their enrollment in the study with any questions and concerns. Lastly, interested individual were instructed to click on a link that directed them to the study Portal and Data Collection Platform for their initial assessment. Screen shots of the study website are provided in Appendix 1.

2.6.2 Online Portal and Data Collection Platform

The Online Portal and Data Collection Platform was customized for this study and developed by Inovex Inc. This platform was designed for the online collection of the study informed consent and all study surveys, including baseline and follow-ups. Data were self-entered by the participants on the forms provided. There were safeguards in place on this platform to prevent individuals from enrolling twice. Specifically, re-enrollment with the same email address was rejected by the server. Once completed, individuals were not able to access the survey to change their answers to survey questions. Similarly, they were not able to change their medication assignment. Furthermore, the server was secure and access to the data was password protected. Therefore, securely stored data was only accessible to the study investigators and delegates. Screen shots of the server are provided in Appendix 2.
2.6.2.1 Study Information and Consent Forms

Upon visiting the study Online Portal and Data Collection Platform, the subjects were provided with the Study Information and Consent Form found in Appendix 3. Informed consent was collected prior to any data collection from the subjects. Consent was provided by clicking on ‘yes’ or ‘no’ at the end of the online form. Additionally, subjects were asked if they provided consent to be contacted for future studies. Individuals were permitted to participate in the study even if they chose not to be contacted for future opportunities. Once consent was collected, subjects were directed to the next page to complete the Baseline Questionnaire. The Study Information and Consent Form also covered consent to provide biological samples as requested throughout the study. A second Study Information and Consent Form, found in Appendix 5, was presented to individuals interested in participating in the Genetic and Personality Sub-Study.

2.6.2.2 Baseline Survey and Initial Assessment

The Baseline Survey was administered online through the study Portal and Data Collection Platform once consent to the study was provided. A copy of this survey is provided in Appendix 4. The primary purpose of this questionnaire was to assess for eligibility for participation into the study and to collect demographic and baseline characteristics. Data on baseline covariates that could affect treatment outcome were also collected. Namely, subjects were asked about their smoking habits at the time of enrollment and previous attempts to quit smoking. They were also asked to rank their importance and confidence in quitting smoking on a scale of 1 to 10. In addition, their levels of nicotine dependence were assessed using the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991b). FTND is a brief six-item questionnaire that is easy to administer and measures the level of dependence on nicotine. The FTND score can range from 0 to 10. A higher score indicates greater nicotine dependence. Specifically, a score of 5 to 7 indicates moderate dependence; whereas, a score of 8 and above indicates high dependence (Heatherton et al., 1991b). Moreover, information on medical history, including mental health conditions, and other substance use, such as alcohol consumption were gathered. Data on personal and demographic characteristics, such as mailing address, age, gender, ethnicity, education, and employment status were also collected. The Patient Health Questionnaire 9 (PHQ9) was also administered to evaluate baseline depressive symptoms (Spitzer, Kroenke, & Williams, 1999). Higher scores correspond to more severe depressive symptoms. The PHQ9 is based on the DSM-IV criteria and is a valid
screening tool for major depression, as well as subthreshold depressive symptoms (Martin, Rief, Klaiberg, & Braehler, 2006).

Once the survey was completed, eligible participants were asked about their interest in participating in the optional MATCH Substudy (described below). If interested, they were then taken to the next page to provide a second Informed Consent for participation in the sub-study. If answered ‘no’, they submitted the completed Baseline Questionnaire and were informed about their eligibility status by a message that appeared on the page. Survey submission prompted the system to send the study Enrollment Confirmation Email to eligible participants. A sample of the email is provided in Appendix 7. This email provided the participants with a copy of the Study Information and Consent Form, as well as a Letter to the Doctor and a Standard Script. These can be found in Appendix 8 and 9, consequently. The Standard Script was prefilled with participant’s personal information and prescription for the medication the subject was assigned to. The email also included instructions on what to do next in order to receive the medication.

2.6.3 MATCH Substudy- Personality Assessment Test

To assess for personality traits of subjects, who consented to the sub-study, the Big Five Aspect Scale (BFAS) personality test was administered online through the study Portal and Data Collection Platform. This personality test is a public domain test created by Colin G. DeYounge, Lena C. Quilty, and Jordan B. Peterson, with demonstrated reliability and validity (DeYoung et al., 2007). BFAS is a self-report test, which assesses the Big Five personality traits. Unlike Eysenck three factor model of personality, which consists of three traits of neuroticism, extraversion, and psychoticism (H. J. Eysenck, 1990), the FFM breaks down personality into five traits. The BFAS personality test also breaks down each of the Big Five traits into two Aspect traits, which are suggested to have distinct genetic and biological underpinnings (DeYoung et al., 2007). The personality traits measured by this test were (2 aspects for each big five domains of personality): neuroticism (withdrawal and volatility), agreeableness (compassion, politeness), conscientiousness (industriousness and orderliness), extraversion (enthusiasm and assertiveness), and openness/ intellect (intellect and openness). These traits are, for the main part, genetically determined and remain constant during the lifetime of an individual. The FFM has also been found applicable across a variety of observations and cultural groups. It has been shown that the neuroticism and extraversion traits from both the Eysenck Three Factor Model and the FFM correlate. However, the psychosis factor is further broken down and has been shown to be correlated with conscientiousness and
agreeableness traits of the FFM (Zuckerman et al., 1993). The BFAS questionnaire consists of 100 questions answered on a five point scale ranging from “strongly disagree” to “strongly agree” (DeYoung et al., 2007). The BFAS personality test and instructions on how to compute the scores are provided in Appendix 6. Subjects who participated in the sub-study received the Enrollment Confirmation Email upon completion of the personality test. They also received a second email to confirm their enrollment in the sub-study, which provided them with a copy of the sub-study Consent Form.

2.7 Visit to Own Physician or Licensed Practitioner

All participants deemed eligible upon completion of the web-based initial assessment, received the Enrollment Confirmation Email, which instructed them to book an appointment with their physician or a licensed practitioner within 5 weeks from the enrollment date to have the Standard Script for their assigned medication signed. Reminder emails were sent out at 2 weeks from the enrollment date to make sure participants booked an appointment with their prescriber. At the visit, participants were advised to discuss their medical history, medications they were on, and any other concerns they had regarding the treatment. Participants provided the prescriber with the Letter to the Doctor and the Standard Script, which were attached in the Confirmation Email. The Letter to the Doctor, as seen in Appendix 8, was composed by the study investigators to convey information about MATCH Study to the prescriber. The Standard Script, shown in Appendix 9, was prefilled with patient’s personal information and prescription information for the medication the participant was randomized to. It was then up to the prescriber’s discretion to sign the Script, or decide not to prescribe the assigned medication to the patient. The prescriber was asked to fax the Standard Script to our contract mail-order pharmacy (MediTrust Rexall Direct), who then filled the prescription. Those eligible participants who did not have the Script signed within 5 weeks from the enrollment date did not receive study medication. However, they were still automatically activated in the system, received weekly motivation emails, and were followed up in a similar manner to those participants who received medication.
2.8 Filling the Prescription by the Contract Mail-Order Pharmacy

All eligible participants were instructed to visit a licensed prescriber and have the Standard Script signed. Signed Scripts were faxed to the study contract mail-order pharmacy. Signed prescriptions from a licensed prescriber, including a Physician, a Nurse Practitioner, or a Pharmacist were accepted and checked for authenticity. In short, once verified to be authentic, the prescriptions were filled and mailed to the participants’ mailing address by MediTrust Rexall Direct. Prior to mailing of the medication, a phone counselling was completed by the pharmacist, in accordance to the Ontario College of Pharmacists’ standard of practice. During the counselling, the pharmacist discussed possible allergies, concomitant medications, and confirmed eligibility of the participant to take the assigned medication. They also informed the participants about directions to use the medication and addressed participants’ questions and concerns. Participants were also advised to practice caution, while operating heavy machinery or driving a vehicle until certain that the medication did not cause drowsiness. Specifically, the following was communicated to the participants during the phone counselling.

On Champix:

- Pharmacist began dialogue with patient by stating you had been prescribed Champix to help you quit smoking. The name of the medication is Champix. Have you had Champix before?
- Instructed the patient that we are sending a Champix Starter Pack and Continuation Packs and to start with the Starter Pack.
- Instructed the patient to set a quit date and start taking the medication 7 to 14 days before the quit date and to stop smoking on the quit date.
- Instructed patient to start with the Starter Pack by taking from Day 1 to 3 one white 0.5 mg tablet once a day, then from day 4 to 7 take one white tablet Champix 0.5 mg twice a day, once in the morning and once in the evening at about same time each day. From day 8 until the end of 12 weeks, take one light blue Champix 1 mg tablet twice a day.
- Instructed patient to take Champix after a meal.
- Instructed patient that the medication may cause drowsiness. Alcohol may intensify the effect. Avoid driving vehicles or operating machines until certain that medication does not affect your mental alertness or physical coordination.
On Bupropion:
- Pharmacist began dialogue by asking patient if he/she is currently taking medications such as Bupropion, Wellbutrin, or Zyban to make sure there is no duplication of therapy.
- Instructed patient that we are sending the generic bupropion 150 mg tablet enough to last the 12 week therapy. Tablets should be swallowed whole, not chewed or crushed and taken after meals.
- Instructed the patient to start taking the medication 7-14 days before quit date and quit on the quit date. To take one tablet once daily from day 1 to 3, then twice a day for the remainder of 12 weeks.
- Instructed patient that medication may cause drowsiness. Alcohol may intensify the effect. Avoid driving vehicles and operating machines until reasonably certain that the medication does not affect your mental alertness.

2.8.1 Study Pharmacy Portal

Once a signed Script was received by the pharmacy, the pharmacy logged on to the Pharmacy Portal on the study Online Portal and Data Collection Platform. The Pharmacy Portal provided a system for the pharmacy to enter their data and have a check list for their process. This data was accessible by study investigators, as well. Once on the portal, the pharmacist searched for the patient by the name that appeared on the Script. Participant profiles under the name appeared. This was another way to ensure that no participant double-enrolled into the study. In the case more than one profile was found under the same personal information, the participant was disqualified from participation in the study and did not receive medication. Once the correct participant profile was identified, his/her personal information were checked against the Script and it was indicated on the profile that Script was received. Then, the pharmacist contacted the participant to complete the brief phone counselling, as mentioned previously. After the participant’s eligibility was confirmed, the assigned medication was dispensed. Upon dispensing, the participant was activated on the system by clicking on the activation button on the participant profile. The activation of the participant prompted the follow-up surveys to be scheduled by the system. In additional, activation notified the study investigators that medication had been dispensed for a participant. Those participants who did not receive medication were automatically activated by the system once their 5 weeks to visit a prescriber was up. Lastly, the medication was couriered to subject’s mailing address and a tracking number was recorded to ensure the medication was received by the participant. A screen shot of the Pharmacy Portal is provided in Appendix 10.
2.9 Study Follow-Up Surveys

Follow-up Surveys were conducted online at 4, 8, and 12 weeks following the start of treatment. Study Follow-up Surveys were scheduled automatically by the system once the participants were activated. Specifically, the follow-up surveys were scheduled 5, 9, and 13 weeks from the date the medication was couriered, allowing a week for the medication to be delivered. Participants were notified by email about their follow-up due dates. The email included a web-based link to the follow-up survey on the study Portal and Data Collection Platform. Five reminder emails were sent out at 3-day intervals. Each Follow-up Survey remained valid for two weeks, after which the survey expired and could not be accessed. This was to ensure that each Follow-up Survey was completed at the correct time-point. Follow-up Surveys were also collected from those eligible participants who did not receive medication. Information on reasons for not visiting a licensed prescriber to have the Script signed was collected.

At each follow-up, data related to outcome measures were collected. The week 4, 8, and 12 Follow-up Surveys are available in Appendix 12, 13, and 14, consequently. Specifically, the Follow-up Questionnaires attempted to collect data on smoking status, changes in smoking pattern, medication use and compliance, effects, and adverse reactions experienced. Also, data on additional support sought by the participants and possible covariates of the study's primary outcome measure, such as use of NRT and electronic cigarettes were collected. Additionally, the PHQ9 was completed as part of the Follow-up Survey to evaluate participants' depressive symptoms. Participants with a high score on the last question, which asks about suicidal thoughts, were notified by the system to visit a healthcare practitioner to discuss their symptoms. Furthermore, the Follow-up Questionnaire assessed any suicidal thoughts or intentions the participant might have been experiencing; and if so, the participants were asked to discontinue the medication immediately and seek emergency medical attention. These were included due to black box warnings of serious neuropsychiatric and suicidality events associated with bupropion and varenicline (FDA). Long-term abstinence was evaluated at 6 and 12 months from the start of treatment via email. However, this thesis focused on short-term abstinence outcome assessed at week 4, 8, and 12.
2.10 Biological Sample Collection and Analysis

MATCH was an internet-based study with no in-person visits between participants and study investigators. As a result, saliva samples were collected by mail. Two saliva samples were collected from the participants, who received the study medications. Specifically, Salivette tubes, purchased from the University of Toronto Med Store, were labelled with participant’ ID and packaged according to the Transport of Dangerous Goods (TDG) for Exempt Human Specimen (CAPost, 2015) by a TDG trained study personnel. The packages were then mailed by Courier or Canada Post to participants’ mailing address. Instructions on preparation, sample collection, and mailing procedure were included in the kit, as seen in Appendix 15. The packages included return envelopes pre-labeled with the MATCH Study mailing address and prepaid postage stamps.

The first sample collection kit was sent out at baseline upon activation of the participants in the Online Portal. The purpose of the baseline sample was to confirm the participants’ baseline smoking status, since biochemical validation of smoking status by expired CO was not possible. Saliva samples were collected and tested for cotinine content, the primary hepatic metabolite of nicotine (Montalto & Wells, 2007). The baseline saliva sample was also used to measure the Nicotine Metabolite Ratio (NMR), which is the phenotypic biomarker of CYP2A6 enzyme activity (Dempsey et al., 2004). For compensation, participants received a $10 electronic gift card from amazon.ca once their baseline saliva sample was received back in mail. Participants, who agreed to participate in the sub-study, were also mailed an Oragene Saliva Collection Kit for DNA analysis in collaboration with Dr. James Kennedy’s lab at CAMH. However, the DNA analysis data is not included as part of this thesis.

The second Saliva Collection Kit was mailed at about mid-treatment, specifically at week 4 from the start of treatment. The primary purpose of this sample was to analyze drug levels to biochemically validate medication compliance. This sample was also analyzed for cotinine levels to assess smoking status. Participants were compensated with a $25 electronic gift card from amazon.ca once their mid-treatment sample was received. At the time of this interim analysis, the number of mid-treatment samples that had been processed was not sufficient. Therefore, this data is excluded from the results provided in this thesis.

Upon arrival to the study site, returned samples were logged and stored in a freezer at -80 °C. The freezer’s temperature was checked daily by the study personnel. The freezer was also
equipped with an alarm that went off in case of a freezer malfunction. Sample analysis was performed in collaboration with Dr. Rachel Tyndale’s Lab using the Liquid Chromatography-Mass Spectrometry (LC-MS). Samples were transferred in batches to Dr. Tyndale’s Lab by MATCH Study personnel. A Transfer Confirmation Form was signed at the time of sample transfer. Saliva samples were analyzed for nicotine, cotinine, and 3’-hydroxycotinine according to the protocol found in Appendix 16. Dry samples were re-dissolved with 1ml of 0.01M HCL. Therefore, these samples were not used quantitatively. They were only used to measure NMR, which assesses the ratio of two metabolites and is not dependent on true concentrations. Sample analysis results were emailed to MATCH Study investigators.

2.11 Medication Compliance

Medication compliance was assessed using both self-report questionnaires and biochemical validation. In particular, data related to adherence to prescribed treatment regimen was collected during and at the end of treatment. Follow-up surveys, at weeks 4 and 8 collected data on treatment start date and intention to continue the treatment. At week 12, participants were also asked if they had finished the full course of treatment. Reasons on discontinuation of treatment were also gathered. Furthermore, as explained in section 2.10, medication compliance was biochemically validated using saliva samples at about week 4 following the start of treatment. However, due to small number of samples having been processed at the time of the interim analysis, only the self-reported compliance is presented.

2.12 Adverse Reactions

Data on adverse reactions were collected at each follow-up time-point, at weeks 4, 8, and 12. Specifically, participants were presented with a list of side effects and were asked if they had experienced them in form of ‘yes’ or ‘no’ questions. The list included the following: dry mouth, trouble sleeping, vivid dreams, rash, nausea, dizziness, and fatigue. They were also given the chance to include any other treatment-related symptoms they had. In case of severe side effects, participants were advised to stop the medication and consult their prescribing practitioner or the pharmacy. Stopping the treatment did not withdraw participants from the study. However, participants were free to withdraw from the study at any point and for any reason.
2.13 Outcome Measures

The primary outcome measures were related to the effectiveness of treatment. Specifically, the primary outcome variable was self-reported 30 days continuous abstinence rates at the end of treatment. Continuous abstinence was defined as not having smoked, even a puff, in the past 30 days and lack of relapse during this time period. This translated to abstinence between weeks 9 to 12 during the treatment period. The following ‘yes’ or ‘no’ question on the week 12 follow-up survey corresponded to this outcome measure: “Have you smoked a cigarette, even a puff, in the last 30 days?”. The secondary variable was self-reported 7-day point prevalence of abstinence (PPA) rates, which was measured at weeks 4, 8, and 12. The 7-day PPA was defined as not having smoked, even a puff, over the last 7 days. The ‘yes’ or ‘no’ question corresponding to this outcome measure was: “Have you smoked a cigarette, even a puff, in the last 7 days?”. These two variables are validated outcome measures widely used in smoking treatment studies (West, Hajek, Stead, & Stapleton, 2005). In fact, the clinical trials of varenicline versus bupropion also used the same measures (D Gonzales et al., 2006; D. Jorenby et al., 2006); thereby, our results can be easily compared to the findings of these trials. These measures are also recommended by a group formed by the Society for Research on Nicotine and Tobacco, who reviewed the literature on abstinence measures used (Hughes et al., 2003). Additionally, quit attempt, defined as having stopped smoking for one day or longer was also measured as a ‘yes’ or ‘no’ question.

Secondary and tertiary outcome measures were related to two factors that could potentially modulate level of nicotine dependence and treatment outcomes. In particular, secondary outcome measures were associated with personality, as measured by the BFAS, and CYP2A6 enzyme activity, as measured by NMR, both described in previous sections. The associations between each personality trait and NMR with nicotine dependence, as measured by the FTND score, were investigated. Moreover, the interactions between personality traits and treatment outcome; and NMR and treatment outcome were examined. This part of the study was considered confirmatory and exploratory.

2.14 Randomization Procedure

Eligible participants were randomly assigned to one of the two medication groups, varenicline or bupropion. The block randomization procedure was performed. Eligible participants were
randomized in a 1:1 ratio in blocks of 100. This process was computerized and was carried out by the Online Portal and Data Collection Platform system.

2.15 Blinding

This was an open label study. Participants and study investigators were not blinded to drug assignments.

2.16 Data Management

All data collections from subjects were in electronic format and stored on a secure password-protected server, managed by the study’s contract vendor, Inovex Inc. No paper copies of participants’ information were kept. Participants’ data were kept strictly confidential and were only accessible to the study principal investigator and delegates by their individual usernames and passwords for the server. For the saliva samples, there were no direct connections between the samples and the subjects’ names and personal information. The saliva collection tubes and analysis results were only labelled with the patient’s unique identifier.

2.17 Data Analysis

2.17.1 Sample Size and Power Analysis

The *a priori* sample size calculation for this study was based on the two clinical trials of head-to-head comparison of bupropion and varenicline, as well as the non-randomized pragmatic feasibility study. In two previous head-to-head randomized controlled trials of varenicline versus bupropion, the 30 days continuous abstinence rates at the end of treatment (weeks 9-12) were approximately 44% in varenicline, compared to 30% in bupropion. The reported 7 day point prevalence of abstinence (PPA) at the end of treatment (week 12) in these two trials were approximately 50% for varenicline, and 36% in subjects treated with bupropion (D Gonzales et al., 2006; D. E. Jorenby et al., 2006). On the other hand, in the pilot for this study, the observed 7 day point prevalence of abstinence rates were 55% and 30% for varenicline and bupropion, respectively. Therefore, we predicted to find similar quit rates to those observed in the
feasibility study. However, because of the randomized design, we assumed lower 30 days continuous abstinence rates of 45% for varenicline, versus 30% for bupropion. The G* power analysis program was used to calculate the sample size (Faul, Erdfelder, Lang, & Buchner, 2007). Specifically, to have 80% power to detect the above difference between groups at a 0.05 level of significant, a sample size of 174 per medication group was needed.

However, a post-hoc power analysis was performed for the actual sample size obtained for the primary outcome measure. At the end of treatment, the intention to treat quit outcome was available for a total of 234 participants. Of the 234, 107 had received bupropion and the other 127 were in the varenicline group. Assuming the hypothesized 30 days continuous quit outcomes, the G*Power program (Faul et al., 2007) calculated a power of 64%, to find a statistically significant difference (at an alpha level of 0.05) between the two medication groups.

2.17.2 Analysis Plan

The analysis of the primary outcome was conducted on an intent-to-treat basis. All eligible participants that were included in the initial randomization and received medication were accounted for in the final analysis, whether or not they completed the follow-up surveys. This method was used to avoid any potential bias that could arise from differential drop-outs and data incompletion, affecting the initial random assignment to medication group. As a result, as per recommended common standard, all randomized participants who completed the steps to receive the study medications were included in the denominator for calculation of quit rates. Participants who were lost to follow-up were considered smokers (West et al., 2005). Additionally, for comparison, the complete/available case analysis of quit outcomes was also conducted on those participants who responded to the end of treatment follow-up survey. Moreover, the complete case method was used for analysis of self-reported medication compliance and side effects.

The data analysis for this study was performed using the SPSS statistical software version 21.0 (IBM, 2012). The baseline characteristics were analyzed and compared between those who were randomized to bupropion versus varenicline, those participants who participated in the sub-study and completed BFAS versus did not, and between those who received medication and those who did not. For those participants, who received medication, baseline and demographic characteristics were compared between subjects randomized to bupropion versus varenicline. The student’s t-test for independent samples was used to compare continuous variables (Press, Teukolsky, Vetterling, & Flannery, 1992), such as age, and two-tailed
significance values are presented. On the other hand, the categorical variables, such as
gender, were compared using the cross-tabs Pearson Chi-square analysis (Press et al., 1992).
Those baseline and demographic characteristics that differed significantly between the two
medication groups were included as covariates in subsequent analysis. Additionally, use of
other smoking cessation aids, such as NRT, self-help, and counselling, during the study’s
treatment period was also added to the model as covariates of predicting quit success.

The participants were categorized into two metabolizer groups, slow and normal, based on the
measured baseline NMR levels. Specifically, similar to previous research in the field, NMR
values were grouped into four quartiles. Slow metabolizers were defined as those whose NMR
value fell into the lowest quartile. The rest of the participants were considered normal
metabolizers (C. Lerman et al., 2006; Schnoll et al., 2009). The baseline and demographic
characteristics were also compared between slow and normal metabolizers. Those
characteristics that differed significantly between the two metabolizer groups were included as
covariates in the analysis looking at NMR as a predictor of quit outcome.

2.17.2.1 Analysis of Treatment Outcomes, Medication Compliance, and Side Effects

Quit attempt defined as “having stopped smoking for one day or longer because of trying to
quit” was assessed at each of the week 4, 8, and 12 follow-up surveys for each of the
medication groups. This categorical outcome variable, measured as ‘yes’ or ‘no’, was
compared between the medication groups at each follow-up survey using the Pearson Chi
Square test.

Quit outcome measures, specifically the 7 day point prevalence of abstinence and 30 days
continuous abstinence rates, were measured at each follow-up time-point. The Pearson Chi
Square test was used to compare these quit outcomes between the medication groups at each
follow-up. Moreover, for each medication, the McNemar’s repeated measure test was used to
look at change over time in quit outcomes between follow-up time-points. The McNemar’s test
is similar to the Chi Square test but for paired (repeated) measures and was used to account
for within subject variations. This statistical test assesses for significant differences in a
dependent dichotomous variable measured at two different time-points (Adedokun, 2011;
Agresti, 2013). Further, the rate of change in quit rates were assessed using slope analysis.

To address the primary objective to assess the effect of intervention on the end of treatment
quit outcomes, the univariable binary logistic regression analysis was initially used for each
abstinence outcome variable, namely the intention to treat 30 days continuous abstenent rate and the 7 day point prevalence of abstinence at the end of treatment. The abstinence rate was entered as the dependent variable and the medication group was the independent variable with bupropion as reference in this regression analysis. The binary logistic regression was appropriate because the treatment quit outcomes were dichotomous as they were asked as “yes” or “no” questions (Maroof, 2012). The above analysis was also conducted with the complete case quit outcomes.

Additionally, the bivariable binary logistic regression was performed to look at the above relationship, adjusting for each additional cessation aid (i.e. NRT, self-help, and counselling), that the participants reported using during the 12 weeks treatment period, one at a time.

The probabilities of quitting, given gender or nicotine dependence, as measured by the FTND score were also assessed. Specifically, quit outcome was input as the dependent variable in the univariable binary logistic regression model. This model accepts both categorical and continuous independent variables as predictors. Therefore, the analysis was run with gender or FTND score as independent variable to obtain the odd ratio (OR) for each predictor.

Medication compliance was assessed as reported at the week 12 follow-up survey. Participants were categorized into three groups: discontinued medication, still taking, and finished the full 12 weeks course of treatment. The intention to treat 7 day point prevalence and continuous abstinence rates were assessed for each of the compliance categories for each medication group. The linear regression slope analysis was used to look at the association between quit outcome and medication compliance, and to test for significance of the linear trend line. This test was appropriate because it accounts for the ordering of the compliance variable and it measures the strength, direction, and significance of a linear relationship between two variables (Agresti, 2013). Furthermore, participants were categorized into two groups of those who finished the medication and those who did not. The univariable binary logistic regression analysis was conducted to assess how compliance predicted quitting. In particular, compliance was input as the independent variable with “did not finish” group as reference. Additionally, the bivariable binary logistic regression was performed to look at the above relationship, adjusting for the medication group.

The self-reported side effects were assessed for each medication group at each follow-up time-point. The proportions of participants, who experienced side effects, were compared between bupropion and varenicline at weeks 4, 8, and 12 follow-up time-points, using the Pearson Chi
Square Test. In addition, the incidences of side effects were compared between follow-up time points for each of the medications using the McNemar’s test.

### 2.17.2.2 Analysis of Roles of Nicotine Metabolism and Personality in Nicotine Dependence and Cessation

The Spearman’s rank-order bivariate correlation test was used to look at the association between saliva cotinine level and baseline NMR with nicotine dependence, as measured by the FTND score. Spearman is a robust nonparametric correlation test that does not make any assumptions about the distribution of the data and the nature of the variables and reports a general monotonic relationship between the two continuous variables. Moreover, Spearman is the appropriate test to use because the dependent variable, FTND score, is an ordinal variable (Mukaka, 2012). The Spearman’s rank correlation coefficients \( r_s \) were obtained for each relationship, indicating the strength and direction of the association. It can range from -1 to 1, where a value close to 1 indicates a strong positive association. Spearman Rho’s significance levels were also reported. Since there have been gender differences in nicotine metabolism (Chenoweth et al., 2014), these correlations were performed in men and women separately, as well.

To examine the effect of nicotine metabolism on quit outcomes, the bivariable binary logistic regression analysis was used, where the intention to treat end of treatment abstinence outcome was input as the dependent variable and the status of nicotine metabolism (slow vs. normal) was entered as the independent variable. Further analysis was conducted to have the odd ratios adjusted for medication group and any characteristics that were different between slow and normal metabolizers at baseline.

Next, to understand if NMR status influenced bupropion and varenicline quitting outcome differently, the participants were categorized into 4 groups of slow metabolizer bupropion, normal metabolizer bupropion, slow metabolizer varenicline, and normal metabolizer varenicline. The intention to treat end of treatment 7 day point prevalence abstinence and 30 days continuous abstinence rates were calculated. The Pearson Chi Square test was used to compare treatment outcomes within metabolizer groups, as well as within each medication group. Further, the univariable binary logistic regression analysis was run to look at how medication group predicted quit outcome within each metabolizer category. Moreover, the same analysis was run to assess how metabolizer group predicted quitting success within each medication group. Odd ratios, 95% confidence intervals, and p values were obtained.
In order to investigate the association between each of the Big Five personality traits and the FTND score (two continuous variables), the Spearman’s rank-order bivariate correlation test was used. This was the appropriate test to use for the same reasons explained previously. The Spearman’s rank correlation coefficients $r_s$ were obtained for each relationship, indicating the strength and direction of the association. It can range from -1 to 1, where a value close to 1 indicates a strong positive association. Spearman Rho’s significance levels were also estimated. These analyses were first performed for the overall sample. Due to gender differences observed in the literature with respect to the relationship between personality and nicotine dependence (Nieva et al., 2011), the analyses were also run for men and women separately.

To explore how well each of the Big Five personality traits predict quit outcomes, univariable binary logistic regression analyses were performed for both the intention to treat end of treatment 7 day point prevalence rate and the continuous abstinence outcome. One at a time, each of the Big Five personality traits were input as the independent variable in the model with the quit outcome as the dichotomous dependent variable. Due to observed gender differences in the literature (Nieva et al., 2011), the above analyses were performed for men and women separately to investigate if different traits predict quitting in male and female smokers. Furthermore, in order to see if personality traits predicted quitting success with bupropion and varenicline differently, similar univariable binary logistic regression analyses were conducted in participants who received bupropion and in those who received varenicline, separately, and odd ratios were obtained.
3. RESULTS

3.1 Flow of Participants through the Study

MATCH Study is an ongoing study and aims to recruit 1500 eligible participants, who will receive medication. However, this thesis is an interim-analysis of the MATCH study and has focused on those participants, for whom the week 4, 8, and 12 follow-up surveys were administered to date. MATCH Study started recruitment on June 6th, 2014. The results presented are focused on the data collected between June 6th, 2014 to May 11th, 2015.

In summary, 1748 interested individuals attempted to enroll and successfully completed baseline assessments. Sixty two individuals attempted to enroll multiple times. Therefore, a total of 1686 unique individuals completed the baseline questionnaire. An additional 144 individuals started the baseline questionnaire, but left it incomplete. Figure 3 shows the flow of participants from enrollment to follow-up surveys in this period of time. Out of 1686 that completed the baseline questionnaire, 1054 were eligible and 632 were ineligible. The most common reason for ineligibility was being on antidepressants or a contraindicated medication, which was observed in 40% of ineligible individuals. Some individuals did not meet multiple eligibility criteria. Out of 1054 eligible individuals, 529 were randomized to bupropion and the other 525 were randomized to varenicline. Also, 742 participants completed the personality test.

At the time of analysis, a total of 283 eligible individuals were in the process to visit a Licensed Practitioner, meaning they still were in the 5 weeks period given to have the Standard Script signed. On the other hand, 424 eligible participants did not have the Standard Script signed within 5 weeks of enrollment in the study. This number did not significantly differ between the two medication groups as tested by the Chi Square Test (p = 0.097). Out of those who did not visit a physician, only 42 responded to the week 4 follow-up survey indicating the reason for not visiting a Practitioner. The most common reason for not having the Script signed was reported as not having a family physician.

A total of 339 eligible participants received medication in mail. 153 of them received bupropion, and the other 186 received varenicline. Two additional Scripts for bupropion were faxed to the pharmacy but were not mailed medication. One participant changed his mind about
participation in the study at the time of the phone counselling. The second person could not be contacted to complete the phone counselling after multiple attempts by phone and email.

A total of 189 baseline saliva samples were returned and processed. Seven participants returned their samples after quitting smoking. Another 17 samples were dry and had to be diluted for NMR analysis. Therefore, a total of 182 samples were included in the NMR analysis and 171 samples were included in the cotinine analysis.

None of the participants who received medication dropped out of the study between enrollment and completion of the week 12 follow-up survey. The week 4 follow-up survey was administered to 278 participants with an overall response rate of 79%. The week 8 follow-up survey was administered to 259 and the overall response rate was 69%. The week 12 follow-up was administered to a total of 234 participants with a response rate of 66%. Percentage of non-respondents at each follow-up time-point did not differ significantly between the two medication groups. The number of participants with BFAS and NMR data included in each of the follow-up analysis can also be found in Figure 3.
Figure 3. Flow of Participants from Enrollment to Follow-up.
3.2 Geographic Distribution of Participants

The geographic distribution of MATCH eligible participants throughout Ontario was explored. According to the Figure 4 and Figure 5, MATCH distribution method reached both urbanized and rural and remotes regions of Ontario.

Figure 4. Dot Distribution Map of MATCH Eligible Participants. The dot distribution of MATCH eligible participants shows that MATCH has been able to effectively reach a geographically disbursed population of smokers in Ontario.
Figure 5. Geographic Breakdown of MATCH Participants across Regions of Ontario. The breakdown of MATCH eligible participants into different regions of Ontario shows that the percentages of participants from each area correspond to the population density of the region. This shows that MATCH has been effective in reaching participants from both urbanized and rural and remote regions of Ontario.

3.3 Baseline Characteristics of Participants

3.3.1 Eligible and Randomized to Medication Group

Table 1 shows the baseline and demographic characteristics of the 1054 eligible participants and compares them between the two medication groups. None of the characteristics shown were different between the two study groups, indicating the randomization was effective. In general, participants were daily dependent middle-aged smokers, more than half females, and highly motivated to quit.
### Table 1. Baseline and Demographic Characteristics of Eligible Participants by Study Group. The two medication groups did not differ on any of the characteristics presented.

<table>
<thead>
<tr>
<th>Mean and proportion within column</th>
<th>Bupropion (n = 529)</th>
<th>Varenicline (n = 525)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>300 (57%)</td>
<td>294 (56%)</td>
<td>0.973</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>45 ± 11</td>
<td>46 ± 12</td>
<td>0.224</td>
</tr>
<tr>
<td>Cigarettes/day:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>48 (9%)</td>
<td>53 (10%)</td>
<td>0.055</td>
</tr>
<tr>
<td>11-20</td>
<td>268 (51%)</td>
<td>225 (43%)</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>179 (34%)</td>
<td>216 (41%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>34 (6%)</td>
<td>31 (6%)</td>
<td></td>
</tr>
<tr>
<td>Fagerstrom Test for Nicotine Dependence (mean ± SD) max. 10</td>
<td>6.0 ± 1.9</td>
<td>6.1 ± 2.0</td>
<td>0.363</td>
</tr>
<tr>
<td>Age first started smoking daily (mean ± SD)</td>
<td>17 ± 4</td>
<td>16 ± 4</td>
<td>0.098</td>
</tr>
<tr>
<td>Annual household income: % ≤ $40,000</td>
<td>229 (43%)</td>
<td>235 (45%)</td>
<td>0.630</td>
</tr>
<tr>
<td>Importance of quitting smoking (mean ± SD) max. 10</td>
<td>9.4 ± 1.1</td>
<td>9.4 ± 1.2</td>
<td>0.609</td>
</tr>
<tr>
<td>Confidence to quit smoking (mean ± SD) max. 10</td>
<td>7.3 ± 2.0</td>
<td>7.4 ± 1.9</td>
<td>0.494</td>
</tr>
<tr>
<td>Past quit attempts (lifetime):</td>
<td></td>
<td></td>
<td>0.708</td>
</tr>
<tr>
<td>Zero</td>
<td>12 (2%)</td>
<td>19 (4%)</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>307 (58%)</td>
<td>306 (58%)</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>132 (25%)</td>
<td>131 (25%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 11</td>
<td>74 (14%)</td>
<td>65 (12%)</td>
<td></td>
</tr>
</tbody>
</table>

### 3.3.2 Participation in the Sub-Study

Out of 1054 eligible participants, 742 participated in the sub-study and completed the BFAS personality test. The baseline characteristics of those participated versus did not were compared. As shown in Table 2, no significant differences between the two groups were observed.
### Table 2. Baseline and Demographic Characteristics of Sub-Study Participants
The characteristics of those who participated in the sub-study did not differ from those who did not.

<table>
<thead>
<tr>
<th>Participated in Sub-Study/Completed BFAS</th>
<th>Yes (n = 742)</th>
<th>No (n = 312)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender ( % female )</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>432 (58%)</td>
<td>162 (52%)</td>
<td>0.147</td>
</tr>
<tr>
<td>No</td>
<td>284 (72%)</td>
<td>150 (48%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age (mean ± SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45 ± 11</td>
<td>45 ± 12</td>
<td>0.783</td>
</tr>
<tr>
<td>No</td>
<td>45 ± 11</td>
<td>45 ± 12</td>
<td></td>
</tr>
<tr>
<td><strong>Cigarettes/day:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>68 (9%)</td>
<td>33 (11%)</td>
<td>0.705</td>
</tr>
<tr>
<td>11-20</td>
<td>342 (46%)</td>
<td>151 (48%)</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>285 (38%)</td>
<td>110 (35%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>47 (6%)</td>
<td>18 (6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Fagerstrom Test for Nicotine Dependence (mean ± SD) max. 10</strong></td>
<td>6.1 ± 1.9</td>
<td>5.9 ± 2.0</td>
<td>0.155</td>
</tr>
<tr>
<td><strong>Age first started smoking daily (mean ± SD)</strong></td>
<td>17 ± 4</td>
<td>17 ± 4</td>
<td>0.497</td>
</tr>
<tr>
<td><strong>Annual household income: % ≤ $40,000</strong></td>
<td>336 (45%)</td>
<td>128 (41%)</td>
<td>0.204</td>
</tr>
<tr>
<td><strong>Importance of quitting smoking (mean ± SD) max. 10</strong></td>
<td>9.4 ± 1.0</td>
<td>9.4 ± 1.3</td>
<td>0.437</td>
</tr>
<tr>
<td><strong>Confidence to quit smoking (mean ± SD) max. 10</strong></td>
<td>7.3 ± 1.9</td>
<td>7.3 ± 2.2</td>
<td>0.729</td>
</tr>
<tr>
<td><strong>Past quit attempts (lifetime):</strong></td>
<td></td>
<td></td>
<td>0.065</td>
</tr>
<tr>
<td>Zero</td>
<td>15 (2%)</td>
<td>16 (5%)</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>429 (58%)</td>
<td>184 (59%)</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>190 (26%)</td>
<td>73 (23%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 11</td>
<td>103 (14%)</td>
<td>36 (12%)</td>
<td></td>
</tr>
</tbody>
</table>

The descriptive statistics of the Big Five personality traits of the 742 participants who completed the BFAS personality test are shown in Table 3.

### Table 3. Descriptive of Personality Traits
The descriptive statistics of the Big Five personality traits of the 742 participants, who completed the sub-study, are presented.

<table>
<thead>
<tr>
<th>Personality Traits</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Openness/Intellect</td>
<td>1.30</td>
<td>5.00</td>
<td>3.6499</td>
<td>.50585</td>
</tr>
<tr>
<td>Conscientiousness</td>
<td>1.85</td>
<td>4.80</td>
<td>3.5889</td>
<td>.52052</td>
</tr>
<tr>
<td>Extraversion</td>
<td>1.45</td>
<td>5.00</td>
<td>3.5709</td>
<td>.54123</td>
</tr>
<tr>
<td>Agreeableness</td>
<td>1.35</td>
<td>5.00</td>
<td>3.9357</td>
<td>.50954</td>
</tr>
<tr>
<td>Neuroticism</td>
<td>1.00</td>
<td>4.75</td>
<td>2.5970</td>
<td>.64080</td>
</tr>
</tbody>
</table>
The baseline, demographic, and personality characteristics of those who participated in the sub-study is presented in Table 4. These traits were compared between the genders. A significantly greater portion of females earned less than $40,000/year. In addition, females scored significantly higher on agreeableness. The other traits did not differ between the men and women.

**Table 4. Baseline and Demographic Characteristics of BFAS Participants by Gender.** A significantly greater portion of females earned less than $40,000, compared to males. Females also scored significantly higher on agreeableness, compared to males.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female (n = 432)</th>
<th>Male (n = 309)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication Group (% bupropion)</td>
<td>219 (51%)</td>
<td>153 (50%)</td>
<td>0.580</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>45 ± 11</td>
<td>46 ± 12</td>
<td>0.311</td>
</tr>
<tr>
<td>Cigarettes/day:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>50 (12%)</td>
<td>18 (6%)</td>
<td>0.080</td>
</tr>
<tr>
<td>11-20</td>
<td>203 (47%)</td>
<td>139 (45%)</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>156 (36%)</td>
<td>128 (41%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>23 (5%)</td>
<td>24 (8%)</td>
<td></td>
</tr>
<tr>
<td>Fagerstrom Test for Nicotine Dependence (mean ± SD) max. 10</td>
<td>6.1 ± 1.9</td>
<td>6.2 ± 1.9</td>
<td>0.622</td>
</tr>
<tr>
<td>Age first started smoking daily (mean ± SD)</td>
<td>16 ± 4</td>
<td>17 ± 4</td>
<td>0.284</td>
</tr>
<tr>
<td>Annual household income: % ≤ $40,000</td>
<td>221 (51%)</td>
<td>115 (37%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Importance of quitting smoking (mean ± SD) max. 10</td>
<td>9.4 ± 1.1</td>
<td>9.4 ± 1.0</td>
<td>0.793</td>
</tr>
<tr>
<td>Confidence to quit smoking (mean ± SD) max. 10</td>
<td>7.3 ± 1.8</td>
<td>7.4 ± 1.9</td>
<td>0.865</td>
</tr>
<tr>
<td>Past quit attempts (lifetime):</td>
<td></td>
<td></td>
<td>0.755</td>
</tr>
<tr>
<td>Zero</td>
<td>8 (2%)</td>
<td>7 (2%)</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>259 (60%)</td>
<td>169 (55%)</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>111 (26%)</td>
<td>79 (26%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 11</td>
<td>52 (12%)</td>
<td>51 (16%)</td>
<td></td>
</tr>
<tr>
<td>Openness to experience (mean ± SD) max. 5</td>
<td>3.64 ± 0.50</td>
<td>3.66 ± 0.52</td>
<td>0.654</td>
</tr>
<tr>
<td>Conscientiousness (mean ± SD) max. 5</td>
<td>3.60 ± 0.51</td>
<td>3.58 ± 0.53</td>
<td>0.722</td>
</tr>
<tr>
<td>Extraversion (mean ± SD) max. 5</td>
<td>3.56 ± 0.54</td>
<td>3.59 ± 0.55</td>
<td>0.548</td>
</tr>
<tr>
<td>Agreeableness (mean ± SD) max. 5</td>
<td>4.05 ± 0.49</td>
<td>3.78 ± 0.49</td>
<td>0.000</td>
</tr>
<tr>
<td>Neuroticism (mean ± SD) max. 5</td>
<td>2.62 ± 0.67</td>
<td>2.56 ± 0.60</td>
<td>0.157</td>
</tr>
</tbody>
</table>
3.3.3 Received Medication in Mail

At the time of analysis, out of 1054 eligible participants, 283 were in process and had time remaining to have the Standard Script signed. On the other hand, 339 participants had received medication in mail and the remaining 432 did not receive medication. The characteristics of ones who did not receive medication were compared to those who did and results are presented in Table 5. Those who visited their doctor and completed the steps to receive medication were significantly older than those who did not. Moreover, these two groups were compared in terms of their personality traits. Personality test data was available for 263 participants who received medication and 277 of those who did not receive medication. As shown in Table 6, the two groups did not differ on any of the Big Five Personality Traits.

Table 5. Baseline and Demographic Characteristic of Eligible Participants who Received Medication, versus Did Not. Those who received medication were significantly older on average compared to those who did not receive medication.

<table>
<thead>
<tr>
<th>Mean and proportion within column</th>
<th>Received Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 339)</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td></td>
</tr>
<tr>
<td>Cigarettes/day:</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>32 (9%)</td>
</tr>
<tr>
<td>11-20</td>
<td>147 (43%)</td>
</tr>
<tr>
<td>21-30</td>
<td>133 (39%)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>27 (8%)</td>
</tr>
<tr>
<td>Fagerstrom Test for Nicotine Dependence (mean ± SD) max. 10</td>
<td>6.1 ± 2.0</td>
</tr>
<tr>
<td>Age first started smoking daily (mean ± SD)</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>Annual household income: % ≤ $40,000</td>
<td>155 (46%)</td>
</tr>
<tr>
<td>Importance of quitting smoking (mean ± SD) max. 10</td>
<td>9.4 ± 1.1</td>
</tr>
<tr>
<td>Confidence to quit smoking (mean ± SD) max. 10</td>
<td>7.4 ± 1.9</td>
</tr>
<tr>
<td>Past quit attempts (lifetime):</td>
<td></td>
</tr>
<tr>
<td>Zero</td>
<td>9 (3%)</td>
</tr>
<tr>
<td>1-5</td>
<td>199 (59%)</td>
</tr>
<tr>
<td>6-10</td>
<td>77 (23%)</td>
</tr>
<tr>
<td>&gt; 11</td>
<td>53 (16%)</td>
</tr>
</tbody>
</table>
Table 6. Personality Traits of Eligible Participants who Received Medication, versus Did Not. The personality traits of those who received medication did not differ from those who did not receive medication.

<table>
<thead>
<tr>
<th>Personality Trait</th>
<th>Mean and standard deviations within column</th>
<th>Yes (n = 263)</th>
<th>No (n = 277)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Openness to experience (mean ± SD) max. 5</td>
<td>3.63 ± 0.48</td>
<td>3.66 ± 0.53</td>
<td>0.583</td>
<td></td>
</tr>
<tr>
<td>Conscientiousness (mean ± SD) max. 5</td>
<td>3.62 ± 0.54</td>
<td>3.55 ± 0.51</td>
<td>0.162</td>
<td></td>
</tr>
<tr>
<td>Extraversion (mean ± SD) max. 5</td>
<td>3.59 ± 0.49</td>
<td>3.56 ± 0.56</td>
<td>0.587</td>
<td></td>
</tr>
<tr>
<td>Agreeableness (mean ± SD) max. 5</td>
<td>3.94 ± 0.51</td>
<td>3.88 ± 0.52</td>
<td>0.207</td>
<td></td>
</tr>
<tr>
<td>Neuroticism (mean ± SD) max. 5</td>
<td>2.54 ± 0.62</td>
<td>2.64 ± 0.65</td>
<td>0.062</td>
<td></td>
</tr>
</tbody>
</table>

The baseline and demographic characteristics of the 339 eligible participants who received medication in mail are presented in Table 7 and compared between the two medication groups. None of the characteristics presented were different between the two medication groups and randomization had remained valid through the steps of the study.

Moreover, of the 339 participants, who received medication, 263 had completed the BFAS personality test. Table 8 compares the personality traits between the two study groups. Participants randomized to varenicline, who received the medication, scored significantly higher on agreeableness, compared to bupropion.
Table 7. Baseline and Demographic Characteristics of Eligible Participants who Received Medication, presented by Medication Group. None of the traits were significantly different between the two groups.

<table>
<thead>
<tr>
<th>Mean and proportion within column</th>
<th>Medication Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bupropion (n = 153)</td>
<td>Varenicline (n = 186)</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>83 (54%)</td>
<td>99 (53%)</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>45 ± 11</td>
<td>48 ± 12</td>
</tr>
<tr>
<td>Cigarettes/day:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>19 (12%)</td>
<td>13 (7%)</td>
</tr>
<tr>
<td>11-20</td>
<td>64 (42%)</td>
<td>83 (45%)</td>
</tr>
<tr>
<td>21-30</td>
<td>53 (35%)</td>
<td>80 (43%)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>17 (11%)</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>Fagerstrom Test for Nicotine Dependence (mean ± SD) max. 10</td>
<td>6.1 ± 1.9</td>
<td>6.1 ± 2.0</td>
</tr>
<tr>
<td>Age first started smoking daily (mean ± SD)</td>
<td>16 ± 3</td>
<td>16 ± 4</td>
</tr>
<tr>
<td>Annual household income: % ≤ $40,000</td>
<td>70 (46%)</td>
<td>85 (46%)</td>
</tr>
<tr>
<td>Importance of quitting smoking (mean ± SD) max. 10</td>
<td>9.4 ± 1.1</td>
<td>9.5 ± 1.2</td>
</tr>
<tr>
<td>Confidence to quit smoking (mean ± SD) max. 10</td>
<td>7.5 ± 1.9</td>
<td>7.3 ± 2.0</td>
</tr>
<tr>
<td>Past quit attempts (lifetime):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zero</td>
<td>2 (1%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>1-5</td>
<td>97 (63%)</td>
<td>102 (55%)</td>
</tr>
<tr>
<td>6-10</td>
<td>31 (20%)</td>
<td>43 (23%)</td>
</tr>
<tr>
<td>&gt; 11</td>
<td>21 (14%)</td>
<td>32 (17%)</td>
</tr>
</tbody>
</table>

Table 8. Personality Traits of Eligible Participants who Received Medication, presented by Medication Group. Participants who received varenicline scored significantly higher on agreeableness, compared to those who received bupropion.

<table>
<thead>
<tr>
<th>Mean and standard deviations within column</th>
<th>Medication Group in those Completed BFAS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bupropion (n = 123)</td>
<td>Varenicline (n = 140)</td>
</tr>
<tr>
<td>Openness to experience (mean ± SD) max. 5</td>
<td>3.63 ± 0.52</td>
<td>3.64 ± 0.45</td>
</tr>
<tr>
<td>Conscientiousness (mean ± SD) max. 5</td>
<td>3.61 ± 0.55</td>
<td>3.62 ± 0.53</td>
</tr>
<tr>
<td>Extraversion (mean ± SD) max. 5</td>
<td>3.61 ± 0.46</td>
<td>3.56 ± 0.51</td>
</tr>
<tr>
<td>Agreeableness (mean ± SD) max. 5</td>
<td>3.87 ± 0.54</td>
<td>4.00 ± 0.48</td>
</tr>
<tr>
<td>Neuroticism (mean ± SD) max. 5</td>
<td>2.58 ± 0.58</td>
<td>2.49 ± 0.65</td>
</tr>
</tbody>
</table>
3.3.4 Returned Baseline Saliva Samples

A total of 189 baseline saliva samples were returned and processed. Seven samples were sent after the participants had quit smoking. Therefore, baseline NMR data was available and valid for 182 participants. Figure 6 shows the frequency distribution of NMR values. The mean of NMR in MATCH participants was $0.578 \pm 0.328$. The measured NMR levels of participants ranged from 0.018 to 1.816. The 25th percentile value was 0.3385, which, based on previous literature (Ho et al., 2009; C. Lerman et al., 2006; Strasser et al., 2011), was used to distinguish between slow/ reduced (RM) and normal metabolizers (NM). As a result, 45 participants were slow metabolizers and 137 were normal metabolizers. The baseline and demographic characteristics of the two metabolizers groups were compared, as seen in Table 9. Normal metabolizers were significantly older, compared to slow metabolizers.

![Histogram of NMR Values](image)

**Figure 6. Frequency Distribution of Measured Nicotine Metabolite Ratios.** The NMR levels of MATCH participants ranged between 0.018 to 1.816. Forty five of the participants fell in the first quartile, categorizing them as slow metabolizers. The remaining 137 were considered normal metabolizers. The 25th percentile value was 0.3385, which divided the participants into the two groups.
Table 9. Baseline and Demographic Characteristics of MATCH Participants by NMR Group. Normal metabolizers were significantly older than slow metabolizers.

<table>
<thead>
<tr>
<th>Mean and proportion within column</th>
<th>CYP2A6 Enzyme Activity by NMR</th>
<th>Slow Metabolizer (n = 45)</th>
<th>Normal Metabolizer (n = 137)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication Group (% Bupropion)</strong></td>
<td></td>
<td>25 (56%)</td>
<td>57 (42%)</td>
<td>0.103</td>
</tr>
<tr>
<td><strong>Gender (% female)</strong></td>
<td></td>
<td>24 (53%)</td>
<td>75 (55%)</td>
<td>0.869</td>
</tr>
<tr>
<td><strong>Age (mean ± SD)</strong></td>
<td></td>
<td>43 ± 10</td>
<td>49 ± 12</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Race (% Caucasian)</strong></td>
<td></td>
<td>40 (89%)</td>
<td>122 (89%)</td>
<td>0.908</td>
</tr>
<tr>
<td><strong>Cigarettes/day:</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.389</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>5 (11%)</td>
<td>14 (10%)</td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td></td>
<td>22 (49%)</td>
<td>51 (37%)</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td></td>
<td>16 (36%)</td>
<td>57 (42%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td></td>
<td>2 (4%)</td>
<td>15 (11%)</td>
<td></td>
</tr>
<tr>
<td><strong>Fagerstrom Test for Nicotine Dependence (mean ± SD) max. 10</strong></td>
<td></td>
<td>6.1 ± 1.9</td>
<td>6.3 ± 2.0</td>
<td>0.712</td>
</tr>
<tr>
<td><strong>Age first started smoking daily (mean ± SD)</strong></td>
<td></td>
<td>17 ± 6</td>
<td>16 ± 4</td>
<td>0.608</td>
</tr>
<tr>
<td><strong>Annual household income:</strong></td>
<td>% ≤ $40,000</td>
<td>14 (31%)</td>
<td>61 (45%)</td>
<td>0.113</td>
</tr>
<tr>
<td><strong>Importance of quitting smoking (mean ± SD) max. 10</strong></td>
<td></td>
<td>9.4 ± 0.75</td>
<td>9.3 ± 1.4</td>
<td>0.645</td>
</tr>
<tr>
<td><strong>Confidence to quit smoking (mean ± SD) max. 10</strong></td>
<td></td>
<td>7.3 ± 1.5</td>
<td>7.5 ± 2.1</td>
<td>0.619</td>
</tr>
<tr>
<td><strong>Past quit attempts (lifetime):</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.554</td>
</tr>
<tr>
<td>Zero</td>
<td></td>
<td>2 (4%)</td>
<td>2 (1%)</td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td></td>
<td>25 (56%)</td>
<td>85 (62%)</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td></td>
<td>8 (18%)</td>
<td>26 (19%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 11</td>
<td></td>
<td>10 (22%)</td>
<td>22 (16%)</td>
<td></td>
</tr>
</tbody>
</table>

3.4 Quit Outcomes

3.4.1 Quit Attempt

The intention to treat analysis of self-reported quit attempts at each follow-up point revealed that overall, 52.5% of participants had made a quit attempt by week 4, which was defined as not having smoked for one day or longer because they were trying to quit. The rates if quit
attempts were 54.4% at week 8 and 54.7% at week 12. Figure 7 shows the rates of quit attempts at each follow-up point separately for bupropion and varenicline group. The Pearson Chi Square test showed that at weeks 8 and 12, a significantly greater proportion of individuals in the varenicline group made quit attempts, compared to individuals assigned to bupropion.

![Figure 7. Quit Attempt Percentages at each Follow-Up Time point by Medication Group.](image)

* p < 0.05, ** p < 0.01

**Figure 7. Quit Attempt Percentages at each Follow-Up Time point by Medication Group.** The quit attempt percentages were relatively similar between the two medication groups as reported in the week 4 follow with 53.1% of participants in bupropion and 52% in the varenicline group. A significantly greater portion of participants randomized to varenicline (60.7%) attempted to quit by week 8, compared to bupropion (47.1%). Similar results were observed as reported in the week 12 follow-up survey, with a 44.9% quit attempt percentage observed in bupropion, versus 63% in the varenicline group.

### 3.4.2 7-Day Point Prevalence of Abstinence

The intention to treat analysis of the self-reported 7 day point prevalence abstinence rates, defined as not having smoked in the 7 days prior to the follow-up survey indicated an overall abstinence rate of 25.6% for end of treatment. The rates were 19.2% and 26.1% for weeks 4 and 8 follow-ups, respectively, in the sample of 234 participants. Figure 8 shows the 7 day point prevalence abstinence rates for each of the medications through the 3 follow-up points at weeks 4, 8, and 12. Using the McNemar’s repeated measure test to look at change in quit outcomes over time, it was found that the rates of 7 days point prevalence of abstinence in the varenicline group significantly increased from week 4 to 8 (p= 0.026) , but not from week 8 to 12 (p= 1.000). On the other hand, in the bupropion group, the point prevalence rates did not
increase from week 4 to 8 (p= 0.774) and from week 8 to 12 (p= 0.727). Moreover, the 7 day point prevalence rates significantly increased from week 4 to 12 in the varenicline group (p= 0.015) but not bupropion (p= 1.000). The slopes of the linear trend lines revealed that the rate in the varenicline group steadily increased from each follow-up time point to the next by an average of 5.2%. On the other hand, the rate remained unchanged in the bupropion group.

Further analysis was conducted comparing the 7 day point prevalence rates of the two medication groups at each follow-up point, using the Pearson Chi Square Test. The p values were 0.585, 0.339, and 0.053 for week 4, 8 and 12 respectively. None of the comparisons were statistically significant. However, the p value became lower from each follow-up to the next.

Figure 8. 7 Day Point Prevalence of Abstinence over Follow-up Time-Points by Medication Group. Varenicline resulted in abstinence rates of 18.9%, 29.9%, and 30.7% as reported at weeks 4, 8, and 12, respectively. In the bupropion group, the rates were 19.6%, 21.5%, and 19.6% at weeks 4, 8, and 12, respectively. The rates of 7 day point prevalence of abstinence in the varenicline group significantly increased from week 4 to 8 (p= 0.026), but not from week 8 to 12 (p= 1.000). In contrast, in the bupropion group, the point prevalence rates did not increase from week 4 to 8 (p= 0.774) and from week 8 to 12 (p= 0.727). In addition, the 7 days point prevalence rates significantly increased from week 4 to 12 in the varenicline group (p= 0.015), but not for bupropion (p= 1.000). The slopes of the linear trend lines revealed that the quit rate for varenicline steadily increased from each follow-up time point to the next by an average of 5.9%. The rate remained unchanged in the bupropion group.
3.4.3 30 Days Continuous Abstinence

The intention to treat analysis of the self-reported 30 days continuous abstinence rates, defined as not having smoked in the 30 days prior to the follow-up survey indicated an overall abstinence rate of 23.1% for end of treatment for the sample of 234 participants. The rate was 17.1% for the weeks 8 follow-up. Figure 9 shows the 30 days continuous abstinence rates for each of the medications for the weeks 8, and 12 follow-up surveys. As indicated by the McNemar’s test, the rate of abstinence in the varenicline group significantly increased from week 8 to 12 (p= 0.007). However, the rate remained relatively unchanged for bupropion from week 8 to week 12 follow-up (p= 1.000).

Further analysis was conducted comparing the 30 days continuous abstinence rates of the two medication groups at each follow-up point, using the Chi Square Test. Varenicline was not significantly more effective than bupropion at week 8 (p= 0.66), the 30 days continuous quit rate for varenicline was significantly higher than bupropion at week 12 (p= 0.037).

![Graph showing 30 Days Continuous Abstinence over Follow-up Time-Points by Medication Group. Varenicline resulted in abstinence rates of 18.1%, and 28.3% as reported at weeks 8 and 12, respectively. In the bupropion group, the continuous abstinence rates were 15.9 % and 16.8% at weeks 8 and 12, respectively. The 30 days continuous abstinence rates significantly increased from week 8 to 12 in the varenicline group (p= 0.007); but not in the bupropion group (p=1.000). Varenicline was not significantly more effective than bupropion at week 8; however, the 30 days continuous quit rates for varenicline were significantly higher than bupropion at week 12.](image)

*P < 0.05
3.5 End of Treatment Comparison of the Medication Groups Outcomes

3.5.1 Comparison of the Intention to Treat Quit Rates

The overall intention to treat (i.e. non-responders are considered smokers) 7 day point prevalence of abstinence rate for the study was 25.6% at the end of treatment. Figure 10 compares this rate between the two medication groups at week 12 follow-up. This rate was 19.6% in bupropion and 30.7% for varenicline. The unadjusted univariable binary logistic regression analysis indicated a trend with varenicline resulting in higher 7 day point prevalence abstinence rates compared to bupropion [OR: 1.81; 95% CI: 0.99 -3.33; p= 0.055].

![Figure 10. Intention to Treat 7 Day Point Prevalence of Abstinence at the End of Treatment by Medication Group. Bupropion resulted in a 7 day point prevalence rate of 19.6% at the end of treatment. This rate was 30.7% for the varenicline group. The unadjusted univariable binary logistic regression analysis showed a trend with varenicline resulting in higher 7 day point prevalence abstinence rate compared to bupropion [OR: 1.81; 95% CI: 0.99 -3.33; p= 0.055].](image)

The overall intention to treat 30 days continuous abstinence rate for the study was 23.1% at the end of treatment. Figure 11 compares this rate between the two medication groups at week 12 follow-up. In the bupropion group, 16.8% of participants remained abstinent for 30 days continuously prior to the week 12 follow-up. This rate was 28.3% for participants randomized to varenicline. The unadjusted univariable binary logistic regression analysis showed that participants who received varenicline were significantly more likely (almost twice) to quit and remain abstinent for 30 days prior to the end of treatment follow-up, compared to those who received bupropion [OR: 1.96; 95% CI: 1.03 -3.70; p= 0.039].
Comparison of the Complete Case Quit Rates

The complete case analysis focused on the 154 participants who responded to the week 12 follow-up survey. Eighty seven of the respondents were assigned to varenicline and the other 67 were in the bupropion group. The overall 7 day point prevalence of abstinence rate observed for the respondents was 38.7%. Figure 12 compares the complete case analysis 7 days point prevalence rates between the two medications groups at the week 12 follow-up. This rate was 30.9% in the bupropion group and 44.8% for the varenicline group. The unadjusted univariable binary logistic regression analysis indicated a trend with varenicline resulting in higher 7 day point prevalence abstinence rates, compared to bupropion [OR: 1.82; 95% CI: 0.93 -3.54; p= 0.078].

Figure 11. Intention to Treat 30 Days Continuous Abstinence at the End of Treatment by Medication Group. Bupropion resulted in a 30 days continuous abstinence rate of 16.8% at the end of treatment. This rate was 28.3% for the varenicline group. The unadjusted univariable binary logistic regression analysis showed that varenicline resulted in a significantly higher quit rate compared to bupropion at the end of treatment [OR: 1.96; 95% CI: 1.03 -3.70; p= 0.039].

Figure 12. Complete Case 7 Day Point Prevalence of Abstinence at the End of Treatment by Medication Group. Bupropion resulted in a 7 day point prevalence rate of 30.9% at the end of treatment. This rate was 44.8% for the varenicline group. The unadjusted univariable binary logistic regression analysis showed a trend with varenicline resulting in higher 7 day point prevalence abstinence rate, compared to bupropion [OR: 1.82; 95% CI: 0.93 -3.54; p= 0.078].
Similar results were observed in the complete case analysis of the 30 days continuous abstinence rates. At the end of treatment, the overall rate was 34.8%. Figure 13 compares this outcome between the two medications groups at the week 12 follow-up. This rate was 26.5% in the bupropion group and 41.4% for the varenicline group. The unadjusted univariable binary logistic regression analysis indicated a trend with varenicline resulting in higher 30 days continuous abstinence rates, compared to bupropion [OR: 1.96; 95% CI: 0.99 -3.90; p= 0.055].

![Figure 13. Complete Case 30 Days Continuous Abstinence at the End of Treatment by Medication Group.](image)

Bupropion resulted in a 30 days continuous abstinence rate of 26.5% at the end of treatment. This rate was 41.4% for the varenicline group. The unadjusted univariable binary logistic regression analysis showed a trend with varenicline resulting in a higher quit rate, compared to bupropion [OR: 1.96; 95% CI: 0.99 -3.90; p= 0.055].

The above models were not adjusted for any baseline characteristics. This was because none of the a priori baseline characteristics that were expected to affect quit success were different between the two medication groups. However, a number of follow-up characteristics, specifically use of additional quit aids, believed to affect quit outcomes were compared between the two medication groups in a complete case analysis of the week 12 follow-up respondents. Table 10 presents the results of this comparison. The percentage of participants accessing each of these additional resources did not differ between the two medication groups.
Table 10. Additional Resources Used by Participants as Reported at the Week 12 Follow-Up. All of the additional quit aids were equally used in the two medication groups.

<table>
<thead>
<tr>
<th>Mean and proportion within column</th>
<th>Medication Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bupropion (n = 66)</td>
</tr>
<tr>
<td>NRT: % Used</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Electronic Cigarette: % Used</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>Self-Help Booklets: % Used</td>
<td>11 (17%)</td>
</tr>
<tr>
<td>Smoker’s Helpline: % Accessed</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Individual Counselling: % Accessed</td>
<td>5 (8%)</td>
</tr>
</tbody>
</table>

Although the two medication groups did not differ in terms of additional quit aids used, the odd ratios were adjusted for them because these variables occurred after the initial randomization. As a result, the binary logistic regression was rerun adjusting for use of each of these quit aids one at a time. Table 11 includes the unadjusted odd ratio for the primary quit outcome, 30 days continuous abstinence rate, at the end of treatment. Table 11 also includes adjusted odd ratios as each of the additional resources were included as covariates. After adjusting for variables, the odd ratios remained very close to the unadjusted odd ratio, indicating little effect on treatment outcome.

Table 11. Odd Ratios for the End of Treatment 30 Days Continuous Abstinence by Medication Group. The adjusted odd ratios remained very close to the unadjusted odd ratio, indicating little effect on treatment outcome.

<table>
<thead>
<tr>
<th>Unadjusted</th>
<th>Variable</th>
<th>Odd ratio of Study Group</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study Group (ref=bupropion)</td>
<td>1.96</td>
<td>0.99-3.90</td>
<td>0.055</td>
</tr>
<tr>
<td></td>
<td>NRT Use</td>
<td>1.94</td>
<td>0.93-3.90</td>
<td>0.061</td>
</tr>
<tr>
<td>Adjusted</td>
<td>Electronic Cigarette Use</td>
<td>1.96</td>
<td>0.98-3.90</td>
<td>0.056</td>
</tr>
<tr>
<td>for:</td>
<td>Self-Help Booklets</td>
<td>1.91</td>
<td>0.96-3.81</td>
<td>0.065</td>
</tr>
<tr>
<td></td>
<td>Smoker’s Helpline</td>
<td>1.89</td>
<td>0.95-3.77</td>
<td>0.071</td>
</tr>
<tr>
<td></td>
<td>Individual Counselling</td>
<td>1.92</td>
<td>0.96-3.82</td>
<td>0.064</td>
</tr>
</tbody>
</table>
3.6 Predictors of Quit Outcome

3.6.1 Gender

The Pearson Chi Square Test was conducted to look at the relationship between gender and the intention to treat end of treatment quit outcomes. The end of treatment quit data was available for 124 females and 109 males. In our sample, there were no significant differences in ability to quit between men and women. The 7 day point prevalence of abstinence p value was 0.799, OR=0.91 and 95% CI of 0.50-1.64. For the 30 days continuous abstinence, the p value was 0.857, OR=0.95, and 95% CI of 0.53-1.79. The bivariable binary logistic regression was conducted, adjusting for medication group. No interaction between gender and medication group was observed.

3.6.2 Nicotine Dependence

The relationship between nicotine dependence, as measured by the FTND Score and the intention to treat end of treatment quit outcomes were assessed using the univariable binary logistic regression. FTND score was not a significant predictor of bupropion and varenicline treatment outcome. Although, there was a trend observed, wherein individuals with higher FTND scores were less likely to be 7 day point prevalence abstinent [OR= 0.88; 95% CI: 0.76-1.02; p= 0.083]. The results for the 30 days continuous abstinence were similar [OR= 0.89; 95% CI: 0.77-1.04; p= 0.145]. The mean FTND score in those who were continuously abstinent for the last 7 days as reported at the week 12 follow-up was 5.68 ± 2.03 and in non-quitters, it was 6.21 ± 1.89. This model was rerun as a bivariable binary logistic regression, adjusting for medication group. The odd ratios remained relatively similar with a small percent change, meaning that FTND does not differentially affect treatment outcome with bupropion versus varenicline.

3.7 Medication Compliance

3.7.1 Compliance Rates

Self-reported compliance was first assessed based on the week 12 follow-up reports. Compliance data was available for 151 participants, where 68 of them had received bupropion
and 83 of them had received varenicline. Five participants, 4 in the bupropion group and 1 in the varenicline group reported that they never started taking the medication they received in mail. Out of 5, 3 (bupropion group) indicated that they never set a quit date. The other 2 (1 varenicline and 1 bupropion group) specified that they set quit dates but did not honor it.

At the week 12 survey, 30 participants indicated that they had finished the full 12 weeks course of treatment, with 15 participants in each of the medication groups. Another 116 indicated they had not finished taking all of the medication that was mailed to them. However, 54 were still using the medication; whereas, 62 had discontinued. Out of those who indicated are still taking the medication, 23 were in the bupropion group and 31 in the varenicline group. Twenty six participants in the bupropion indicated that they discontinued the medication and 36 of the participants taking varenicline indicated not adhering to the full 12 weeks course of treatment. The most common reported reason for discontinuing medication was experiencing side effects, followed by having relapsed, not finding it helpful, stopping having cravings for cigarettes, and believing they did not need it anymore after quitting. About 10% of participants also reported not knowing how to use the medication. At p value of 0.371, the Pearson chi square test showed that this compliance data was not different between the two medication groups.

In order to take a closer look at the time of discontinuation of medication, an analysis of combination of all follow-up surveys was conducted. It was found that a total of 84 participants indicated that they had discontinued medication at some point during the 12 weeks treatment period. Out of these 85 individuals, 18 discontinued the medication by week 4, 41 by week 8, and 25 by week 12. The portion of participants discontinuing medication at these 3 time points were not significantly different between the two medication groups, as tested by the Pearson chi Square Test (p= 0.189).

### 3.7.2 Relationship between Compliance and Quit outcomes

The relationship between medication use and complete case end of treatment quit outcomes are shown in figure 14 and 15. Figure 14 shows the 7 day point prevalence abstinence rates associated with each of the compliance groups by medication group. Figure 15 shows this relationship for the 30 days continuous abstinence quit outcome. For both of these quit outcome measures, a clear trend is observed with both of the medications’ compliance having a direct positive relationship with quit outcomes. The linear regression slope analysis was performed for the overall sample of 146 participants, with quit outcome as the dependent variable and compliance as the independent variable. It was found that compliance was not
statistically significantly associated with the end of treatment 7 day point prevalence of abstinence (β = 0.153, p = 0.066); but it was significantly associated with the continuous abstinence (β = 0.169, p = 0.041).

Figure 14. End of Treatment 7 Day Point Prevalence Abstinence Rates by Medication Use. Figure a) shows the relationship between bupropion and its 7 day point prevalence of abstinence rate at the end of treatment and figure b) shows this relationship for varenicline use. With both medications, a clear trend is observed, where compliance predicts quit rate.

Figure 15. End of Treatment 30 Days Continuous Abstinence Rates by Medication Use. Figure a) shows the relationship between bupropion and its end of treatment 30 days continuous abstinence rate and figure b) shows this relationship for varenicline use. A clear trend is observed, where compliance predicts quit rate with both medications.
The participants were categorized into two groups with one being those who finished the full 12 weeks course of treatment (n=30) and group 2 comprised of individuals who did not (n=121). The overall end of treatment 7 days point prevalence abstinence rate was 53.3% and 33.9% in those who finished the medication versus did not, respectively. There was a trend observed, where finishing the medication resulted in higher successful quit outcome compared to not finishing the medication [OR= 2.23; 95% CI: 0.99-5.01; p= 0.052]. Comparable results were obtained for the end of treatment 30 days continuous abstinence measure [OR= 2.36; 95% CI: 1.04-5.33; p= 0.039]. Those who finished the medication had a significantly higher quit success (50.0%), compared to those who did not finish the medication (29.8%).

The above analysis was rerun, excluding those 54 participants, who indicated are still using the medication at the week 12 follow-up. The point prevalence abstinence was found significantly higher in those who finished the medication compared to those who discontinued or never started the medication [OR= 2.50; 95% CI: 1.03-6.06; p= 0.042]. The results for the continuous abstinence measure were similar [OR= 2.72; 95% CI: 1.11-6.67; p= 0.029].

Further analysis was conducted to investigate if discontinuation time point was associated with treatment outcome. There were no significant differences found between the follow-up time-point at which the medication was reported to be discontinued and the end of treatment 7 days point prevalence outcome (p= 0.841). Similarly, no significant differences were found for the end of treatment 30 days continuous abstinence outcome (p = 0.390).

The bivariable binary logistic regression was conducted to reassess end of treatment quit outcomes with medication group, adjusting for compliance. Both study group and medication compliance were input as covariates in order to see the influence of each on quit outcomes and their interaction. Table 12 shows the results of this analysis for the complete case end of treatment 7 days point prevalence rates and table 13 shows the findings for the complete case continuous abstinence outcome. The unadjusted treatment outcome complete case analysis odd ratios were 1.82 and 1.96 for the point prevalence abstinence and continuous abstinence outcomes, respectively. With a small percent change of less than 1% in medication group odd ratio, compliance did not confound the relationship between varenicline and bupropion quit outcome. The trend still held with varenicline resulting in higher quit rates compared to bupropion. With greater and significant odd ratios, compliance was a better predictor of the quit outcome compared to the medication group.
Table 12. Odd Ratios for the End of Treatment Point Prevalence Abstinence in the Bivariate Model of Medication Group and Medication Compliance. After adjusting for medication compliance, a trend was still observed with varenicline resulting in higher quit rates compared to bupropion. Medication compliance was a significant predictor of quit outcome with an odd ratio greater than that of medication group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Odd ratio</th>
<th>Adjusted Odd ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication Group (ref= bupropion)</td>
<td>1.82</td>
<td>1.81</td>
<td>0.91-3.59</td>
<td>0.091</td>
</tr>
<tr>
<td>Medication Compliance (ref= did not finish)</td>
<td>2.23</td>
<td>2.35</td>
<td>1.03-5.36</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Table 13. Odd Ratios for the End of Treatment Continuous Abstinence in the Bivariate Model of Medication Group and Medication Compliance. After adjusting for medication compliance, a trend was still observed with varenicline resulting in higher quit rates compared to bupropion. Medication compliance was a significant predictor of quit outcome with an odd ratio greater than that of study group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Odd ratio</th>
<th>Adjusted Odd ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication Group (ref= bupropion)</td>
<td>1.96</td>
<td>1.95</td>
<td>0.96-3.97</td>
<td>0.066</td>
</tr>
<tr>
<td>Medication Compliance (ref= did not finish)</td>
<td>2.36</td>
<td>2.52</td>
<td>1.10-5.78</td>
<td>0.029</td>
</tr>
</tbody>
</table>

3.8 Medication Side Effects

The incidences of side effects were calculated at each follow-up time-point. Table 14 shows the incidences of self-reported side effects for bupropion and varenicline at each follow-up time point. The rate of reported side effects remained relatively stable over follow-up time-points. Overall, having trouble sleeping, dry mouth, and fatigue were the top 3 reported side effects for bupropion. For varenicline, having vivid dreams, fatigue, and nausea were the most reported side effects.

The self-reported side effects for bupropion and varenicline were compared at weeks 4, 8, and 12 follow-up points, using the Pearson Chi Square Test. At week 4, bupropion resulted in a
significantly higher incidence of dry mouth compared to varenicline; whereas, varenicline led to significantly higher incidences of vivid dreams, nausea, and fatigue. At week 8, varenicline resulted in significantly higher incidence of vivid dreams and nausea, as well. This was also the case for week 12 reports as varenicline resulted in higher incidences of vivid dreams, nauseas, and fatigue. As a result there were more reports of side effects experienced in the varenicline group, compared to the bupropion group.

Table 14. Self-Reported Incidences of Side Effects at each Follow-Up by Medication Group.
There were no significant changes in incidences of side effect over time. Overall, the most reported side effects for bupropion were having trouble sleeping, dry mouth, and fatigue. For varenicline, having vivid dreams, fatigue, and nausea were the most commonly experienced side effects. Asterisks denote significant differences between the two medication groups at each follow-up time point. At week 4, bupropion resulted in a significantly higher incidence of dry mouth compared to varenicline; whereas, varenicline led to significantly higher incidences of vivid dreams, nausea, and fatigue than bupropion. At week 8, varenicline resulted in significantly higher incidence of vivid dreams and nausea compared to bupropion. At week 12, varenicline resulted in higher incidences of vivid dreams, nausea, and fatigue compared to bupropion.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bupropion (n = 85)</td>
<td>Varenicline (n = 97)</td>
<td>Bupropion (n = 72)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>45 (53%)</td>
<td>33 (35%)*</td>
<td>34 (47%)</td>
</tr>
<tr>
<td>Trouble Sleeping</td>
<td>43 (51%)</td>
<td>45 (47%)</td>
<td>38 (53%)</td>
</tr>
<tr>
<td>Vivid Dreams</td>
<td>26 (31%)</td>
<td>60 (63%)*</td>
<td>26 (36%)</td>
</tr>
<tr>
<td>Rash</td>
<td>6 (7%)</td>
<td>4 (4%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (18%)</td>
<td>55 (58%)*</td>
<td>13 (18%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21 (25%)</td>
<td>21 (22%)</td>
<td>22 (31%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31 (36%)</td>
<td>57 (60%)*</td>
<td>30 (42%)</td>
</tr>
<tr>
<td>Other</td>
<td>16 (19%)</td>
<td>20 (21%)</td>
<td>11 (15%)</td>
</tr>
</tbody>
</table>

* p < 0.05, ** p < 0.01, *** p < 0.001
3.9 Role of Nicotine Metabolism in Smoking Behavior

3.9.1 Saliva Cotinine Level and Nicotine Dependence as Measured by the FTND Score

To investigate the relationship between mailed in saliva samples’ cotinine level and nicotine dependence, measured by the FTND score, the Spearman’s rank-order bivariate correlation was performed. It was shown that the FTND score and baseline saliva cotinine levels were significantly positively correlated in the overall sample of 171 participants, with a correlation coefficient of 0.236 ($p=0.002$). The graphical presentation of this relationship is found in Figure 16.

![Figure 16. Baseline saliva Cotinine Level and Nicotine Dependence.](image)

The Spearman bivariate correlation was performed. The Spearman’s rank correlation coefficient $r_s$ is presented for the relationship, indicating the strength and direction of the association. The Spearman Rho’s significance level is also presented for the relationship. Saliva cotinine level was significantly positively associated with nicotine dependence in the overall sample of 171 participants.

$$r_s = 0.236 \quad p = 0.002$$

Because of gender differences in nicotine metabolism and the FTND Score, the above analysis performed with a gender split, with 95 females and 76 males. The Spearman’s rank correlation coefficients were 0.283 ($p=0.005$) and 0.181 ($p=0.118$) for female and male smokers, respectively. Therefore, cotinine level was significantly positively correlated to FTND Score in females, but not males. These relationships are presented in the scatter plot in figure 17.
To explore the relationship between the nicotine metabolite ratio (NMR) and nicotine dependence, measured by the FTND score, the Spearman’s rank-order bivariate correlation was performed. It was shown that the FTND score and NMR were not correlated in the overall sample of 182 participants, with a correlation coefficient of 0.011 (p= 0.885). The graphical presentation of this relationship is found in Figure 18. Because of the observed significant differences in age between slow and normal metabolizers in our sample, the partial correlation analysis was performed adjusting for age. However, the relationship between FTND and NMR remained insignificant with a correlation coefficient of -.013 (p= 0.866).
Because of gender differences in nicotine metabolism and the FTND score, the above analysis was performed with a gender split, with 99 females and 83 males. NMR was not significantly correlated with the FTND Score in either of the genders. The Spearman’s rank correlation coefficients were -0.111 (p= 0.275) and 0.108 (p= 0.332) for female and male smokers, respectively. Figure 19 presents the scatter plot for this relationship in each gender. The trend lines for this relationship in men and women are in opposite directions.

Figure Legend:
- ○ Female: n=99
- □ Male: n=83

Figure 19. Nicotine Dependence and Nicotine Metabolite Ratio by Gender. The Spearman bivariate correlation was performed. The Spearman’s rank correlation coefficients $r_s$ are presented for the relationship in men and women, indicating the strength and direction of the association. The Spearman Rho’s significance levels are also presented for each relationship. NMR was not associated with nicotine dependence in either men or women.
3.9.3 Nicotine Metabolite Ratio and Quit Outcome

The role of nicotine metabolite ratio in the end of treatment intention to treat quit outcomes was assessed. The total sample size for the intention to treat analysis of quit outcome was 161, with 41 slow metabolizers and 120 normal metabolizers. Overall, slow metabolizers had an intention to treat end of treatment 7 day point prevalence abstinence rate of 34.1%; whereas, the rate for normal metabolizers was 28.3%. The 30 days continuous abstinence rate at week 12 was 34.1% for slow metabolizers and 24.2% for normal metabolizers.

The Chi Square Test showed no significant differences between the quit outcomes in the two NMR groups. NMR group was not a significant predictor of the continuous abstinence quit outcome as shown by the univariable binary logistics regression [OR of 0.61; 95% CI 0.28-1.33; p=0.215]. However, a trend was observed, where normal metabolizers did poorly, compared to slow metabolizers. The same analysis was run for the end of treatment 7 day point prevalence of abstinence [OR: 0.76; 95% CI: 0.36-1.63, p=0.483]. The same analysis was conducted and adjusted for medication group in the bivariable binary logistic regression analysis. Results are shown in Table 15. Because normal and slow metabolizers significantly differed on age, this relationship was also adjusted for age. Adjusting for these variables did not affect the relationship.

Table 15. Odd Ratios for the End of Treatment Quit Outcomes by Nicotine Metabolite Ratio Group. Slow metabolizers were input as the reference in the model. The relationship was adjusted for study medication and age. Adjusting for variables did not affect the relationship significantly. NMR group was not a significant predictor of the end of treatment quit outcomes. However, a trend was observed, where normal metabolizers did poorly, compared to slow metabolizers.

<table>
<thead>
<tr>
<th>Quit Outcome</th>
<th>Odd ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Days Point Prevalence of Abstinence</td>
<td>0.76</td>
<td>0.36-1.63</td>
<td>0.483</td>
</tr>
<tr>
<td>30 Days Continuous Abstinence</td>
<td>0.61</td>
<td>0.28-1.33</td>
<td>0.215</td>
</tr>
<tr>
<td>Adjusted for Study Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Days Point Prevalence of Abstinence</td>
<td>0.72</td>
<td>0.34-1.56</td>
<td>0.412</td>
</tr>
<tr>
<td>30 Days Continuous Abstinence</td>
<td>0.57</td>
<td>0.26-1.24</td>
<td>0.156</td>
</tr>
<tr>
<td>Adjusted for Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Days Point Prevalence of Abstinence</td>
<td>0.71</td>
<td>0.32-1.56</td>
<td>0.390</td>
</tr>
<tr>
<td>30 Days Continuous Abstinence</td>
<td>0.54</td>
<td>0.24-1.21</td>
<td>0.133</td>
</tr>
<tr>
<td>Adjusted for Study Group and Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Days Point Prevalence of Abstinence</td>
<td>0.68</td>
<td>0.31-1.51</td>
<td>0.344</td>
</tr>
<tr>
<td>30 Days Continuous Abstinence</td>
<td>0.50</td>
<td>0.22-1.15</td>
<td>0.210</td>
</tr>
</tbody>
</table>
3.9.4 Nicotine Metabolite Ratio and Treatment Interaction

In order to investigate if NMR differentially affected quit outcomes with the two medication groups, the sample was categorized into four groups by medication and NMR groups. There were a total of 22 participants who were slow metabolizers and received bupropion. The other 19 slow metabolizers received varenicline. Out of the 120 normal metabolizers, 46 received bupropion, and the other 74 received varenicline. Figures 20 and 21 show the intention to treat end of treatment 7 day point prevalence of abstinence and 30 days continuous abstinence for the 4 aforementioned categories. The Chi Square significance levels are presented on the graph comparing the treatment outcomes within each NMR group. None of the comparisons were statistically significant, meaning there was no significant interaction between NMR and medication group. Additionally, the Chi Square significance levels are presented on the graph comparing the quit outcomes by NMR category within each medication group. None of the comparisons were statistically significant.

Figure 20. 7 Day Point Prevalence of Abstinence at the End of Treatment by Medication and NMR Groups. In slow metabolizers, bupropion resulted in a 7 day point prevalence rate of 31.8% at the end of treatment. This rate was 36.8% for the varenicline group. In normal metabolizers, the rates were 23.9% and 31.3% for bupropion and varenicline, respectively. The Chi Square significance levels are presented on the graph comparing the treatment outcomes within each NMR group and the quit outcomes associated with metabolizer groups within each medication group. None of the comparisons were statistically significant, meaning one medication was not superior to the other within a specific NMR category, and vice versa.
Figure 21. 30 Days Continuous Abstinence at the End of Treatment by Medication and NMR Groups. In slow metabolizers, bupropion resulted in a rate of 31.8% at the end of treatment. This rate was 36.8% for the varenicline group. In normal metabolizers, the rates were 17.4% and 28.4% for bupropion and varenicline, respectively. The Chi Square significance levels are presented on the graph comparing the treatment outcomes within each NMR group and the quit outcomes associated with metabolizer groups within each medication group. None of the comparisons were statistically significant, meaning one medication was not superior to the other within a specific NMR category, and vice versa.

In order to take a closer look at this relationship, the univariable binary logistic regression, looking at medication treatment effect within each group of metabolizers, was performed and results are presented in Table 16. For the continuous abstinence results, a trend was observed, where varenicline was more effective compared to bupropion within normal metabolizers [OR= 1.88; 95% CI: 0.75-4.70; p=0.172]. But, varenicline was not superior to bupropion in slow metabolizers [OR= 1.25; 95% CI: 0.34-4.56; p=0.735].
Table 16. Odd Ratios for the End of Treatment Quit Outcomes by Medication Group (ref=bupropion) in each of the NMR Categories. The odd ratios for the medication groups are presented within each of the NMR categories. For the continuous abstinence results, a trend was observed, where varenicline was more effective compared to bupropion within normal metabolizers. But, varenicline was not superior to bupropion in slow metabolizers.

<table>
<thead>
<tr>
<th>Quit Outcome</th>
<th>Metabolizer Group</th>
<th>Odd ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of Treatment 7 Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Point Prevalence of Abstinence</td>
<td>Slow (n=41)</td>
<td>1.25</td>
<td>0.34-4.56</td>
<td>0.735</td>
</tr>
<tr>
<td></td>
<td>Normal (n=120)</td>
<td>1.43</td>
<td>0.62-3.31</td>
<td>0.397</td>
</tr>
<tr>
<td>End of Treatment 30 Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous Abstinence</td>
<td>Slow (n=41)</td>
<td>1.25</td>
<td>0.34-4.56</td>
<td>0.735</td>
</tr>
<tr>
<td></td>
<td>Normal (n=120)</td>
<td>1.88</td>
<td>0.75-4.70</td>
<td>0.172</td>
</tr>
</tbody>
</table>

In addition, the univariable binary logistic regression looking at NMR metabolizer group effect within each medication group was performed and results are presented in Table 17. For the continuous abstinence results, a trend was observed, where within the bupropion group, normal metabolizers had lower quit rates, compared to normal metabolizers [OR= 0.45; 95% CI: 0.14-1.46; p=0.185].

Table 17. Odd Ratios for the End of Treatment Quit Outcomes by Metabolizer Category (ref=slow) in each of the Medication Groups. The odd ratios for the NMR categories are presented within each of the medication groups. A trend was observed, where within the bupropion group, normal metabolizers had lower 30 days continuous quit rates, compared to normal metabolizers.

<table>
<thead>
<tr>
<th>Quit Outcome</th>
<th>Medication Group</th>
<th>Odd ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>End of Treatment 7 Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Point Prevalence of Abstinence</td>
<td>Bupropion: (n=68)</td>
<td>0.67</td>
<td>0.22-2.07</td>
<td>0.491</td>
</tr>
<tr>
<td></td>
<td>Varenicline (n=93)</td>
<td>0.77</td>
<td>0.27-2.22</td>
<td>0.632</td>
</tr>
<tr>
<td>End of Treatment 30 Days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous Abstinence</td>
<td>Bupropion (n=68)</td>
<td>0.45</td>
<td>0.14-1.46</td>
<td>0.185</td>
</tr>
<tr>
<td></td>
<td>Varenicline (n=93)</td>
<td>0.68</td>
<td>0.23-1.96</td>
<td>0.475</td>
</tr>
</tbody>
</table>
3.10 Role of Personality in Smoking Behavior

3.10.1 The Big Five Personality Traits and Nicotine Dependence

To investigate the association between nicotine dependence, as measured by the FTND score, and each of the Big Five Personality traits, the Spearman’s rank-order bivariate correlation tests were performed. Figure 22 shows the scatter plot for each of the big five personality traits as independent variable and the FTND score as the dependent variable for the overall sample. The Spearman’s rank correlation coefficients or spearman’s rho (r_s) are presented, indicating the strength and direction of the association. The Spearman Rho’s significance levels are also presented for each relationship. It was found that extraversion was significantly negatively correlated with nicotine dependence (r_s=−0.080 ; p= 0.030). None of the other personality traits were significantly correlated with the FTND score in the overall sample of 742 participants.

3.10.2 Gender Differences in the Role of Personality in Nicotine Dependence

The Spearman’s rank-order bivariate correlation tests looking at the relationship between nicotine dependence and each of the big five personality traits were rerun for men (n=309) and women (n=432) separately. Figure 23 shows the scatter plot for each of the big five personality traits as independent variable and the FTND score as the dependent variable by gender. The Spearman’s rank correlation coefficients or spearman’s rho (r_s) are presented for men and women, indicating the strength and direction of the association. The Spearman Rho’s significance levels are also presented for each relationship for men and women. It was found that none of the personality traits were significantly associated with nicotine dependence in female smokers. On the other hand, in male smokers, extraversion, negatively (r_s= -0.143 ; p= 0.012), and neuroticism, positively (r_s= 0.122 ; p= 0.032), were significantly associated with nicotine dependence.
Figure 22. Nicotine Dependence and the Big Five Personality Traits. The Spearman bivariate correlation test was performed. The Spearman’s rank correlation coefficient $r_S$ is presented for each relationship, indicating the strength and direction of the association. Spearman Rho’s significance levels are also presented for each relationship. Extraversion, as seen in graph d, was significantly negatively associated with nicotine dependence in the overall sample of 742 participants.

$r_S = 0.068$  $p = 0.063$

$r_S = -0.066$  $p = 0.071$

$r_S = -0.080$  $p = 0.030$

$r_S = -0.008$  $p = 0.864$

$r_S = -0.059$  $p = 0.107$
Figure 23. Nicotine Dependence and the Big Five Personality Traits by Gender. The Spearman bivariate correlation test was performed. The Spearman’s rank correlation coefficient $r_s$ is presented for each relationship, indicating the strength and direction of the association. Spearman Rho’s significance levels are also presented for each relationship. Extraversion (graph d), negatively, and neuroticism (graph a), positively, were significantly associated with nicotine dependence in men only.
3.10.3 Role of the Big Five Personality Traits in Quit Outcome

The role of personality traits in predicting intention to treat end of treatment quit outcomes were assessed using the univariable binary logistic regression, having each of the personality traits as the independent variable one at a time. The results are presented in Table 18. None of the personality traits significantly predicted end of treatment point prevalence of abstinence and the end of treatment continuous abstinence outcome in the overall sample of 180 participants.

Table 18. Odd Ratios for the End of Treatment Quit Outcomes by Personality. None of the Big Five personality traits significantly predicted end of treatment 7 day point prevalence of abstinence and the end of treatment 30 days continuous abstinence outcome.

<table>
<thead>
<tr>
<th>Quit Outcome</th>
<th>Personality Trait</th>
<th>Odd ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 Day Point Prevalence of Abstinence</td>
<td>Openness/Intellect</td>
<td>1.66</td>
<td>0.84-3.28</td>
<td>0.148</td>
</tr>
<tr>
<td></td>
<td>Conscientiousness</td>
<td>1.69</td>
<td>0.89-3.23</td>
<td>0.109</td>
</tr>
<tr>
<td></td>
<td>Extraversion</td>
<td>0.89</td>
<td>0.44-1.78</td>
<td>0.741</td>
</tr>
<tr>
<td></td>
<td>Agreeableness</td>
<td>0.79</td>
<td>0.43-1.48</td>
<td>0.471</td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>0.75</td>
<td>0.44-1.30</td>
<td>0.309</td>
</tr>
<tr>
<td>30 Days Continuous Abstinence</td>
<td>Openness/Intellect</td>
<td>1.56</td>
<td>0.77-3.16</td>
<td>0.216</td>
</tr>
<tr>
<td></td>
<td>Conscientiousness</td>
<td>1.69</td>
<td>0.87-3.31</td>
<td>0.123</td>
</tr>
<tr>
<td></td>
<td>Extraversion</td>
<td>0.78</td>
<td>0.38-1.62</td>
<td>0.507</td>
</tr>
<tr>
<td></td>
<td>Agreeableness</td>
<td>0.76</td>
<td>0.40-1.44</td>
<td>0.402</td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>0.79</td>
<td>0.45-1.38</td>
<td>0.404</td>
</tr>
</tbody>
</table>

The analysis of baseline characteristics of those who participated in the substudy indicated that men and women differed on income. Also, due to gender differences in the role of personality in smoking behavior reported in the literature, the above analyses were rerun for women (n=103) and men (n=77), separately. Table 19 shows the results for the intention to treat end of treatment 7 day point prevalence of abstinence and table 20 shows the results for the intention to treat 30 days continuous abstinence rates at the end of treatment. Conscientiousness significantly predicted both of the quit outcome measures in men only, with individuals scoring higher on this trait having a greater chance of successfully quitting. Neuroticism significantly predicted the end of treatment 7 day point prevalence of abstinence, but not the 30 days continuous abstinence outcome, in men only. Male smokers scoring higher on neuroticism had a lower chance of being 7 day point prevalence abstinent at the end of treatment. A trend was observed, where extraversion predicted both quit outcomes in women. Women scoring higher
on extraversion were less likely to successfully quit. Lastly, a trend was observed, where male smokers scoring higher on extraversion were more likely to be 7 day point prevalence abstinent at the end of treatment. A similar negative trend was observed with neuroticism in males predicting the 30 days continuous abstinence outcome.

Table 19. Odd Ratios for the End of Treatment 7 Day Point Prevalence of Abstinence by Personality by Gender. Conscientiousness, positively, and neuroticism, negatively, significantly predicted quitting success in men only. In women, a trend was observed with extraversion negatively predicting quitting success. On the other hand, a trend was observed with extraversion positively predicting quit outcome in men.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Personality Trait</th>
<th>Odd ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female n= 103</td>
<td>Openness/Intellect</td>
<td>1.22</td>
<td>0.43-3.42</td>
<td>0.707</td>
</tr>
<tr>
<td></td>
<td>Conscientiousness</td>
<td>1.18</td>
<td>0.52-2.65</td>
<td>0.694</td>
</tr>
<tr>
<td></td>
<td>Extraversion</td>
<td>0.38</td>
<td>0.14-1.04</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>Agreeableness</td>
<td>0.72</td>
<td>0.27-1.91</td>
<td>0.511</td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>1.19</td>
<td>0.59-2.39</td>
<td>0.626</td>
</tr>
<tr>
<td>Male n= 77</td>
<td>Openness/Intellect</td>
<td>2.09</td>
<td>0.84-5.23</td>
<td>0.114</td>
</tr>
<tr>
<td></td>
<td>Conscientiousness</td>
<td>3.03</td>
<td>1.03-8.94</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>Extraversion</td>
<td>3.04</td>
<td>0.92-10.03</td>
<td>0.068</td>
</tr>
<tr>
<td></td>
<td>Agreeableness</td>
<td>0.85</td>
<td>0.34-2.10</td>
<td>0.722</td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>0.39</td>
<td>0.16-0.95</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Table 20. Odd Ratios for the End of Treatment 30 Days Continuous Abstinence by Personality by Gender. Conscientiousness positively significantly predicted quitting success in men only. In women, a trend was observed with extraversion negatively predicted quitting success. Another trend was observed with neuroticism negatively predicting quit outcome in men only.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Personality Trait</th>
<th>Odd ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female n= 103</td>
<td>Openness/Intellect</td>
<td>1.18</td>
<td>0.40-3.46</td>
<td>0.758</td>
</tr>
<tr>
<td></td>
<td>Conscientiousness</td>
<td>1.10</td>
<td>0.47-2.55</td>
<td>0.823</td>
</tr>
<tr>
<td></td>
<td>Extraversion</td>
<td>0.37</td>
<td>0.13-1.04</td>
<td>0.060</td>
</tr>
<tr>
<td></td>
<td>Agreeableness</td>
<td>0.75</td>
<td>0.27-2.03</td>
<td>0.567</td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>1.16</td>
<td>0.56-2.40</td>
<td>0.679</td>
</tr>
<tr>
<td>Male n= 77</td>
<td>Openness/Intellect</td>
<td>1.92</td>
<td>0.75-4.91</td>
<td>0.172</td>
</tr>
<tr>
<td></td>
<td>Conscientiousness</td>
<td>3.38</td>
<td>1.09-10.46</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td>Extraversion</td>
<td>2.20</td>
<td>0.67-7.21</td>
<td>0.194</td>
</tr>
<tr>
<td></td>
<td>Agreeableness</td>
<td>0.76</td>
<td>0.30-1.93</td>
<td>0.565</td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>0.46</td>
<td>0.19-1.12</td>
<td>0.086</td>
</tr>
</tbody>
</table>
3.10.4 The Big Five Personality Traits and Treatment Interaction

The binary logistic regression for the end of treatment 30 days continuous abstinence outcome was run to look at the effect of each of the Big Five personality traits within each medication groups with 88 individuals in the bupropion group and 92 in the varenicline group. This was to examine if personality traits predicated quit outcomes within each medication groups. Results are shown in Table 21. Within the bupropion group, two trends were observed, where individuals with higher neuroticism did worse, and individuals with higher conscientiousness did better. A trend was also observed within the varenicline group, where individuals with higher level of agreeableness did worse.

Table 21. Odd Ratios for the End of Treatment 30 Days Continuous Abstinence by Personality by Medication Group. Within the bupropion group, two trends were observed, where individuals with higher neuroticism did worse, and individuals with higher conscientiousness did better. A trend was also observed within the varenicline group, where individuals with higher level of agreeableness did worse.

<table>
<thead>
<tr>
<th>Medication Group</th>
<th>Personality Trait</th>
<th>Odd ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bupropion n=88</strong></td>
<td>Openness/Intellect</td>
<td>1.15</td>
<td>0.38-3.43</td>
<td>0.802</td>
</tr>
<tr>
<td></td>
<td>Conscientiousness</td>
<td>2.59</td>
<td>0.84-7.97</td>
<td>0.096</td>
</tr>
<tr>
<td></td>
<td>Extraversion</td>
<td>1.75</td>
<td>0.49-6.27</td>
<td>0.392</td>
</tr>
<tr>
<td></td>
<td>Agreeableness</td>
<td>1.28</td>
<td>0.42-3.88</td>
<td>0.668</td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>0.34</td>
<td>0.10-1.11</td>
<td>0.074</td>
</tr>
<tr>
<td><strong>Varenicline n=92</strong></td>
<td>Openness/Intellect</td>
<td>2.03</td>
<td>0.77-5.32</td>
<td>0.151</td>
</tr>
<tr>
<td></td>
<td>Conscientiousness</td>
<td>1.35</td>
<td>0.57-3.21</td>
<td>0.497</td>
</tr>
<tr>
<td></td>
<td>Extraversion</td>
<td>0.52</td>
<td>0.21-1.33</td>
<td>0.174</td>
</tr>
<tr>
<td></td>
<td>Agreeableness</td>
<td>0.40</td>
<td>0.15-1.05</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td>Neuroticism</td>
<td>1.08</td>
<td>0.57-2.07</td>
<td>0.811</td>
</tr>
</tbody>
</table>
4. DISCUSSION

4.1 General Discussion

To our knowledge, MATCH Study is the first study evaluating the real-world use and effectiveness of bupropion and varenicline through an innovative internet-based approach. The principle finding of the study was that the participants who were randomized to and received varenicline had a significantly higher 30 days continuous abstinence rate at the end of treatment (28.3%), compared to those who were randomized to and received bupropion (16.8%). This was despite having comparable rates of successful quit attempts between the two medication groups as reported at the week 4 follow-up. In addition, a trend was observed, where in the varenicline group, quit rates increased over the 12 weeks treatment period, but not for bupropion. Moreover, it was found that, regardless of the medication group, compliance was a significant predictor of quit outcomes.

As secondary and tertiary objectives, we also explored the roles of the nicotine metabolite ratio and the Big Five personality traits in nicotine dependence and smoking cessation. Nicotine metabolite ratio was not associated with nicotine dependence, nor was it a significant predictor of quit success with bupropion and varenicline treatment. However, the end of treatment 30 days continuous abstinence rate was about 10% higher in slow metabolizers (34.1%), compared to normal metabolizers (24.2%). On the other hand, it was observed that neuroticism, negatively, and extraversion, positively, were significantly correlated with nicotine dependence in men, but not women. Furthermore, in male smokers, conscientiousness was a significant positive predictor of both the 7 day point prevalence of abstinence and 30 days continuous abstinence at the end of treatment; whereas, neuroticism significantly negatively predicted the 7 day point prevalence rate in men. Although trends were observed, none of the personality traits significantly predicted differential quitting with bupropion or varenicline. These findings are discussed in details in the following sections.

4.1.1 Baseline and Demographic Characteristics

There were no differences observed in baseline and demographic characteristics in participants, who were randomized to bupropion versus varenicline, as well as in those who received varenicline compared to bupropion. This indicates that the randomization process for the study was effective. On the other hand, an analysis of the personality traits revealed that participants,
who received varenicline scored significantly higher on agreeableness, compared to participants in the bupropion group. This could likely be due to a trend observed, where participants who received varenicline were older than those who received bupropion. In fact, a study conducted on two national samples found that agreeableness was positively significantly associated with age (Donnellan & Lucas, 2008). The different agreeableness levels observed across treatment groups may have implications with regards to medication compliance (Axelsson, Brink, Lundgren, & Lötvall, 2011), even though compliance in the two medications groups were similar in our sample. With that being said, no studies have found an association between agreeableness with nicotine dependence and smoking cessation.

Moreover, no differences in baseline and demographic characteristics of those who participated in the sub-study and those did not were observed. This suggests that the decision to participate in the sub-study was not driven by any baseline and demographic characteristics. However, due to the self-referral nature of the study, our sample might have been skewed with respect to certain personality features. For instance, one study has shown that volunteers of research studies score lower on neuroticism and higher on conscientiousness and in some cases are more agreeable and extroverts (Lönnqvist et al., 2007). Nevertheless, our objective of exploring the role of these personality traits in nicotine dependence and smoking cessation is not affected as wide ranges of scores for the personality traits were observed. Furthermore, gender differences in those who completed the personality test were observed with respect to a couple of characteristics. Firstly, there was a significantly higher percentage of female smokers, who made less than $40,000 annually, compared to male smokers. This is in line with a report by Statistics Canada, based on the data from 2008, where it was shown that women had lower income than men. In the literature, socioeconomic status has been shown to be associated with smoking (WHO, 2010). Secondly, women scored significantly higher on agreeableness compared to men. This is consistent with the findings in the literature in a large sample of individuals across different cultures (P. T. Costa, Jr., Terracciano, & McCrae, 2001). To account for these observed differences and gender differences reported in the literature (Nieva et al., 2011), the influence of personality on smoking and quitting smoking was explored in men and women, separately.

Furthermore, the characteristics of those eligible participants, who visited a licensed practitioner to receive medication versus those who did not, were compared. The two groups did not differ on any baseline, demographic, smoking, and personality characteristics, with the exception of age. It was found that those participants, who completed the next steps after randomization, specifically visiting a practitioner to have the prescription signed, were
significantly older, by 4 years, than those who did not. It has been shown that older smokers are more likely to seek help to stop smoking (H. Gilbert, Sutton, & Sutherland, 2005). This is likely due to the fact that smoking-related health problems appear as they get older.

Furthermore, baseline NMR levels of participants were analyzed. The 25th percentile value in our sample was 0.3385, which was used to distinguish between slow and normal metabolizers. In contrast, the cut-off value used by the recent study investigating effect of NMR on treatment was lower at 0.31 (Caryn Lerman et al., 2015). The higher observed NMR value in our sample could possibly be due to a number of reasons. For instance, our participants were about 90% Caucasian, versus less than 50% of the participants of the aforementioned study. In addition, about 54% participants in our study were females, compared to 44% in the published study. A recent study have shown that both being Caucasian and female are associated with higher NMR levels (Chenoweth et al., 2014).

4.1.2 Treatment Outcome

The first variable assessed with respect to treatment outcome was quit attempts. It was found that by week 12, only about 55% of participants made a quit attempt, defined as not having smoked for 24 hours or longer to try quitting (Starr G, 2005). This is despite having favorable conditions, including being highly motivated and confident, having an intention to quit, and receiving smoking cessation medication free of charge. This may be indicative of the challenges associated with stopping smoking in the early hours of quitting. In fact, studies have shown that symptoms of intensive withdrawal from nicotine and craving for cigarettes onset within one to two hours after stopping smoking and they peak within 1 to 3 days (Hughes, 2007). In addition to physical symptoms, which are mostly relieved by use of pharmacotherapies, smokers identify psychological factors as barriers. For instance, smokers report that they find it difficult to handle daily stress and be around other smokers without smoking cigarettes (White, Bush, Kai, Bhopal, & Rankin, 2006). Furthermore, studies suggest that predictors of abstinence in the early hours can be different from those factors that predict long term abstinence success (Bailey, Bryson, & Killen, 2011). Collectively, these demonstrate a need for interventions, which are specifically targeted at physical and psychological factors in the early hours after stopping smoking cigarettes around the time of the target quit date. Moreover, despite being highly motivated to quit smoking at the time of enrollment in the study, some might have lost their motivation by the time they received the medication. In addition, participation in smoking cessation clinical studies often requires adherence to a protocol-defined target quit date (Borrelli, Papandonatos, Spring, Hitsman, & Niaura, 2004). However, in
our real-world study, we did not have means of enforcing individuals to honour quit dates they had set. Therefore, this may explain the low rates of quit attempts observed, and consequently the quit outcomes in our study.

Looking at quit attempts by medication group, there was no significant difference observed based on the data collected at the week 4 follow-up survey. However, a significantly higher percentage of successful quit attempts were observed for varenicline, compared to bupropion, as reported at week 8 and 12 follow-ups. According to the directions given to participants regarding the use of medications, they were expected to take the medication for one to two weeks and then stop smoking. The fact that relatively equal percentages of participants made a quit attempt by week 4 demonstrates that participants in both medication groups took the first step and made an attempt to quit. This suggests that the observed differences in quit outcomes, described later in this section, are not due to lack of trying in one medication group versus the other. On the other hand, the difference in quit attempt reported at weeks 8 and 12 may be due to varenicline’s superior efficacy as more participants on varenicline quit later in the treatment period. This is explained in the segment to follow.

The intention to treat 7 day point prevalence of abstinence was evaluated at each follow-up time-point at weeks 4, 8 and 12. The 30 days continuous abstinence rate was assessed at week 8 and 12. Observing change over time, it was shown that for bupropion, the rate of both quit outcomes remained relatively constant. This suggests that with bupropion, participants quit early on in the treatment period, remain abstinent throughout, and unlike varenicline, there are no late-quitter with bupropion treatment. One explanation could be that because actions of bupropion as a smoking cessation aid are mediated by its primary metabolite, hydroxylbupropion (A. M. Lee et al., 2007), if due to being a slow CYP2B6 metabolizer, optimal levels of this active metabolite are not achieved early on in the treatment, taking bupropion for longer will not further help the smoker quit. On the other hand, in the varenicline group, overall, the rate of abstinence significantly increased over time. This means that, unlike bupropion, if participants are unsuccessful at quitting in the early weeks of treatment, they are still able to succeed later in the treatment. These findings further suggest that an early assessment of bupropion treatment outcome (i.e. at week 4) can be an accurate representation of its end of treatment results; whereas, for varenicline, an early assessment can underestimate the end of treatment quit rates. These findings are in line with the results from clinical trials of bupropion versus varenicline. In fact, Gonzales et al (D Gonzales et al., 2006), provided a graph of change in the 7 day point prevalence of abstinence over the treatment period, where the rate of
abstinence for bupropion remained relatively constant from week 4 to 12. In contrast, for varenicline, the rate fluctuated more, but overall, it increased from week 4 to 12.

The observed differences in quit rates over time with the two medications could also be due to different mechanism of actions by which these two medications aid with smoking cessation. In the initial phase of treatment, through different mechanisms, both bupropion and varenicline alleviate nicotine withdrawal symptoms by increasing dopamine action in the nucleus accumbens of the brain reward system. Specifically, varenicline does this by releasing dopamine via partial agonism on the nicotinic acetylcholine α4β2 receptor, and bupropion by increasing the duration of action of dopamine by inhibiting its reuptake in the synapse (Coe et al., 2005; Wilkes, 2008). However, this effect plateaus early on in the treatment explaining why the quit rates with bupropion remained unchanged from week 4 to 12 during the treatment period. On the other hand, varenicline has dual effects. Because varenicline has higher affinity for the α4β2 receptor, it continues to provide its smoking cessation benefits over time by blocking the reinforcing effects of cigarettes. (Coe et al., 2005). This could explain why increased quit rates are observed later in the treatment with varenicline. In other words, the individual may continue smoking while on varenicline, but will not receive the reinforcing effects. As a result, this will additionally help them to stop smoking later on, which may not be the case with bupropion treatment, as the smoker can continue to smoke and still receive rewarding effects.

The self-reported end of treatment intention to treat abstinence rates were compared between the two medication groups. It was shown that varenicline (28.3%) was significantly more effective than bupropion (16.8%) with an unadjusted OR of 1.96 and an adjusted OR of 1.94, doubling the chances of being 30 days continuous abstinence. This is keeping with previous research that found similar results. In clinical trials of varenicline versus bupropion, it was also found that varenicline was significantly more efficacious than bupropion, where similar odd ratios of 1.90 and 1.93 were observed (D. Gonzales et al., 2006; D. E. Jorenby et al., 2006). The 7 day point prevalence rates were also compared and although a trend was observed, varenicline was not statistically significantly more effective than bupropion. Nevertheless, varenicline resulted in higher 7 day point prevalence rate of 30.7%, compared to 19.6% in those who received bupropion. In contrast to our findings, previous research found varenicline to result in significantly higher point prevalence rates (51%) than bupropion (36%) (D. E. Jorenby et al., 2006). However, this can be due to the larger sample sizes for these studies, and consequently, higher statistical power, compared to the current analysis.
It is important to note that, as expected, the observed quit rates in our real-world study were lower than that of clinical trials. Specifically, the intention-to-treat 7 day point prevalence and 30 days continuous abstinence rates at end-of-treatment in our sample were 19.6% and 16.8% for bupropion, and 30.7% and 28.3% for varenicline. In clinical trials, the reported rates were about 30-36% for bupropion and 44-50% for varenicline (D. Gonzales et al., 2006; D. E. Jorenby et al., 2006). These differences could partially be explained by the dissimilarities between design and settings of a real-world versus a clinical trial. In particular, in clinical trials, smoking cessation behavioral counselling was provided on a weekly basis for the duration of treatment (D. Gonzales et al., 2006; D. E. Jorenby et al., 2006); whereas, in MATCH Study, there were brief email messages sent that are more representative of real-world settings. Compliance to the treatment regimen is also higher in a clinical trial setting than real-world (D. Gonzales et al., 2006). Therefore, these could have contributed to the higher quit rates that are observed in clinical trials. Moreover, the drop-out rate is lower and the response rates to follow-up surveys are higher in clinical trials, compared to a real-world study. In the MATCH Study, follow-up surveys were administered via emails and no in-person visits were required. In fact, the end of treatment follow-up survey response rate in our study was 66%. This rate was about 72% in the aforementioned clinical trials. Moreover, in clinical trials, as part of the intention to treat analysis of treatment efficacy, participants, who missed a visit but reported being abstinent at the next unmissed visit, were considered abstinent at the time of the missed visit (D. Gonzales et al., 2006; D. E. Jorenby et al., 2006). Altogether, these suggest that our intention to treat analysis of effectiveness was robust, increasing the denominator of smokers in quit rate calculations, and consequently, resulting in lower quit rates observed. For this reason, a complete case analysis of quit rates in those who responded to the follow-up surveys was performed. These quit rates were higher and closer to what was observed in clinical trials. Bupropion resulted in complete case 7 day point prevalence of 30.9% and 30 days continuous abstinence rate of 26.5% at the end of treatment. These rates were 44.8% and 41.4% in the varenicline group. Regardless, it should be noted that the real-world effectiveness of these smoking cessation pharmacotherapies are lower than what has been shown in clinical trials.

The influence of gender on treatment outcome was evaluated. Gender was not a significant predictor of quitting and no interaction with medication group was observed. The reports on gender differences with respect to smoking cessation are usually from research studies settings. Overall in smoking treatment studies, it has been reported than men are more successful at quitting smoking than women. This is not as commonly observed in the real-world (Caponnetto & Polosa, 2008). In fact, even in the clinical trial of varenicline versus bupropion, similar to our findings, it was reported that there were no gender differences in quit outcomes in
smokers being treatment with varenicline or bupropion (D. Gonzales et al., 2006). It should be noted that this was an exploratory finding and the study was underpowered to detect statistical significance.

Furthermore, nicotine dependence, as measured by the FTND score, was evaluated for its role as a predictor of quitting success. Nicotine dependence was not a significant predictor of quit outcome, even after adjusting for medication group. A trend was observed with the FTND score being a negative predictor of quitting success. Previous studies on predictive validity of the FTND for smoking cessation has been inconsistent and dependable on the interventions used (Timothy B. Baker et al., 2007; Caponnetto & Polosa, 2008). The fact that FTND was not a significant predictor of quitting with bupropion or varenicline may suggest that the dosing regimen for these medications is sufficient to adequately relieve even the more intense withdrawal experienced by highly dependent smokers.

4.1.3 Medication Compliance

Self-reported compliance to medication was evaluated. Only 3% of participants never started taking the mailed medication. About 41% of participants (38% in the bupropion group and 43% of the varenicline group) reported discontinuing treatment at some point during the 12 weeks treatment period. Only 20% of participants, (22% of the bupropion group and 18% of the varenicline group) reported finishing the medication at the week 12 follow-up survey. However, the other 36% were still using the medication at the time of week 12 follow-up. These participants may have either delayed their quit date; or had paused treatment at some point during treatment and restarted using the medication, again. With 41% of participants discontinuing medication, compliance to medication was low, despite receiving the medication free of charge, and in line with what is reported for smoking cessation pharmacotherapies (Barrueco et al., 2005; Kohlenberg et al., 2004; Liberman et al., 2013), and lower than what is observed in the clinical trials (D Gonzales et al., 2006; D. Jorenby et al., 2006). In a pooled analysis of the two clinical trials of varenicline versus bupropion, the percentage of individuals who adhered to the treatment regimen was 70% for varenicline and 65% for bupropion (Hays, Leischow, Lawrence, & Lee, 2010). This once again points out that although clinical trials have high internal validity, it is data from real-world and population-based studies that give insight on use and effectiveness of these medications under conditions for which they are intended (Hughes, Peters, & Naud, 2011). Nevertheless, compliance may be higher in clinical settings or in a structured smoking cessation program, compared to low rates observed in our internet-based real-world study.
Further analysis was conducted to compare compliance between the two medications and no significant differences were observed. This indicates that even though participants, who were taking varenicline, reported more side effects overall, this did not affect their compliance to the medication. Moreover, because compliance was not significantly different between the two medication groups, the superior effectiveness of varenicline compared to bupropion cannot be attributed to difference in treatment adherence.

The relationship between medication compliance and complete case analysis of treatment outcome was assessed. Trends were observed for both medications, where the end of treatment point prevalence of abstinence and 30 days continuous abstinence rates increased with each compliance group of discontinued, still using, and finished. Overall, a significant positive linear trend was observed, where compliance was associated with end of treatment 30 days continuous abstinence rate. The rates of 30 days continuous abstinence in those who finished the medication was 46.7% for bupropion and 53.3% for varenicline. These rates were much lower, at 19.2% and 33.3% for bupropion and varenicline, respectively, in those who discontinued the medication. Similar analyses were conducted by a study looking at adherence in clinical trials of varenicline versus bupropion. Comparable results were found, where medication compliance was correlated with treatment outcome. In clinical trials, the rate of end of treatment week 9-12 continuous abstinence were 43.1% for bupropion and 59.4% for varenicline in those, who were compliance to the treatment regimen. These rates were 29.8% for bupropion and 44.2% for varenicline in those, who did not adhere to the treatment (Hays et al., 2010). In a retrospective cohort study, looking at varenicline treatment adherence, similar results were observed, wherein those who were fully adherent had an abstinence rate of 50.7% , compared to only about 30% of those that were non-adherent or partially adherent (Liberman et al., 2013).

The univariable logistic regression showed that compliance was a significant positive predictor of quit outcome. For the end of treatment 30 days continuous abstinence outcome, those who finished the medication (53.3%) were significantly more likely to quit compared to those who did not finish the medication (33.9%) (OR= 2.36). The faith of those who were still taking the medication at the time of week 12 follow-up was assumed unknown because it was undetermined if they were going to finish the medication or stop. Therefore, the analysis was rerun with compliance in two categories of finished and discontinued; the obtained OR was higher at 2.73. These results are in keeping with the literature. Although studies on this topic are limited, a number of studies have reported on compliance as a significant predictor of end of treatment quit success (Hays et al., 2010; Siahpush et al., 2015). Similar results on the
association of adherence to nicotine replacement therapy and quit outcome have also been reported (Shiffman, Dunbar, & Benowitz, 2014). Moreover, a bivariable logistic regression analysis was conducted with both medication group and compliance as independent variables. With a greater odd ratio, compliance was a better predictor of quit outcome than medication group. This shows that even though the effectiveness of smoking cessation pharmacotherapies is low, the success rate is additionally hindered by their low compliance rate. Therefore, effectiveness of these medications can be improved if their adherence to treatment is improved. For instance, in our sample, one of the commonly reported reasons for discontinuing medication was that they experienced side effects. A solution can be to adjust the dose of medication for these patients to an optimal level, where side effects are minimized but medication is still effective at controlling their withdrawal symptoms and cravings. Altogether, compliance should be recognized as an important predictor of quitting with smoking cessation pharmacotherapies. As a result, more studies should be investigating the reasons for incompliance and focus on strategies that would improve it.

Furthermore, compliance at all follow-up time-points was evaluated. It was found that discontinuation time point was not associated with treatment outcome at the end of treatment. This means that duration of treatment is insignificant and discontinuing treatment at any point results in low quit success. These findings suggest that adherence to treatment for the full treatment course of 12 weeks is an important determinant of tobacco abstinence. In fact, a study investigating the efficacy of different dosing regimens, found the current standard dosing of 1.0 mg twice daily for 12 weeks to be the most effective (M Nides et al., 2006). It is important to note that motivation and intention to quit smoking might be acting as a mediator in the relationship between medication compliance and quit outcomes. In other words, the participants who discontinued medication at any point during the treatment could have lost their motivation to quit smoking, whereas those who finished the medication were highly motivated. Another interpretation is that those who discontinued medication were unable to quit early on and that is why they lost their motivation and stopped the treatment. In fact, Hays et al. showed that early abstinence in the first 2 weeks of treatment was a significant predictor of adherence to treatment regimen (Hays et al., 2010). Regardless, compliance has been shown to be a significant predictor of quit outcome and needs attention in future studies.

4.1.4 Side Effects

The most commonly reported side effects for bupropion were having dry mouth, trouble sleeping, and fatigue. Bupropion has many targets in the central nervous system. In fact,
bupropion is a dual inhibitor of dopamine and noradrenaline, and to a weaker extent, serotonin reuptake, as well as a weak nAChR antagonist (Stahl et al., 2004; Warner & Shoaib, 2005; Wilkes, 2008). As a result, its actions on different neurotransmitters could be responsible for the variety of side effects experienced (Stahl et al., 2004). In the varenicline group, the top 3 reported side effects were having vivid dreams, fatigue and nausea. Unlike bupropion, for varenicline, it has been suggested that the side effects are due to it action on targets other than the ones responsible for its cessation benefit. At therapeutic doses, varenicline has been shown to also act on α3β4 nAChR, α7 nAChR, and 5-HT₃A. It is believed that the adverse effects associated with varenicline treatment are modulated by its actions on these receptors (Lummis, Thompson, Bencherif, & Lester, 2011). Knowing the mechanism of side effects can help and direct designing new drugs with improved safety profiles.

It is important to note that the side effects experienced are very similar to that of nicotine withdrawal symptoms, making them hard to distinguish for the participants and researchers (Hurt et al., 1997; C. Jimenez-Ruiz et al., 2009). Nevertheless, the observed side effects in the current sample are comparable to what has been seen in the literature. In fact, dry mouth and insomnia are consistently reported in individual taking bupropion (Boshier et al., 2003; Johnston et al., 2001; West, 2003; Wilkes, 2008). Similarly, for varenicline, nausea and having abnormal dreams are frequently reported in the literature (Garrison & Dugan, 2009; Lam & Patel, 2007). However, the rates of these in the current study were higher than what is commonly seen. This could be partly explained by the method of data collection. In particular, participants were presented with the list of side effects, which may prime their recall ability. Furthermore, fatigue as a side effect of smoking pharmacotherapies is less commonly reported. Because these symptoms were not assessed at baseline, it is hard to decide if it was a treatment-emergent effect. Moreover, even though the severity of side effects was not assessed, participants were able to contact the study investigators by email or phone to report any adverse effects that were intolerable. No reports of such serious side effect that needed clinical interventions to be resolved were received. Therefore, it is assumed that the side effects were tolerable.

The rates of side effect for each medication over the treatment period remained relatively unchanged. As a matter of fact, unlike what is reported in the literature, the adverse effects did not resolve later in the treatment period (Barrueco et al., 2005). However, this may be due to inaccuracy of the survey questions assessing side effects. In particular, participants were asked if they had experienced any of the side effects, rather than being asked if they had experienced the side effects since the last follow-up. As a result, even at later follow-ups,
participants might have interpreted the question as if it was asking for side effects happening ever during treatment. Therefore, they might have answered as ‘yes’ even if the side effects had resolved by the 4 weeks prior to follow-up survey.

Side effects were also compared between the two medications. It was found that overall, varenicline resulted in higher rates of side effects than bupropion. Therefore, even though varenicline is more effective than bupropion, bupropion may be a better choice for smokers, who cannot tolerate the side effects associated with varenicline. In fact, one study analyzing the FDA’s Adverse Event Reporting System (AERS) database found that varenicline results in higher rate of serious adverse effects, compared to bupropion, as well (Moore, Furberg, Glenmullen, Maltsberger, & Singh, 2011). As a result, the choice of the smoking cessation pharmacotherapy should be in accordance with a risk and benefit assessment for the individual.

4.1.5 Role of Nicotine Metabolism in Nicotine Dependence and Quitting Smoking

The relationship between cotinine, the primary metabolite of nicotine (Dempsey et al., 2004), and nicotine dependence, as measured by the FTND was examined. The levels of salivary cotinine in mailed samples were significantly positively correlated with the FTND score. This finding is in line with another study of 196 smokers from the general population, which also reported on this relationship (Fu et al., 2012). Moreover, another study reported that urinary cotinine was also significantly correlated with nicotine dependence measured by the FTND score (Jung et al., 2012). The relationship can be explained by the items the FTND score is derived from. For instance, item-4 evaluates cigarette consumption (Blackford et al., 2006). The more cigarettes mean more nicotine exposure; and more nicotine exposure results in higher production of its metabolite, cotinine. Another item on the FTND evaluates the time to first cigarettes after waking up in the morning, which is highly related to plasma cotinine levels, as highly dependent smokers are more affected by depleted nicotine levels (Timothy B. Baker et al., 2007; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991a).

Moreover, this finding confirms that, in a general population of smokers, the FTND score is a valid measure of nicotine dependence and in line with biochemical measures. However, cotinine level is a better measure because it is a measure of actual exposure to nicotine and takes into account the differences in smoking topography (E. M. Lee et al., 2003; UDHHS, 1988). It is also not affected by subjective bias, which is associated with self-report assessments. Although, based on these findings, the accuracy of self-reported FTND was high, this is not always the case in specific sample of smokers, such as those with psychiatric
comorbidities (Balhara, Jain, Sundar, & Sagar, 2012). As a result, cotinine can be potentially clinically used to guide smoking cessation treatment. For instance, NRT doses prescribed to patients can be adjusted according to their nicotine exposure for optimal control of withdrawal and craving symptoms. It is important to take into account that level of cotinine concentration is affected by a combination of level of nicotine concentration, as well as its rate of metabolism, in which case, NMR needs to be taken into account (N. L. Benowitz & Jacob, 1994). Furthermore, what is unique about our samples was that they were mailed in by participants. Participants were instructed to collect the sample first thing in the morning and mail it the same day. As explained previously, collecting samples by mail is a reliable method and cotinine remains stable during transit time (Etter et al., 2005). All in all, mailed in saliva samples taken first thing in the morning can be a valid, objective, informative, and noninvasive measure of nicotine dependence in daily dependent smokers.

Due to variability in nicotine metabolism between men and women reported in the literature (Chenoweth et al., 2014), this relationship was evaluated for male and female smokers, separately. The relationship remained significant for women, but not men. The sample size for women was larger at 95 participants, whereas the sample size was 76 for men. Therefore, this gender difference observed could in part be explained by lack of statistical power. In addition, gender differences in smoking behavior have been identified. In other words, scientists believe that men and women smoke for different reasons. In fact, women are believed to be more sensitive to effects of nicotine and smoke for the physical experience of cigarettes (Silverstein, Feld, & Kozlowski, 1980). Since FTND measures physical dependence to nicotine, it would make sense that cotinine, a measure of how much nicotine a smoker intakes, correlates to FTND in women only, who smoke for the biological effects to relieve negative affect. In contrast, men’s dependence to nicotine can be derived from other factors, such as habitual aspect of smoking behavior, and not necessary the amount of nicotine they inhale from cigarettes (UDHHS, 2001). Differences in smoking topography between male and female smokers can also modulate this relationship. Male smokers take deeper puffs and bigger puff volumes (Battig, Buzzi, & Nil, 1982; Zang & Wynder, 1996), therefore inhaling more nicotine than women with same smoking characteristics based on the items on the FTND score. Nonetheless, cotinine level can be a more accurate and objective measure of actual exposure to cigarettes and their components.

In contrast to above findings, NMR, the phenotypic biomarker of CYP2A6 activity, was not correlated with the FTND score, neither in the overall sample, nor in men and women separately. Although NMR has been shown to correlate with cigarette consumption (Strasser et
al., 2011), we replicated the findings of past studies that did not find an association between this measure and nicotine dependence (N. L. Benowitz et al., 2003; Strasser et al., 2011; UDHHS, 2001). The lack of a linear association suggests that nicotine dependence is influenced by multiple factors and NMR only explains the cigarette consumption aspect rather than dependence as a whole. This means that the rate by which a smoker metabolizes nicotine does not determine their dependence to nicotine by itself; other factors such as demographic characteristics and psychological factors, not measured by FTND, may play roles (DiFranza et al., 2013). In addition, smokers may be compensating for their rate of nicotine metabolism other ways. For instance, one study demonstrated that normal metabolizers take deeper puffs on their cigarettes, compared to slow metabolizers (Lea et al., 2006). Since FTND does not measure smoking topography, this self-reported measure does not account for these differences that affect exposure to nicotine and dependence to it. In conclusion, NMR and the FTND score function independently of each other and the nicotine metabolite ratio does not predict nicotine dependence, measured by the FTND score.

The role of NMR in quitting success was explored. Quit rates were assessed in the two groups of metabolizers determined by the first quartile cut off point. The rates did not significantly differ between the two metabolizer groups; although, a 10% difference in the 30 days continuous abstinence rate was observed. With small sample sizes, we had low statistical power to detect a difference and this analysis should be revisited with a bigger sample size. Furthermore, a binary logistic regression analysis revealed that, in the unadjusted model, NMR was not a significant predictor of quitting success with bupropion and varenicline. In contrast, a study on transdermal nicotine patches has shown that baseline NMR level predicts quitting success. In particular, normal metabolizers were found to do poorly on the nicotine patches compared to slow metabolizers using patches with the same dose (C. Lerman et al., 2006). This is expected as the effective concentration of the nicotine-based pharmacotherapy is affected by its rate of metabolism. On the other hand, the concentration of non-nicotine pharmacotherapies, bupropion and varenicline, are not affected. However, recent studies report that NMR predicts early onset of withdrawal symptoms in the absence of smoking. Specifically, normal metabolizers experience early and more severe nicotine withdrawal symptoms once they quit smoking (Hendricks et al., 2014). This can be explained by the fact that the remaining plasma nicotine after stopping smoking is depleted faster in normal metabolizers and the duration of action on brain nicotinic receptors is decreased. Moreover, a functional Magnetic Resonance Imaging study has reported that slow metabolizers have reduced cue-reactivity to smoking-related cues. This could be because the level of nicotine fluctuates more in normal metabolizers and they experience burst firings of dopamine neurons mediating the conditioning...
process of smoking cues in this group. This does not happen in slow metabolizers as their nicotine level remains stable over time. (Tang et al., 2012). In our sample, even though statistically insignificant, an adjusted odd ratio of 0.5 was obtained, where normal metabolizers did poorly, compared to slow metabolizers. The model was adjusted for age, due to baseline differences between the two metabolizer groups, as well as for medication group.

Further analyses were conducted to explore if NMR differentially predicted treatment outcome with bupropion versus varenicline. The participants were categorized into four groups according to their medication and metabolizer groups. Quit rates were compared between metabolizer categories within each medication group; and between medication groups within each metabolizer category. None of the comparisons were statistically significant, meaning one medication was not superior to the other within a specific NMR category. However, this finding is preliminary and could be due to the small sample sizes and low statistical power, and should be revisited with a bigger sample size. In addition, the binary logistic regression analysis was conducted to investigate the predictability of these factors for quit outcomes. Unlike the overall sample, medication group was not a significant predictor of quitting success in slow metabolizers or normal metabolizers. But, a trend was observed for the end of treatment continuous abstinence outcome, where, similar to the overall sample, varenicline was superior to bupropion. In fact, it is important to note that the difference in quit rates was 11%. Similarly, NMR was not a significant predictor of quitting success with varenicline or bupropion. However, a trend was observed with the continuous abstinence outcome in participants who received bupropion, where normal metabolizers did poorly compared to slow metabolizers. The difference in quit rates was approximately 14%. If this finding is confirmed with the bigger sample size once the target recruitment is reached, it can indicate that bupropion is not effective at addressing the differences in cue-sensitivity and severity of withdrawal symptoms that exist between the two metabolizer groups.

Two previous studies have looked at the role of NMR in smoking cessation with bupropion versus placebo, and varenicline versus nicotine patch. Our study is the first to explore the role of NMR in treatment with varenicline versus bupropion. The adequately powered previous studies showed that bupropion and varenicline result in equivalent quit rates in slow metabolizers, compared to placebo and transdermal nicotine patch, respectively. However, they were both superior to their control groups in normal metabolizer smokers (C. Lerman et al., 2015; Patterson et al., 2008). Additionally, in the study of varenicline and nicotine patch treatment, it was shown that slow metabolizers experienced more side effects with varenicline treatment, compared to normal metabolizers (C. Lerman et al., 2015). Unlike in placebo and
NRT treatment, our study found that the quit rates of slow and normal metabolizers do not significantly differ in participants, who received bupropion or varenicline. These indicate that normal metabolizers, who have a harder time quitting, benefit from non-nicotine pharmacotherapies, bupropion and varenicline, to achieve similar quit rates to that of slow metabolizers. As a result, NMR may have clinical utility in determining optimal treatment option for the individual needs of smokers.

4.1.6 Role of Personality Traits in Nicotine Dependence and Quitting Smoking

The correlation between the Big Five personality traits and nicotine dependence, measured by the FTND, were evaluated. Extraversion was significantly negatively correlated with the nicotine dependence in the overall sample. Due to gender differences reported in the literature (Nieva et al., 2011), this relationship was reevaluated in men and women separately and interaction between gender and personality was observed. Extraversion, negatively, and neuroticism, positively, were significantly associated with nicotine dependence in male smokers, but not females. It is worth noting that most past studies on this topic were conducted with small sample sizes of about 100 smokers (D. G. Gilbert, Crauthers, Mooney, McClernon, & Jensen, 1999; Nieva et al., 2011; Shadel, Cervone, Niaura, & Abrams, 2004); whereas, our sample size for this analyses was 742. It should also be acknowledged that even though these correlations are statistically significant, they are only weakly associated. Therefore, the clinical significance and implications of these associations may be limited. Nevertheless these findings are addressed.

Firstly, the gender differences observed emphasizes the fact that men and women smoke for different reasons (Grunberg et al., 1991; Waldron, 1991). Personality traits partly affect dependence to nicotine in men; but not in women. Men and women did not score significantly different on these personality traits. Yet, the association of these traits with nicotine dependence is different between genders. Previous studies have suggested that sex hormones may be playing a role in the relationship between personality and smoking behavior. It has been proposed that testosterone, the male sex hormone, induces personality traits that promote smoking behavior (Bauman, Foshee, Koch, Haley, & Downton, 1989). Nevertheless, a limited number of studies have looked at gender differences in the relationship between personality and smoking behavior. Similar to our findings, most studies found that personality correlated with nicotine dependence in men only (Granô et al., 2004; Nieva et al., 2011).
Neuroticism was positively associated with nicotine dependence in male smokers. This association has been inconsistently shown in the literature, though most studies have shown an association between this trait and smoking behavior. Neiva et al. looked at this relationship using the Alternative Five Factor model of personality in men and women separately and found no significant association (Nieva et al., 2011). This can be in part attributed to their small sample size of about 55 male smokers. Another study, using the Big Five model of personality, similar to our study, also found that higher level of neuroticism was associated with greater FTND score (Hooten et al., 2005). Although, differences in this relationship with respect to gender were not explored in this study. Moreover, a study using the Eysenck’s personality model to explore this relationship in a sample of male smokers found that neuroticism was positively associated with dependence (McChargue et al., 2004). The relationship between neuroticism and nicotine dependence can be explained by the fact that individuals with high levels of neuroticism have higher tendencies to feel anxious, stressed, and experience negative affect (Watson & Clark, 1984). Smokers often report smoking in order to relieve stress and control negative affect (Kassel et al., 2003). Hence, those who experience more of these emotions smoke more often and have higher chances of becoming dependent.

As previously mentioned, we also found that extraversion was negatively associated with nicotine dependence. The Big Five personality model, used in our study, defines extraversion as being sociable, talkative, and warm (R. R. McCrae & Costa, 1987). Reports on the relationship between nicotine dependence and extraversion have been equivocal. Some studies report a positive correlation between this personality trait and nicotine dependence. For instance, a study using the Quick Big Five personality test found that extraversion was positively associated with nicotine dependence. However, it is important to note that this study was conducted in a sample of adolescent smokers and nicotine dependence was measured using a combination of modified Fagerström Tolerance Questionnaire (mFTQ) and the Hooked on Nicotine Checklist (HONC) (Kleinjan et al., 2012). In contrast, another study assessing this relationship in women using the Eysenck’s model of personality found a negative association (KENDLER et al., 1999). On the other hand, Nieva et al. found that sociability, measured by the Alternative Five Factor model, was negatively associated with the FTND score in men only, but not women (Nieva et al., 2011). In addition, using the Big Five model, Hooten et al, found a negative association between extraversion and daily cigarette use (Hooten et al., 2005). The inconsistency in findings in the literature can be because smokers are not homogenous and individuals smoke for different reasons (Arai et al., 1997; Rondina et al., 2007). Regardless, the negative relationship between extraversion and personality can be explained by the fact that in recent year, smoking has become a less socially desirable behavior. Therefore, the more
sociable the smoker, the more he is discouraged to smoke and encouraged to moderate the habit (Gilbert DG, 1997). Moreover, less sociable individuals do not have a support system in forms of family and friends to motivate them to stop smoking or lesson the habit (Mermelstein, Cohen, Lichtenstein, Baer, & Kamarck, 1986). As a result, the lonelier the smoker, the more chances that the behavior persists, and the more dependent on nicotine he becomes.

Despite the association between personality traits and smoking behavior, few studies have explored the role of personality traits in quitting success. Knowledge on this relationship can in fact help identify those personality dispositions that act as barrier to quitting smoking and help tailor interventions to the needs of individuals. Therefore, we explored the role of personality in quit outcomes in our sample of smokers being treated with bupropion or varenicline. It should be noted that our sample was small and we had low statistical power to detect a difference. Therefore, this analysis should be revisited with a bigger sample size. None of the personality traits were a significant predictor of the intention to treat end of treatment quit outcomes in the overall sample. Due to reports of gender differences in this relationship by Nieva et al. (Nieva et al., 2011), the analysis was performed in men and women separately. Personality traits were significant predictor of end of treatment quit outcome in men, but not women. Specifically, conscientiousness was a significant positive predictor of end of treatment 7 day point prevalence of abstinence and 30 days continuous abstinence. On the other hand, neuroticism only significantly negatively predicted the 7 day point prevalence of abstinence outcome at the end of treatment, which suggests that this trait only significantly predicts short term abstinence. However, a trend was observed with neuroticism negatively predicting continuous abstinence, which did not reach statistical significance. Another trend was observed, where extraversion was a positive predictor of the 7 day point prevalence outcome in men. Although no statistically significant findings were observed for women, a trend was observed, where extraversion was a negative predictor of point prevalence and continuous abstinence outcomes in women. Similar to findings on personality and nicotine dependence, gender differences observed can be explained by the fact that men and women smoke for different reasons (Grunberg et al., 1991; Waldron, 1991). In addition, it should be noted that these findings with respect to the relationship between personality trait and abstinence cannot be attributed to the correlation between personality traits and nicotine dependence. As a matter of fact, in our sample, the FTND score was not a significant predictor of quit outcomes. Therefore, personality predicts quitting success independent of its association with the FTND score.

A limited number of past studies have reported on the relationship between personality traits with quitting success and relapse. Most of these studies did not investigate this relationship in
men and women, separately. However, one study, looking at male smokers who received monetary compensation to quit smoking, found that high neuroticism, as assessed by the Big Five model of personality, predicted decreased time to relapse (D. G. Gilbert et al., 1999). Nieva et al, using the Alternative Five Factor model, did not find an association between neuroticism and abstinence in men or women in their overall sample of 103 participants. However, they found that high level of sociability predicted relapse at 12-month is women (Nieva et al., 2011). This is similar to the trend observed in our sample, where higher score of extraversion was associated with lower chances of being quit in women. In addition, Cosci et al. investigated the relationship between the Eysenck’s personality traits and long-term abstinence at one year with NRT. They found that neuroticism was a negative predictor of success in their overall sample of smokers (Cosci et al., 2009). Moreover, a recent population-based study in the US with a sample size of 2101, which evaluated the personality traits using the Big Five model of personality, reported that openness to experience and neuroticism predicted smoking initiation and progression. On the other hand, conscientiousness was found to have a protective role against smoking progression and persistence (Zvolensky et al., 2015). Hooten et al. also showed that in a sample of 250 patients attending a smoking clinic, high neuroticism and low conscientiousness and agreeableness predicted poor quit outcome (Hooten et al., 2005). Similarly, Teracciano et al. reported that current smokers scored higher on neuroticism and lower on conscientiousness and agreeableness compared to never smokers; former smokers scored intermediate on these traits (Terracciano, 2004). None of the studies above, reported on a positive associated between extraversion and abstinence outcome in men.

The last three studies mentioned seem to be the most consistent with our findings and better explain the association between high neuroticism and low conscientiousness with lower quit success in men (D. G. Gilbert et al., 1999; Terracciano, 2004; Zvolensky et al., 2015). This could be due to the fact that all of these studies were conducted on a sample of smokers representing the real-world smokers’ population, rather than in clinical trials. Nevertheless, the findings on the impact of personality on smoking cessation are inconsistent and need further research. These inconsistencies can be explained by differences in the models of personality used, treatments provided, abstinence measures, settings, and population of smokers being studies. For instance, in our sample, neuroticism was only significantly associated with the 7 day point prevalence quit outcome, but not with 30 days continuous abstinence. This could point out that neuroticism may only affect being quit for a short period of time and needs to be addressed in the initial phase of quitting. Therefore, studies looking at long-term abstinence may not find a significant relationship with this trait. As a result, these variables need to be
standardized for application in real-world settings. If specific personality traits are found to predict smoking cessation, use of personality profiles as a guide for choice of psychosocial and behavioral interventions can be implemented in clinical settings.

Furthermore, to explore if there was an interaction between personality and medication group with respect to the role of personality in treatment outcome, the analyses were rerun in those who received bupropion or varenicline, separately. To our knowledge, our study is the first to look at this relationship in smokers being treated with prescription smoking pharmacotherapies. Our results showed that none of the personality traits were significant predictors of abstinence in participants, who received bupropion or varenicline. However, two trends were observed in the bupropion group, where conscientiousness was a positive predictor, and neuroticism was a negative predictor of the intention to treat end of treatment continuous abstinence outcome. In the varenicline group, a trend was observed with agreeableness being a negative predictor of continuous abstinence. The lack of statistically significant observations may be due to the fact that the two genders were analyzed together, as well as lack of statistical power in our small sample sizes. In our overall sample analysis, none of the personality traits were a significant predictor of abstinence. Therefore, once a bigger sample size is obtained in the MATCH study, these analyses should be rerun for men and women separately in each medication group. If significant results are observed, a smoker’s personality profile can be used to determine which medication will be more effective to prescribe.

Even though, none of the personality traits were a significant predictor of quit outcome at the end of treatment, the most profound trend was related to the finding that individuals with higher neuroticism did poorly on bupropion. This trend was not observed in those who received varenicline. As mentioned previously, a number of previous studies report on the relationship between neuroticism and poor quit outcomes in their samples (D. G. Gilbert et al., 1999; Terracciano, 2004; Zvolensky et al., 2015). However, our findings show that treatment with varenicline is not affected by a person’s neuroticism level. This can be explained by varenicline’s dual mechanism of action. All in all, if results hold with bigger samples size, these findings indicate that varenicline may be a better treatment for smokers with high level of neuroticism.
4.2 Strengths of the Study

This study had a number of strengths. Firstly, to our knowledge, with its patient-driven design, this was the first study looking at the real-world use and effectiveness of varenicline and bupropion in comparison to each other. This is important because findings of clinical trials cannot always be extrapolated to the general population of smokers, who try to quit smoking in real-world settings (D. E. Jorenby et al., 2006; Nallamothu, Hayward, & Bates, 2008). Our study also had an advantage because participants were randomly allocated to the medication group. This ensured that our results are not affected by bias from preferences of patients or prescribers and that the differences in baseline characteristics between the two medication groups were minimal and did not act as confounders of outcome (Suresh, 2011). These ensured that the two medication groups were unbiased and easily comparable. Furthermore, to our knowledge, our study is the first to explore possible interactions between nicotine metabolism and personality variables with treatment with bupropion versus varenicline. Knowledge on the roles of these factors in smoking behavior and quitting success can help tailor smoking interventions for the needs of smokers to maximize effectiveness of treatment and minimize side effects experienced.

Additional methodological advantage included a cost-effective internet-based approach for mass-distribution of prescription-only smoking cessation medications. Due to no in-person visits with the study investigators, the study condition and procedures were more appealing to smokers, easier to adhere with, and allowed for more smokers to participate in the study. In fact, it has been reported that internet-based smoking interventions are convenient, cost-effective, and offer an option of anonymity due to no in-person visits (Civljak et al., 2013). Similarly, our study design was very appealing to the Public Health Units across the province and was widely promoted by clinicians. The study was even picked up by the Windsor local CBC and an article was posted about it (CBC, June 24th, 2014). Moreover, because our study was internet-based and participation was not restricted by where the individual resided in Ontario, participants from both urbanized and rural and remote regions could participate. In fact, our findings showed that our sample was a great representation of smokers all across the province. The majority of participants were from Central and South Western Ontario. This reflects where the majority of Ontario population resides. Nevertheless, about 12% of our eligible participants were from Northern Ontario, which is only sparsely populated.
Additional strengths of the study included high rate of participation in the optional sub-study. In fact, more than 70% of participants completed the optional personality assessment test. In another study by Hooten et al., evaluation of personality traits in smokers, who received treatment at a smoking cessation clinic, was attempted by mail. Only about 53% of personality tests were returned (Hooten et al., 2005). Our response rate was higher because personality was assessed as part of the enrollment process in those eligible participants, who consented to participate in the sub-study. Another strength of our study is that more than 70% of participants, who received medication, returned their baseline saliva samples by mail for analysis of NMR.

This is comparable to another study assessing the feasibility of saliva sample collection by mail, which had a return rate of 80% (Etter et al., 2005). Follow-up survey completion rate was also satisfactory at about 66% for the end of treatment 12 weeks follow-up time-point. The treatment period completion rate for the clinical trial of varenicline versus bupropion was about 68% (D. Gonzales et al., 2006). Our response rate was relatively high for a real-world study, considering the follow-up surveys were administered online via email.

4.3 Limitations of the Study

Our study had several limitations. The first that can be argued is that our sample was not representative of the population of Ontario smokers due to its internet-based design. However, previous studies in the field with an internet-based recruitment and follow-up method have demonstrated that being an online study does not lead to sample representation bias (Pew, 2014). In addition, reports suggest that internet access and use is high among Ontarians, with about three quarter of Ontarian smokers having access in 2007 (Cunningham, 2008). Internet access and use is expected to have increased since. Moreover, the age of our eligible participants ranged from 19 to 75 years old. This indicates that even though our study was internet-based, the design was compatible for smokers of all ages.

The second disadvantage with our study was that our recruitment rate was slower than anticipated based on the pilot study that was conducted. The pilot study was able to recruit 893 eligible participants in about 6 months, with about two third of the participants visiting a physician and receiving medication (Selby P). There are a couple of reasons that could explain the slower recruitment rate. Firstly, the pilot study was conducted back in 2010. The number of smoking treatment programs that are available now has increased since. For instance, the Smoking Treatment for Ontario Patients (STOP) program, which provides free NRT to
interested smokers (Zawertailo L, 2012), is now widely offered at many PHUs. Therefore, smokers with an intention to quit smoking have more treatment options and more programs are available to help them quit. Secondly, the pilot study did not have a randomized design. Therefore, eligible participants and their prescribing physicians had a choice of Zyban or Champix. In the current study, eligible participants were randomly assigned to one of the medication groups and that could have discouraged some treatment-seeking smokers from participating in the study. Nevertheless, we had over a 1000 eligible participants, who enrolled in the study in less than a year. MATCH is an ongoing study. Therefore, we have plans for new methods of recruitment that will be implemented to attract more smokers to participate. These include having pamphlets at pharmacy counters and informing Ontario Physicians about the study via their newsletter.

Another limitation of our study was that about 55% of eligible participants did not follow through with the next steps after the enrollment process. Specifically, they did not visit a Practitioner to have the Standard Script signed in order to receive their medication. Even though signed Scripts from any Licensed Practitioner were accepted, the study’s Enrollment Confirmation email indicated that the participants needed to visit their family physician. Indeed, the most common reason for not having the Script signed was not having a family physician, which was reported by 57% of respondents. As an attempt to resolve this issue, the Enrollment Confirmation email is set to be revised to specify that Scripts from all Licensed Prescribers are accepted. This is to ensure that participants are informed about their options. To further understand the reasons for not visiting a family doctor, reports on access to regular medical doctor in Canada were reviewed. In 2013, Statistics Canada reported that 8.8% of Ontario residents aged 12 years and older did not have a regular medical doctor. The rate was a lot higher in those aged between 20 to 44 years old (CAGov, 2014). Nonetheless, the percentage of participants in our study that reported not having a family doctor was much greater than the rate in the general population of residents of Ontario. This can suggest that smokers are less concerned with their health and do not have a regular doctor to perform medical checkups. This is in line with the fact that generally, smokers have unhealthier lifestyles (Revicki, Sobal, & DeForge, 1991). Hence, it is important to encourage smokers to obtain a family doctor. The family doctor can play a role in initiation and maintenance of smoking cessation.

Moreover, our findings were limited by the fact that the outcomes, such as smoking status and medication use were self-reported. Smoking status was not biochemically confirmed at the end of treatment. With that being said, studies have explored the reliability of self-reported smoking status with high correlation to biochemically confirmed results (Caraballo et al., 2001; Frei et
In fact, most of the nondisclosure happens in special populations, such as pregnant women (Tong et al., 2015). However, self-reported measures are generally reliable and accurate in the general population. Similarly, medication compliance was self-reported. Although medication compliance was biochemically assessed in the MATCH Study, the sample size for the samples analyzed to date was not sufficient. On the positive side, we do not believe that self-reported medication compliance was biased in our sample. This is because the participants were mailed the 12 weeks supply of medication at once and medication adherence did not affect their participation in the study in any way. Additionally, studies demonstrate that self-reported measures of compliance in forms of questionnaire and diary are comparable to nonself-reported measures of medication compliance (Garber, Nau, Erickson, Aikens, & Lawrence, 2004).

Lastly, the response rate to our end of treatment survey was about 66%. The method that was used to deal with the missing data was the intention to treat approach. This method was chosen according to the recommended standard guidelines. Specifically, those participants, whose smoking status could not be determined, were considered smokers (West et al., 2005). However, it should be noted that the intention to treat analysis limited the quit rates that were observed. Using the intention to treat approach as described assumed that all non-responders were smokers, therefore resulting in conservatively lower estimated quit rates associated with treatments. Having said that, studies suggest that if the objective of a study is to address effectiveness in the real-word, the intention to treat approach should be employed as the main analysis (Armijo-Olivo, Warren, & Magee, 2009). This method ensured that the initial randomization of participants into comparable groups was maintained valid.

All things considered, none of the limitations mentioned above critically affected our study. These disadvantages were addressed. None are expected to have biased our findings.

### 4.4 Future Directions

As mentioned previously, MATCH Study is ongoing and is aiming to recruit 1500 participants, who will receive medication. Therefore, the analyses conducted should be reevaluated once the target recruitment is reached. Hierarchical analyses with the use of interaction terms can be performed to further explore the role of metabolic and personality variables in treatment.
response with smaller error terms. Due to small sample sizes and low statistical power, these types of statistical analyses were not appropriate during this interim evaluation of study data.

One of the observations in our study was that only about 50% of participants were able to make a successful quit attempt while on medication, that is remain abstinent for 24 hours or longer. Therefore, future studies can identify those smokers with certain characteristics, who have a harder time making a successful quit attempt and tailor inventions to address the needs of these smokers in the early hours of quitting smoking to improve treatment outcomes. In our study, it was also noted that real-world compliance to varenicline and bupropion treatment was equally low. Quit rates were significantly higher in those participants, who adhered to the medication regimen and finished the full 12 weeks course of therapy. Therefore, future studies should focus on compliance and investigate the factors that influence it. This can help design strategies that will increase compliance to treatment and consequently, effectiveness of these medications.

Additionally, the findings reported here should be replicated in different settings and within different populations of smokers. In order to advance towards personalized medicine, further studies need to be conducted to assess the roles of nicotine metabolism and personality traits. For instance, studies can be designed, where participants are stratified into slow and normal metabolizers based on their NMR level. Then, within each metabolizer category, participants can be randomized to pharmacotherapies to compare effectiveness of each therapy within and between metabolizer groups. In terms of personality traits, currently, the literature is very heterogeneous with regards to the model of personality assessment and type of quitting outcome measure used. Therefore, first, these measures should be standardized. Then, cut off points should be determined, where participants can be categorized into groups based on their personality trait scores. After, the same pretreatment stratifying strategy can be used to determine what personality traits predict quitting outcome with each pharmacotherapy. Additionally, the roles of lower-order levels of personality, specifically the ten aspects, in treatment outcome can be explored. In fact, the association between certain domains of personality and treatment outcome could have been missed if the two aspects predicted quitting in opposite directions. The ultimate goal would be to tailor tobacco interventions to the need of individual smokers to improve cessation outcomes.

Furthermore, to this point, it has been recognized that it is very challenging to quit smoking. Tobacco addiction is multifactorial and there are several biological, psychological, and environmental influences that determine how difficult it is for a smoker to quit. MATCH is a
large study that follows participants for a period of one year. Therefore, the data available can be explored further to gain a better understanding of these factors, which can help improve smoking cessation interventions. For instance, the roles of baseline and demographic characteristics can be explored to see if they differentially affect treatment outcome with bupropion versus varenicline. In other words, data can be examined to find out if smokers with certain baseline and demographic characteristics do better on one pharmacotherapy versus the other. Knowledge on these factors can be used clinically to guide the choice of the medication prescribed. Furthermore, the neurogenetic of these medications are also to be investigated. In fact, as part of the MATCH Sub-study, saliva samples are collected for the purpose of DNA analysis. The aim is to determine genetic factors that can help personalize smoking cessation treatments.

Lastly, MATCH has an innovative internet-based design for mass-distribution of smoking cessation pharmacotherapies. The only factor limiting the effectiveness of the process was that only about half of the eligible participants visited a Licensed Prescriber to have their prescription signed. Therefore, future efforts should be focused on understanding the reasons for this limitation and improving the process. Ultimately, this innovative method can become an effective smoking cessation program, which can be easily accessed by interested smokers, with the hope of reducing prevalence of tobacco use in Ontario.

4.5 Conclusions

Our study aimed to look at the real-world use and effectiveness of bupropion and varenicline for smoking cessation. It was found that comparable to clinical trials (D. Gonzales et al., 2006; D. E. Jorenby et al., 2006), varenicline was more effective than bupropion in the real-world. However, the quit rates observed were even lower than that of the clinical trials. This emphasizes the need for development of more effective and safer pharmacotherapies and combination of interventions to increase success rates. Additionally, medication compliance was low in the real-world; thereby, further affecting treatment outcomes. As results, strategies to increase treatment adherence need further attention.

Furthermore, due to low success rates mentioned with current smoking treatments, there is a need to increase the efficacy of these available interventions. Therefore, the role of nicotine metabolite ratio and personality traits in smoking and treatment outcome were explored. Based
on the current findings, it is suggested that normal metabolizers particularly benefit from non-nicotine pharmacotherapies. Moreover, it was found that certain personality traits, such as neuroticism, determine treatment outcome. Therefore, pharmacological interventions should be accompanied by personalized behavioral counselling that gives smokers an understanding of how to handle other factors, such as stress, that are barriers to quitting smoking. Implementing personalized pharmacological and behavioral interventions are promising approaches to increase both short-term and long-term effectiveness of tobacco cessation treatments.

Lastly, in order for a treatment to make an impact at the population level, it needs to be accessible and affordable. A very small percentage of treatment seeking smokers use bupropion and varenicline to quit (HC, 2007). It was shown that MATCH study’s innovative design can cross the barriers and reach smokers over a broad geographic area across the province, while maintaining treatment effectiveness. Therefore, in order to reduce the prevalence of tobacco use and the cost its consequences have to our healthcare system, this strategy is useful for policy makers to consider as part of a comprehensive tobacco control strategy. In fact, it has been demonstrated that more smokers make serious quit attempt, when treatment is free of charge (C. A. Jimenez-Ruiz et al., 2008). All in all, effectiveness and use of smoking cessation pharmacotherapies need to be improved in order to reduce the burden smoking has on our society.
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Appendix 1. Study Website: www.matchstudy.ca
Appendix 2. Online Portal and Data Collection Platform
Appendix 3. Study Information and Consent Form

You are being asked to participate as a research subject in the study titled “Evaluating the real-world effectiveness of varenicline and bupropion for long-term smoking cessation” (MATCH Study). This study is being conducted by Dr. Laurie Zawertailo, a scientist at the Centre for Addiction and Mental Health. The study is funded by the Global Research Awards for Nicotine Dependence, a peer-reviewed research grant competition funded by Pfizer Pharmaceuticals. The purpose of the study is to measure the long-term quit rates associated with Zyban and Champix treatment in a real-world setting, outside clinical trials. About 1500 participants from Ontario will participate in this study. The study provides 12 weeks of bupropion (Zyban®) or varenicline (Champix®) to help you quit smoking.

Procedure

If you agree to participate in this study you will first complete an online questionnaire to ensure you are eligible for the study. Some of the questions may not seem to be related to smoking or quitting smoking, for example, questions about your education or employment. However, these are important pieces of information that will help us answer our research questions more completely. You may refuse to answer some of these questions if you wish. The questionnaire will take about 10 minutes. If you are eligible you will be asked to print two documents, a Letter to the Doctor and a Standard Script. You may also print a copy of this consent form for your records. The Letter to the Doctor contains information about the study and informs your doctor that you are eligible to participate in this study. The Standard Script is an unsigned prescription form for the medication you have been assigned to receive (either Champix (varenicline) or Zyban (bupropion)), which your doctor would need to sign and fax to the pharmacy indicated at the bottom of the prescription form. Once the fax is received by the pharmacy, they will fill the prescription and mail the medication to you along with a ‘saliva collection kit’ for confirmation of your current smoking status. Prior to starting the medication, you will need to provide a small sample of your saliva and mail it back to us using the stamped addressed envelope provided in the kit. Your saliva sample will be analyzed for a chemical called cotinine, a by-product of nicotine metabolism.

Based on your medical history or based on his/her discretion your doctor may choose not to prescribe you the study medication. From the day you enroll in the study by completing the online questionnaire mentioned above, you have five weeks to visit your doctor to discuss in detail the medication you have been assigned to and to have the Standard Script signed. You will also receive weekly motivational emails for 12 weeks, starting on the 5th week after you enroll. You will be contacted by email and/or phone 9, 13, and 17 weeks after enrolling (this is approximately 4, 8 and 12 weeks after starting treatment, assuming that you have visited a doctor within 5 weeks of enrolling). The purpose of these emails is to ask you a few questions to see how you are doing with your attempt to quit smoking. We will also contact you with similar questions 6 and 12 months later. You may also be required to mail in another saliva sample for analysis of cotinine at these times. This is an important way of measuring the effectiveness of providing these smoking cessation treatments free of charge. If you did not visit a doctor to have the Standard Script signed after enrolling, we will still attempt to contact you with the same questions, as the information we collect from you would be used to compare to the information we collect from those who have visited a doctor.
Risks and Benefits

Using Zyban or Champix when quitting smoking is approved by Health Canada. There are both risks and benefits of participating in this study. The risk is that there are some possible side effects of Zyban and Champix. The most common side effects of dry mouth and insomnia in about 5% of users. The major side effects, which are clinically significant, are seizures (1 in 1000 users), hypertension (in less than 5% of users) and rash (in 1% of users). These conditions are all reversible. The most common side effects of Champix are nausea, abnormal dreams, constipation, flatulence and vomiting in 30, 13, 8, 6 and 5% of users, respectively. They are reversible and usually not severe. As you may have heard in the media that some people who were taking Champix have experienced some psychiatric symptoms. These symptoms have not been proven to be caused by Champix, but Health Canada has endorsed a public announcement about this issue that we ask you to read carefully (you may find this announcement at http://www.pfizer.ca/en/our_products/products/bulletin/152?ProductBulletinID=25

The benefit of participating in this study is that you will receive the medication free of charge, which may increase your chances of quitting smoking and stopping smoking is the single most beneficial thing that smokers can do to improve their health.

Confidentiality

Your answers to the questions are confidential to the full extent permitted by law and will be available only to the study investigators. As part of continuing review of the research, your records may be assessed on behalf of the Research Ethics Board at CAMH. A person from the research ethics team may contact you 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. The information you provide will not be made available to anyone else without a court order or your written permission. As part of the Research Services Quality Assurance role, studies may be audited by the Manager of Quality Assurance. Your research records and CAMH records may be reviewed during which confidentiality will be maintained as per CAMH policies and to the extent permitted by law. Any reports or publications based on this study will not mention your name or identify you in any way. You will be provided with an email address and telephone number to contact us, if you have any questions about the study. You will be informed in a timely matter of any new information or changes to the study that may affect your willingness to participate. Please remember that your participation is voluntary and you may withdraw your consent at any time.

Contacts

If you have any further questions or desire further information about this study, you may contact Dr. Laurie Zawertailo at 416 535 8501, extension 77422. You may also contact us by sending an email to match.study@camh.ca. If you have any questions about your rights as a study participant, you may contact Dr. Padraig Darby, Chair of the Research Ethics Board, Centre for Addiction and Mental Health, at 416 535 8501, extension 6876.

Consent

You have the option to consent to any or all of the study components and we have two statements requesting consent. If you agree to participate in the following components of the study please click on the YES button. If you do not agree to participate in any one of the components, please click on the NO button. Even if you consent to participate you are free to withdraw from the study at any time and for any reason. If you have any questions regarding this study please click here to access Frequently Asked
Questions. If your question is still not answered you will be able to send an e-mail to study personnel who will respond within 24 hours.

1. **I consent to participate in the study.** I have read the above information about the study named “Evaluating the real-world effectiveness of varenicline and bupropion for long-term smoking cessation” (MATCH Study). I also understand that my role is that of a subject in this study. My questions, if any, have been answered to my satisfaction, so that I now understand the procedures to be followed in the study, the risks to me from my participation, and my right to the confidential treatment of the information that is collected about me. I understand that providing my consent does not waive my legal rights or relieve the legal responsibilities of the investigators, study sponsors or institutions.

☐ YES  
☐ NO (if selected, following pop up will appear)

Are you sure that you do not want to participate?
Clicking ‘Yes’ will return you to the home page.
☐ YES  ☐ NO

2. **I consent to being contacted for future studies.** This is optional, so you can still participate in this study even if you select ‘NO’

☐ YES  
☐ NO
Appendix 4. Baseline Survey

1. Please write down your contact information below:

   First Name: ________________________________

   Last Name: ________________________________

   Home Address:
   __________________________________________

   City: _______________________________________

   Postal Code: ________________________________

   Province: _________________________________

2. If you are eligible to participate, your medication will be mailed to your daytime mailing address. Please enter your daytime mailing address below. If your daytime mailing address is the same as your home address, please re-enter it below. Please make sure your mailing address is entered correctly to avoid any shipping delays.

   Daytime Mailing Address:
   __________________________________________

   City: _______________________________________

   Postal Code: ________________________________

   Province: _________________________________

3. Please enter your telephone number(s) where we can contact you:

   Primary: __________________________________

   Secondary: __________________________________

   Tertiary: ___________________________________

4. What is your date of birth: ________________________________ (dd/mm/yyyy)

5. How old are you? ________________________________

6. What is your gender?
   □ I am female □ I am male □ Other

7. For the past year, have you smoked cigarettes every day?
8. At present time, how often do you smoke cigarettes?

- [ ] Daily
- [ ] Occasionally / Non-daily  
  [IF OCCASIONALLY / NON-DAILY, HIDE QUESTION 11 AND SECTION 3]
- [ ] I do not currently smoke  
  [IF I DO NOT CURRENTLY SMOKE, SKIP TO SECTION 4]

9. How old were you when you smoked your first whole cigarette?  
   ________________

10. How old were you when you first started smoking occasionally?  
    ________________

11. How old were you when you first started smoking daily?  
    ________________

12. How many of your first degree relatives (parent, sibling, child) smoke cigarettes?

- [ ] None
- [ ] 1 or 2
- [ ] 3 or 4
- [ ] 5 or 6
- [ ] More than 6
- [ ] Don’t know / prefer not to answer

13. In order to participate in this study, you need to have a target quit date. When do you plan to quit smoking?

- [ ] Within 30 days of receiving the assigned study medication
- [ ] Sometime beyond 30 days of receiving the assigned study medication
- [ ] I do not plan to quit smoking

14. In your whole life, how many times did you stop smoking for at least 24 hours because you were trying to quit?

- [ ] Zero  
  [IF ZERO, HIDE QUESTION 15 AND 16]
- [ ] 1 to 5 times
15. What is the longest time that you have quit smoking for?
- One day or less
- More than 1 day but less than 1 week
- More than 1 week but less than 1 month
- 1-5 months
- 6-11 months
- 1 year or more but less than 2 years
- 2 or more years but less than 5 years
- More than 5 years
- Don’t know / prefer not to answer

16. In the past 12 month, how many times did you stop smoking for at least 24 hours because you were trying to quit?
- Zero
- 1 or 2 times
- 3 or more times
- Don’t know / prefer not to answer

17. On a scale of 1 to 10, where 10 means this is the most important thing you have to do and 1 is the least important, how important is it for you to quit smoking?

18. On a scale of 1 to 10, where 10 means that you are very confident that you can quit smoking and 1 means you have very little confidence, how confident are you that you can quit smoking?

19. How soon after you wake up do you smoke your first cigarette?
Within 5 minutes
☐  6 to 30 minutes
☐  31 to 60 minutes
☐  After 60 minutes

20. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, cinema, etc?
☐  Yes  ☐  No

21. Which cigarette would you hate most to give up?
☐  The first one in the morning
☐  All the others

22. How many cigarettes a day do you smoke?
☐  Less than 10
☐  10
☐  11-20
☐  21-30
☐  31 or more

23. Do you smoke more frequently during the first hours of waking than during the rest of the day?
☐  Yes  ☐  No

24. Do you smoke if you are so ill that you are in bed most of the day?
☐  Yes  ☐  No

25. Do any of the following apply to you?
   I have a history of bulimia and/or anorexia:
☐  Yes  ☐  No
   I have had brain injury in my lifetime:
26. Have you ever been diagnosed with any of the following?

- **Depression:**
  - Yes □
  - No □

- **Anxiety:**
  - Yes □
  - No □

- **Schizophrenia:**
  - Yes □
  - No □

- **Bipolar Disorder:**
  - Yes □
  - No □

27. Are you currently taking any medications regularly?

□ Yes □ No [IF YES, GO TO NOTE]

(Note: Please review your list of medications with your family physician prior to starting your bupropion or varenicline. Some medications may require adjustment while you are taking bupropion or varenicline.)

28. How many caffeinated beverages (e.g. coffee, tea, cola) do you drink per day?

□ None □ 1 to 2 □ 3 to 5
29. How often, if ever, did you drink alcoholic beverages during the past 12 months?

☐ More than once a day
☐ About every day
☐ 4-5 times a week
☐ 2-3 times a week
☐ Once a week
☐ 2-3 times a month
☐ Once a month
☐ Less than once a month
☐ Never

☐ Don’t know / prefer not to answer  [IF NEVER OR DON’T KNOW / PREFER NOT TO ANSWER, HIDE QUESTION 3]

30. In the past 12 months, how many drinks containing alcohol have you had on a typical day when you were drinking?

☐ Less than 1
☐ 1 to 2
☐ 3 to 5
☐ 6 to 10
☐ More than 10

(Note: When you stop smoking, your body does not break down caffeine as much. You may need to reduce your caffeine intake. Talk to your health care provider if you have any concerns or notice any symptoms such as anxiety.)
31. Have you ever used any of these substances?

Marijuana: ☐ No  ☐ Past  ☐ Currently (last 30 days)

Cocaine:  ☐ No  ☐ Past  ☐ Currently (last 30 days)

Sedatives:  ☐ No  ☐ Past  ☐ Currently (last 30 days)

Opiates:  ☐ No  ☐ Past  ☐ Currently (last 30 days)

Stimulants:  ☐ No  ☐ Past  ☐ Currently (last 30 days)

Other:  ☐ No  ☐ Past  ☐ Currently (last 30 days)

32. Over the last 2 weeks, how often have you been bothered by any of the following problems?

[SCORE: NOT AT ALL = 0, SEVERAL DAYS = 1, MORE THAN HALF THE DAYS = 2, NEARLY EVERY DAY = 3. PARTICIPANTS ARE PRESENTED WITH a) AND b) FIRST, IF SCORE A SUM OF 3 OR HIGHER FOR a) AND b), GO TO c) – i)]

a). Little interest or pleasure in doing things
☐ Not at all
☐ Several days
☐ More than half the days
☐ Nearly every day

b). Feeling down, depressed, or hopeless
☐ Not at all
☐ Several days
☐ More than half the days
☐ Nearly every day

c). Trouble falling or staying asleep, or sleeping too much
☐ Not at all
☐ Several days
☐ More than half the days
☐ Nearly every day

d). Feeling tired or having little energy
e). Poor appetite or overeating
   □ Not at all
   □ Several days
   □ More than half the days
   □ Nearly every day
f). Feeling bad about yourself, or that you are a failure, or have let yourself or your family down
   □ Not at all
   □ Several days
   □ More than half the days
   □ Nearly every day
g). Trouble concentrating on things, such as reading the newspaper or watching TV
   □ Not at all
   □ Several days
   □ More than half the days
   □ Nearly every day
h). Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around a lot more than usual
   □ Not at all
   □ Several days
   □ More than half the days
   □ Nearly every day
i). Thoughts that you would be better off dead, or of hurting yourself in some way
   □ Not at all
   □ Several days
   □ More than half the days
   □ Nearly every day

We are now going to ask you some general questions about yourself.

33. What is the highest level of education you have completed?
   □ Some primary school
   □ Primary School
   □ Some high school
   □ High school diploma
   □ Some college
☐ College diploma
☐ Some university
☐ University degree
☐ Don’t know / prefer not to answer

34. What is your current employment status?
☐ Full Time
☐ Part Time
☐ Self Employed
☐ Unemployed
☐ Retired
☐ Student
☐ Don’t know / prefer not to answer

35. What is your approximate total household income for the past year before income tax deduction (from all sources)?
☐ Less than $10,000
☐ $10,001 - $20,000
☐ $20,001 - $40,000
☐ $60,001 - $80,000
☐ $80,001 - $100,000
☐ Over $100,000
☐ No Income
☐ Don’t know / prefer not to answer
36. Which ethnic or cultural group do you most closely identify with? (Based on heritage of parents/grandparents)

☐ European / Caucasian

☐ African Descent / African American

☐ East Indian Caucasian (e.g. Pakistani, Indian)

☐ Asian (e.g. Chinese, Japanese)

☐ Hispanic / Latino

☐ Native N. American

☐ Pacific Islander

☐ Don’t know / prefer not to answer

☐ Other: ___________________________
Appendix 5. Substudy Information and Consent Form

Study Title: “Evaluating the real-world effectiveness of varenicline and bupropion for long-term smoking cessation” (MATCH Study)

Principal Investigator: Dr. Laurie Zawertailo
Co-Investigators: Dr. Peter Selby, Dr. Bernard Le Foll

1. What is the background and purpose of this study?

As part of the main study entitled “Evaluating the real-world effectiveness of varenicline and bupropion for long-term smoking cessation” (MATCH Study) you will be prescribed medication for smoking cessation. Some people can experience poor response or side effects from these drugs. There is evidence that drug response and side effects are related to the genetic factors that people inherit from their parents. For instance, a person can inherit a factor from their parents that leads them to poorly break down their medication, and makes him/her more likely to develop side effects. Moreover, evidence suggests a relationship between phenotypic personality characteristics and smoking behaviour and treatment outcome.

Our researchers would like to understand how genetic and personality characteristics variations among people taking prescription medications for smoking cessation alter their capacity to respond better or worse to the medication. We can see if your ability to break down your medication is normal, too slow, or too fast by looking at your DNA. We will also look at your DNA to see if we can find new changes that may alter your response to the medication and influence your ability to quit smoking.

2. What will I be asked to do if I agree to take part in the study?

If you agree to enroll in this part of the study you will complete some additional questionnaires online. In particular, you will be asked questions about your personality traits. The personality test administered is called BFAS (Between Facets and Domains), a public domain test created by Colin G. DeYounge, Lena C. Quilty, and Jordan B. Peterson. The questionnaire contains 100 questions answered on a five point scale ranging from “strongly disagree” to “strongly agree”. It will take you about 10 minutes to complete this test. All of your responses will be kept completely confidential and will only be available to the study investigators. We will then mail you a kit so you can provide some of your saliva (approximately half a teaspoon) as a sample for DNA testing.

Your contact information will be kept on file in our records so that you may be contacted in the future if we need additional information about your current or past medical treatment. If at any point you do not wish to engage in further follow-up, your contact information will be permanently deleted from our files.

3. Are there any risks?

There are no physical risks related to providing a saliva sample.

The non-physical risk of this research is the possibility of a disclosure of your research results or your study participation to people not involved in the research such as insurers and employers. Dr.
Zawertailo’s team will take all reasonable steps to protect your research information. This is done to reduce the potential for harm to you from an unintended disclosure of genetic or clinical information.

In the event that you suffer injury as a direct result of participating in this study, normal legal rules on compensation will apply. By signing this consent form you are in no way waiving your legal rights or releasing the investigator from their legal and professional responsibilities.

4. What are the benefits to me?

The information collected may help to increase the knowledge of how genetic make-up affects response and side effects to smoking cessation medications. In the future this knowledge may increase the effectiveness of these medications by identifying those who would most likely benefit.

5. Will personal information about me be kept confidential?

To protect your confidentiality, Dr. Zawertailo’s team will label (“code”) your sample and your medical information with a number, not your name. This number will be how researchers keep track of samples and information.

Your name will not be in any publications or external reports about this research. The investigative team will control access to files that hold your medical information and results.

Your medical information and any coded results will be put on a computer and stored in an electronic database on an encrypted server. When processing and storing personal information, we will comply with the relevant laws to protect the confidentiality of research participants.

We may collaborate with other research organizations in other locations, including commercial companies, who may want to use your sample and already collected medical information for studying genetic material and substances related to research on psychiatric disorders. Your name or any other information that could identify you will not be released. We will require that other collaborators keep your anonymized medical information confidential.

We will not give your genetic research results to anyone, unless required by law. “Anyone” includes you, your family, your insurance company, and your employer. Your genetic results are for research purposes only and have no established use for clinical diagnosis or treatment. Even with these precautions and although your sample and your information are coded, we cannot guarantee that a connection between you and your results will not be established.

As part of the Research Services Quality Assurance role, this study may be audited by the Manager of Quality Assurance. You research records and CAMH records may be reviewed, during which confidentiality will be maintained as per CAMH policies and to the extent permitted by law.

6. What will happen to my sample and my medical information?

We will work with your coded sample and will store your sample securely for an indefinite period of time. We will require anyone handling your sample to hold the research information and any results in confidence so as not to be able to divulge them to a third party without the approval from us.
7. Is my participation voluntary? What happens if I no longer wish to take part in the study?

Taking part in this study is entirely voluntary. You may decide not to take part or you may decide to take part and then change your mind. You can withdraw from the study at any time without giving a reason and without affecting your future medical treatment. If you withdraw from this study, all biological samples will be destroyed including any genetic material. However, we will keep any genetic results and clinical information collected up to that point.

8. Can I be excluded from the study?

You are being asked to participate in the genetics part of the study because you have qualified for the main study. In special cases, your sample may not be used and will be destroyed. This might occur if the study is stopped for other reasons.

9. Will I benefit financially from the study?

For compensation for your time and effort in participating in the study you will be mailed a $25 gift card once we receive your saliva sample back in the mail. The results of this research might be used for commercial and/or intellectual property (for example, patents) purposes by our group, or to another party to which we might license or sell them. There is no intention to provide financial compensation to you as a research participant.

10. Will I be contacted again?

After study entry, you will be contacted by e-mail to complete follow-up questions. This is a very important part of your participation in the study as we need to know how the smoking cessation medication that was provided to you affected your smoking behaviour. If you agree, we may contact you in the future to invite you to participate in other studies at the Centre for Addiction and Mental Health. If you would prefer not to be contacted for participation in future research, this will not affect your participation in this study.

Conclusion

If you agree to take part in the study, please click “I Agree” below. If you have unanswered questions please click on the “I have questions” button below. The study staff will be more than happy to answer any questions about this research and will respond to your questions by e-mail.

Contact Name

If you would rather speak to someone, please contact Dr. Laurie Zawertailo at telephone number 416-535-8501 x77422 at any time if you have questions about this study or wish to withdraw from this research. For questions about your rights as a research participant, contact Dr. Padraig Darby of the Research Ethics Board at telephone number 416-535-8501 x6876.
PATIENT CONSENT FORM

Clicking on the “I Agree to participate” button below, indicates that:

- I voluntarily agree to take part in this study.
- I have read this informed consent form and had the opportunity to ask about anything I do not understand. I am satisfied with the answers I have been given.
- I have been given the time to consider whether or not to take part in this research.
- I am aware that I am free to withdraw from the study at any time and that this withdrawal would not affect my future medical treatment.
- Information will be treated in the strictest confidence. By signing and dating this consent form I agree that ethics committees/institutional review boards can and will access my medical records for research purposes.
- I agree to my sample being used in this study and in any future research
- I agree that Dr. Zawertailo’s research group may apply for and use patents relating to the research results, records and developments. I acknowledge that I will not derive any financial benefit from these patents and applications.
Appendix 6. Big Five Aspect Scale Personality Test

Here are a number of characteristics that may or may not describe you. For example, do you agree that you seldom feel blue, compared to most other people? Please fill in the number that best indicates the extent to which you agree or disagree with each statement listed below. Be as honest as possible, but rely on your initial feeling and do not think too much about each item.

Use the following scale:

1 - - - - - - - 2 - - - - - - - 3 - - - - - - - 4 - - - - - - - 5
StronglyNeither AgreeStronglyDisagreeNor DisagreeAgree

1. ___ Seldom feel blue.
2. ___ Am not interested in other people's problems.
3. ___ Carry out my plans.
4. ___ Make friends easily.
5. ___ Am quick to understand things.
6. ___ Get angry easily.
7. ___ Respect authority.
8. ___ Leave my belongings around.
9. ___ Take charge.
10. ___ Enjoy the beauty of nature.
11. ___ Am filled with doubts about things.
12. ___ Feel others' emotions.
13. ___ Waste my time.
14. ___ Am hard to get to know.
15. ___ Have difficulty understanding abstract ideas.
16. ___ Rarely get irritated.
17. ___ Believe that I am better than others.
18. ___ Like order.
19. ___ Have a strong personality.
20. ___ Believe in the importance of art.
21. ___ Feel comfortable with myself.
22. ___ Inquire about others' well-being.
23. ___ Find it difficult to get down to work.
24. ___ Keep others at a distance.
25. ___ Can handle a lot of information.
26. ___ Get upset easily.
27. ___ Hate to seem pushy.
28. ___ Keep things tidy.
29. ___ Lack the talent for influencing people.
30. ___ Love to reflect on things.
31. ___ Feel threatened easily.
32. ___ Can't be bothered with other's needs.
33. ___ Mess things up.
34. ___ Reveal little about myself.
35. ___ Like to solve complex problems.
36. ___ Keep my emotions under control.
37. ___ Take advantage of others.
38. ___ Follow a schedule.
39. ___ Know how to captivate people.
40. ___ Get deeply immersed in music.
41. ___ Rarely feel depressed.
42. ___ Sympathize with others' feelings.
43. ___ Finish what I start.
44. ___ Warm up quickly to others.
45. ___ Avoid philosophical discussions.
46. __ Change my mood a lot.
47. __ Avoid imposing my will on others.
48. __ Am not bothered by messy people.
49. __ Wait for others to lead the way.
50. __ Do not like poetry.
51. __ Worry about things.
52. __ Am indifferent to the feelings of others.
53. __ Don't put my mind on the task at hand.
54. __ Rarely get caught up in the excitement.
55. __ Avoid difficult reading material.
56. __ Rarely lose my composure.
57. __ Rarely put people under pressure.
58. __ Want everything to be “just right.”
59. __ See myself as a good leader.
60. __ Seldom notice the emotional aspects of paintings and pictures.
61. __ Am easily discouraged.
62. __ Take no time for others.
63. __ Get things done quickly.
64. __ Am not a very enthusiastic person.
65. __ Have a rich vocabulary.
66. __ Am a person whose moods go up and down easily.
67. __ Insult people.
68. __ Am not bothered by disorder.
69. __ Can talk others into doing things.
70. __ Need a creative outlet.
71. __ Am not embarrassed easily.
72. __ Take an interest in other people's lives.
73. __ Always know what I am doing.
74. __ Show my feelings when I'm happy.
75. __ Think quickly.
76. __ Am not easily annoyed.
77. __ Seek conflict.
78. __ Dislike routine.
79. __ Hold back my opinions.
80. __ Seldom get lost in thought.
81. __ Become overwhelmed by events.
82. __ Don't have a soft side.
83. __ Postpone decisions.
84. __ Have a lot of fun.
85. __ Learn things slowly.
86. __ Get easily agitated.
87. __ Love a good fight.
88. __ See that rules are observed.
89. __ Am the first to act.
90. __ Seldom daydream.
91. __ Am afraid of many things.
92. __ Like to do things for others.
93. __ Am easily distracted.
94. __ Laugh a lot.
95. __ Formulate ideas clearly.
96. __ Can be stirred up easily.
97. __ Am out for my own personal gain.
98. __ Want every detail taken care of.
99. __ Do not have an assertive personality.
100. __ See beauty in things that others might not notice.
BFAS Scoring Key:

**Neuroticism**

**Agreeableness**
Compassion: 2R, 12, 22, 32R, 42, 52R, 62R, 72, 82R, 92

**Conscientiousness**

**Extraversion**
Enthusiasm: 4, 14R, 24R, 34R, 44, 54R, 64R, 74, 84, 94

**Openness/Intellect**
Openness: 10, 20, 30, 40, 50R, 60R, 70, 80R, 90R, 100

Reverse response scores for items followed by “R” (i.e. 1=5, 2=4, 4=2, 5=1). To compute scale scores, average completed items within each scale. To compute Big Five scores, average scores for the two aspects within each domain.

Reference:

Contact Colin DeYoung (cdeyoung@umn.edu) for additional information.
Appendix 7. Enrollment Confirmation Email

Dear [PATIENT-FIRSTNAME],

Congratulations! You have successfully enrolled in the MATCH Study and are eligible to receive 12 weeks of [MEDICATION-GROUP]. This e-mail contains important information on what you need to do next.

**Here is the email you registered with:** [PATIENT-EMAIL]
Please note this information, as you will be contacted via this e-mail with instructions to fill out the follow-up survey.

---

**What you need to do next:**

You will find **three** documents attached to this e-mail:

**Step 1:** Click to open the document titled MATCH Study Information and Consent Form. Please print this for your records.

**Step 2:** Click to open the document titled LETTER to the DOCTOR. **Print this document.**

**Step 3:** Click to open the document titled STANDARD SCRIPT. **Print this document also.**

**Step 4:** Make an appointment with your physician about smoking cessation within the **next five weeks**. During the visit, forward the LETTER to the DOCTOR, and the STANDARD SCRIPT to your physician. If your doctor agrees that it is safe for you to take the medication, he/she needs to sign and fax the STANDARD SCRIPT to our research pharmacy. Please note that your doctor may advise you not to take the medication that has been assigned to you.

**Step 5:** The **pharmacy will call** you to confirm your mailing address and will send you 12 weeks of assigned medication by courier.

Please NOTE that you will also receive a Saliva Collection kit in mail once you visit your doctor and the phone counseling is completed by the pharmacy. Prior to starting the medication, you will need to provide a small sample of your saliva. Detailed instructions are included with the package. You will be compensated with a $10 gift card once we receive your sample back in mail.

Thank you for participating in the MATCH Study.

Best regards,

The MATCH Study Team
Appendix 8. Letter to the Doctor

Date: [PATIENT-SCREENING_DATE]

RE: Your patient’s decision to participate in a research study and the action requested from you

<table>
<thead>
<tr>
<th>Study Title:</th>
<th>Medication Aids for Tobacco Cessation and Health (MATCH) Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective:</td>
<td>The purpose of the study is to measure the long-term quit rates associated with bupropion and varenicline treatment in a real-world setting, outside clinical trials.</td>
</tr>
<tr>
<td>Design:</td>
<td>Open-label, Randomized Controlled Trial</td>
</tr>
<tr>
<td>Intervention:</td>
<td>12 weeks of bupropion or varenicline (randomly assigned) or neither (when doctor decides not to prescribe) plus weekly motivational emails</td>
</tr>
<tr>
<td>Significance:</td>
<td>If the proposed trial on providing free medication mailed to smokers is proven to be logistically feasible and effective in terms of cessation rates, it would provide an innovative way to target and substantially reduce the overall prevalence of smoking in Ontario as part of a comprehensive tobacco control strategy. This can help reduce prevalence of smoking, as well as the cost its consequences have for our healthcare system.</td>
</tr>
<tr>
<td>Investigators:</td>
<td>Dr. Laurie Zawertailo (Principal Investigator), Dr. Peter Selby (Co-Investigator),</td>
</tr>
<tr>
<td>REB/IRB:</td>
<td>The research methods and protocol for this study have been approved by the standing Research Ethics Board at the Centre for Addiction and Mental Health.</td>
</tr>
</tbody>
</table>

Dear Physician,

This is to inform you that your patient, [PATIENT-FIRSTNAME] [PATIENT-LASTNAME] has chosen to participate in the aforementioned research study. According to the study’s eligibility criteria the patient has qualified for the study; however, the protocol resigns to your discretion to prescribe the assigned medications, [MEDICATION-GROUP] to this patient. As the prescribing physician, the study intends to fully defer to the patient-doctor relationship and thus leave the patient under your clinical care. The study is beneficial to your patient as it offers 12 weeks of [MEDICATION-GROUP] free of charge. The medication is delivered to the patient via mail from the Research Pharmacy. It is necessary for the Research Pharmacy to receive a signed prescription from you; please use the enclosed Standard Script.

We have embarked on a number of tobacco control initiatives ranging from research to training. If you wish to learn more about these projects or have questions or comments about this particular study please feel free to contact us.

Sincerely,

Dr. Laurie Zawertailo
Scientist, Clinical Neuroscience
Centre for Addiction and Mental Health
laurie.zawertailo@camh.ca
T: 416-535-8501 ext. 77422

Dr. Peter Selby
Clinical Director, Nicotine Dependence Clinic
Centre for Addiction and Mental Health
peter.selby@camh.ca
T: 416-535-8501 ext. 77432
Appendix 9.a. Standard Script- Bupropion

Study Title: Medication Aids for Tobacco Cessation and Health (MATCH Study)

Principal Investigator: Dr. Laurie Zawertailo
Institutional Affiliation: Centre for Addiction and Mental Health (CAMH), 175 College St. Toronto, ON M5T 1P7 (416) 535-8501 ext. 77422

Patient’s Medical Information

Current medications: 
Allergies: 
Other:

Rx
Bupropion SR 150 mg for 12 weeks. Start taking the medication about 7-14 days before quit date. Take 1 tablet once daily for first three days, then twice daily for the remainder of 12 weeks.

MAY CAUSE DROWSINESS. ALCOHOL MAY INTENSIFY EFFECT. AVOID DRIVING VEHICLES AND OPERATING MACHINES UNTIL REASONABLY CERTAIN THAT MEDICATION DOES NOT AFFECT YOUR MENTAL ALERTNESS OR PHYSICAL COORDINATION.

Patient’s Medical Information

M.D.

Name 
CPSO # 
Signature 
ADDRESS 
TELEPHONE # 
E-MAIL ADDRESS

This form is void after 36 days from: [PATIENT-SCREENING_DATE]

Must fax signed copy of this form from physician’s office to the research Pharmacy:

Fax: 1 800 563 8934
Phone: 905 770 9795
Appendix 9.b. Standard Script - Varenicline

Study Title: Medication Aids for Tobacco Cessation and Health (MATCH Study)

Principal Investigator: Dr. Laurie Zawertailo
Institutional Affiliation: Centre for Addiction and Mental Health (CAMH),
175 College St. Toronto, ON
MST 1P7 (416) 535-8501 ext. 77422

Rx
Varenicline tartrate for 12 weeks. Start taking the medication about 7-14 days before quit date. Take 0.5 mg once daily for first three days, then 0.5 mg twice daily for next four days, then 1 mg twice daily for the remainder of 12 weeks.

MAY CAUSE DROWSINESS. ALCOHOL MAY INTENSIFY EFFECT. AVOID DRIVING VEHICLES AND OPERATING MACHINES UNTIL REASONABLY CERTAIN THAT MEDICATION DOES NOT AFFECT YOUR MENTAL ALERTNESS OR PHYSICAL COORDINATION.

Patient’s Medical Information

Current medications:

Allergies:

Other:

M.D.

Name

Signature

CPSO #

ADDRESS

TELEPHONE #

E-MAIL ADDRESS

Must fax signed copy of this form from physician’s office to the research Pharmacy:

Fax: 1 800 563 8934
Phone: 905 770 9795
Appendix 11. MATCH Weekly Motivational Emails

Subject Line: “MATCH Study Quitting smoking tip of the week #”

[Introduction statements for all weekly motivational emails]:

“Congratulations on your decision to quit smoking! In addition to using smoking cessation medications such as bupropion and varenicline, and behavioural support such as smoker’s Helpline Online (www.smokershelpline.ca), there are several other things you can do to help you quit smoking.

[Insert weekly tip]:

Weekly Tip #1:
Creating a smoke-free environment is important during your quit attempt. Make a decision not to smoke in your home and vehicle and ask others to do the same. If your entire home cannot go smoke-free, explore areas where you can restrict smoking. At work, avoid smoking areas during your breaks. Making your physical environment smoke-free can help reinforce your decision to quit smoking.

Weekly Tip #2:
Support systems are important during any big change. Identify all of the positive supports in your life and tell them you are quitting smoking and need their support. Also identify any negative influences who may not want you to quit and figure out how you are going to deal with them during this time. Take advantage of other supports available to you, such as Smoker's Helpline, websites, your doctors or other health care providers. Surrounding yourself with positive and supportive people can help you quit and stay quit.

Weekly Tip #3:
Slips and lapses are a part of the quitting process and can be common. Use any slip or lapse as a learning experience. Identify what happened, how you could have prevented the situation, and what you can do if you’re in the situation again. Use these experiences to re-assess your quit plan and then try quitting again. It is important that you realize your quit attempt is not over; refocus and restart immediately after your lapse. Remember, quitting smoking is a process not an event and may take several attempts before you get it right. If you’re taking smoking cessation medications, it is very important that you continue taking the medication as directed.

Weekly Tip #4:
One of the benefits of quitting smoking is the amount of money you save. The price of a pack of cigarettes is about $12; so that means if you smoked about 15 cigarettes a day you would save about $810 in three months (enough to purchase a new 42-inch flat-screen LED HD TV) or $3,240 in one year (enough for a long vacation abroad or a whole new wardrobe). In 10 years you will have enough money to make a down payment on a house! Therefore, take advantage of quitting smoking and reward yourself. You deserve it and you can now afford it.

You
can also download a free quit meter by visiting http://www.dedicateddesigns.com/qk/. The quit meter with help you track various statistics and milestones as you quit smoking to keep you motivated.

**Weekly Tip #5:**

Quitting smoking is a significant change in your life that can transform how you think of yourself. Sit back and picture yourself as a confident non-smoker...close your eyes and visualize yourself socializing with family and friends, going through your daily routines, or dealing with a problem. Imagine not having to think about smoking or searching for your cigarettes or matches. Now, feel yourself relaxed, see yourself confident and without the craving for a cigarette. Guess what? You’ll be there sooner than you think!

**Weekly Tip #6:**

Your smoking may be associated with certain people, places, or things. These can act as triggers for you to want to smoke. Identify your personal triggers and think about how you will deal with them. For example, change your day-to-day routine or find alternative activities to smoking. Problem solving ahead of time can help you deal with these situations when they arise and help you quit and stay quit.

**Weekly Tip #7:**

While it’s not easy for most people, quitting smoking has many positive results. In addition to the long-term health benefits of quitting smoking, there are many benefits you’ll notice immediately. For example, within days and weeks of quitting smoking you may notice that you have more energy, better smell and taste, whiter teeth and fresher breath. To reinforce your motivation, make a list of all of the benefits of quitting smoking and keep it close by.

**Weekly Tip #8:**

There are many good reasons why people want to quit smoking. Sometimes it’s easy to forget why you wanted to quit in the first place. Write down your personal reasons for quitting and use them as reminders when things seem tough. Your reasons may change over time so review your list regularly. Reminding yourself of all the reasons you want to quit can help you stay focused on achieving your goal.

**Weekly Tip #9:**

Quitting smoking can make a big difference to your health and the health of your family (and others who are around you). Among smokers who have already had a heart attack, quitting smoking reduces the chance of a second heart attack by 50%, compared to those who continue to smoke. Also, when non-smokers are exposed to second hand smoke, even occasionally, their risk of coronary heart disease increases by more than 50%. The message is clear: when you quit smoking everyone benefits!
Weekly Tip #10:

When some smokers quit, they need to find something to do with their hands. You may want to pick up a new activity, such as knitting, writing or reading.

Some people find that they have a lot of extra time when they quit smoking, which can lead to boredom. Starting a new hobby is a good idea.

People who used to smoke during their breaks at work might need to find something new to do during those breaks after they quit smoking. Spending the break with non-smoking colleagues is a good option; taking a brief walk is also a healthy alternative.

Weekly Tip #11:

It’s very common for people to experience withdrawal symptoms and cravings for several weeks after they quit smoking. Withdrawal symptoms are unpleasant but they’ll pass. Cravings are momentary feelings and will pass within 20 minutes. When you experience withdrawal remind yourself that each symptom is a sign of recovery – your body is healing itself.

Weekly Tip #12:

Someone may offer you a cigarette while you are trying to quit smoking. This is a high-stakes situation because often one cigarette is enough to make you start smoking again. So, what can you do in these scenarios?
- you can politely say “No thanks” – no explanation required
- you can tell the person you’ve recently quit and ask for their support
- leave the scene momentarily (or avoid this person or situation in the future, if necessary)

[Closing statements for e-mails 1 to 11]:

“We will send you another motivational tip next week. Good luck with your quit attempt.”

[Closing statements for email 12]:

“We will email you follow-up questionnaires at about 3 months and 9 months from now that take about 5-10 minutes to complete. Even if you have not quit smoking yet, your answers are still very important to our research. Thank you and good luck with your quit attempt.”

[Included with Week 4 Email]

Please NOTE that you may receive a Saliva Collection kit in mail. You will need to provide a small sample of your saliva and mail it back to us. Detailed instructions are included with the package. You will be compensated with a $25 gift card once we receive your sample back in mail.
Appendix 12. Week 4 Follow-Up Survey

We would like to ask you some questions about your smoking behaviour. All of your responses will be kept completely confidential and will only be available to the study investigators. The results we report will not identify you. You may refuse to answer any of the survey questions and are free to withdraw from the study at any time and for any reason. If you have questions or concerns regarding the ethics of this study, please contact Dr. Padraig Darby, Chair of Research Ethics Board at the Centre for Addiction and Mental Health at 416-535-8501 ext. 6876 or padraig_Darby@camh.net.

1. At the present time, how often do you smoke cigarettes?
   - Daily [IF DAILY, GO TO QUESTION #3]
   - Occasionally / Non-daily [IF OCCASIONALLY / NON-DAILY, GO TO QUESTIONS #4, #5]
   - Not at all

2. Have you smoked a cigarette, even a puff, in the last 7 days?
   - Yes [IF YES, GO TO QUESTION #6]
   - No [IF NO, GO TO QUESTION #7, SKIP QUESTIONS #3, #4, #5]
   - Don’t know / prefer not to answer

3. How many cigarettes a day do you smoke now?
   - 10 or less
   - 11-20
   - 21-30
   - More than 30

4. On the days that you smoke, how many cigarettes do you usually smoke?
   - 5 or less
   - 6-10
   - 11 or more

5. In the past 30 days, on how many days did you smoke 1 or more cigarettes?
   - 10 or less
   - 11-20
   - 21-30

6. Since you enrolled in the study, have you stopped smoking, for one day or longer because you were trying to quit?
   - Yes
   - No
   - Don’t know / prefer not to answer
7. If you have quit, which statement best describes your smoking behavior since your quit date?

☐ I have not smoked since my quit date
☐ I have smoked rarely since my quit date (for example, less than once per week)
☐ There was a period where I smoked at least once per week for 2 weeks in a row OR there was a period where I smoked 7 days in a row
☐ I have not quit
☐ Don’t know / prefer not to answer

8. How helpful were the weekly motivational emails? (5 means you have found them to be very helpful and 1 means you did not find them helpful at all)

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

9. Were you able to make an appointment with your doctor to have the prescription signed after you enrolled in the study?

☐ Yes [IF YES, GO TO QUESTION #11]
☐ No [IF NO, GO TO QUESTION #10]
☐ Don’t know / prefer not to answer

10. If you were not able to make an appointment, what was the reason?

☐ I didn’t have a family doctor
☐ I had a family doctor but could not get an appointment within 5 weeks as the study required
☐ I made an appointment but did not keep it
☐ I changed my mind about quitting at the time
☐ Other [IF OTHER, GO TO QUESTION #2.1]
☐ Don’t know / prefer not to answer

2.1 Please specify other:

11. Did your doctor sign the Standard Script and prescribe you the assigned study medication?

☐ Yes [IF YES, GO TO QUESTION #12]
☐ No

12. Did you receive 12 weeks supply of medication in mail?

☐ Yes [IF YES, GO TO QUESTION #13]
☐ No

13. Have you started using the medication?

☐ Yes [IF YES, GO TO QUESTIONS #5.1, #9.1, #9.2, #9.3, #9.4, #9.5, #9.6, #9.7, #9.8, #15, #17]
14. If you have not started using the free bupropion/ varenicline, please indicate if any of the following reasons apply by choosing option "yes".
   6.1 I haven’t set a quit date:  
     [□] Yes  [□] No  [□] Don’t know / prefer not to answer
   6.2 I set a quit date but did not honour it:  
     [□] Yes  [□] No  [□] Don’t know / prefer not to answer
   6.3 I quit without bupropion or varenicline:  
     [□] Yes  [□] No  [□] Don’t know / prefer not to answer
   6.4 I changed my mind about quitting smoking:  
     [□] Yes  [□] No  [□] Don’t know / prefer not to answer
   6.5 Other reason(s):  [□] Yes  [□] No  [□] Don’t know / prefer not to answer

15. Are you continuing to use the free bupropion/ varenicline that was mailed to you?
   [□] Yes
   [□] No  [□] Don’t know / prefer not to answer

16. If you have stopped using the free bupropion/ varenicline, please indicate if any of the following reasons apply by choosing option "yes".
   8.1 Did not find it helpful:  
     [□] Yes  [□] No  [□] Don’t know / prefer not to answer
   8.2 Relapsed to smoking:  
     [□] Yes  [□] No  [□] Don’t know / prefer not to answer
   8.3 Did not know how to use it:  
     [□] Yes  [□] No  [□] Don’t know / prefer not to answer
   8.4 Stopped experiencing withdrawal or craving:  
     [□] Yes  [□] No  [□] Don’t know / prefer not to answer
   8.5 Quit smoking and I did not need it anymore:  
     [□] Yes  [□] No  [□] Don’t know / prefer not to answer
   8.6 Experienced side-effect(s):  
     [□] Yes  [□] No  [□] Don’t know / prefer not to answer
   8.7 Other reason(s):  [□] Yes  [□] No  [□] Don’t know / prefer not to answer
8.8 Please specify other reason(s):

________________________________________________________________________

17. Have you experienced any of the following side-effects?

9.1 Dry mouth:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

9.2 Trouble Sleeping:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

9.3 Vivid dreams:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

9.4 Rash:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

9.5 Nausea:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

9.6 Dizziness:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

9.7 Fatigue:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

9.8 Other side-effect(s):
[IF YES, GO TO QUESTION #9.9]

☐ Yes ☐ No ☐ Don’t know / prefer not to answer

9.9 Please specify other side-effect(s) experienced:

________________________________________________________________________

18. Did you use any nicotine replacement therapy (NRT) patch, gum, inhaler or lozenges over the last 4 weeks?
☐ Yes
☐ No
☐ Don’t know / prefer not to answer

19. Over the last 4 weeks, did you puff on an electronic cigarette, also known as an e-cigarette? Please include any e-cigarette with or without nicotine.
☐ Yes
☐ No
☐ Don’t know / prefer not to answer

20. Did you use e-cigarettes to help you to quit or reduce your smoking or to remain smoke free?
☐ Yes
☐ No
☐ Don’t know / prefer not to answer
21. Over the last 2 weeks, how often have you been bothered by any of the following problems? [SCORE: NOT AT ALL = 0, SEVERAL DAYS = 1, MORE THAN HALF THE DAYS = 2, NEARLY EVERY DAY = 3. PARTICIPANTS ARE PRESENTED WITH a) AND b) FIRST, IF SCORE A SUM OF 3 OR HIGHER FOR a) AND b), GO TO c) – i)]

a). Little interest or pleasure in doing things
- Not at all
- Several days
- More than half the days
- Nearly every day

b). Feeling down, depressed, or hopeless
- Not at all
- Several days
- More than half the days
- Nearly every day

c). Trouble falling or staying asleep, or sleeping too much
- Not at all
- Several days
- More than half the days
- Nearly every day

d). Feeling tired or having little energy
- Not at all
- Several days
- More than half the days
- Nearly every day

e). Poor appetite or overeating
- Not at all
- Several days
- More than half the days
- Nearly every day

f). Feeling bad about yourself, or that you are a failure, or have let yourself or your family down
- Not at all
- Several days
- More than half the days
- Nearly every day

g). Trouble concentrating on things, such as reading the newspaper or watching TV
- Not at all
- Several days
- More than half the days
- Nearly every day
h). Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around a lot more than usual

- Not at all
- Several days
- More than half the days
- Nearly every day

i). Thoughts that you would be better off dead, or of hurting yourself in some way

- Not at all
- Several days
- More than half the days
- Nearly every day

22. Please read this question carefully and pick out the one statement that best describes how you are feeling for the past 2 weeks. If several statements seem to apply equally well, select the one with the highest number:

- 0: I don’t have any thoughts of killing myself
- 1: I have thoughts of killing myself, but I would not carry them out
- 2: I would like to kill myself
- 3: I would kill myself if I had the chance

[IF SCORE 2 OR 3, GO TO QUESTION #1.1]

1.1 Please review your answer to question 22. If not correct, please select the correct option. If you have chosen the correct answer, please choose 'Answer to question 22 confirmed'.

- Answer to question 22 confirmed [IF ANSWER TO QUESTION 22 CONFIRMED, GO TO QUESTION #2]

2. If you scored "2" or "3" on question 22, please discontinue your use of varenicline/ bupropion and contact your physician immediately to report this feeling. If your physician is not immediately available, please go to the nearest Emergency Department.
Appendix 13. Week 8 Follow-Up Survey

We would like to ask you some questions about your smoking behaviour. All of your responses will be kept completely confidential and will only be available to the study investigators. The results we report will not identify you. You may refuse to answer any of the survey questions and are free to withdraw from the study at any time and for any reason. If you have questions or concerns regarding the ethics of this study, please contact Dr. Padraig Darby, Chair of Research Ethics Board at the Centre for Addiction and Mental Health at 416-535-8501 ext. 6876 or padraig_Darby@camh.net.

1. At the present time, how often do you smoke cigarettes?
   [ ] Daily [IF DAILY, GO TO QUESTION #3]
   [ ] Occasionally / Non-daily [IF OCCASIONALLY / NON-DAILY, GO TO QUESTIONS #4, #5]
   [ ] Not at all

2. Have you smoked a cigarette, even a puff, in the last 7 days?
   [ ] Yes [IF YES, GO TO QUESTION #6]
   [ ] No [IF NO, GO TO QUESTIONS #7 and #8, SKIP QUESTIONS #3, #4, #5]
   [ ] Don’t know / prefer not to answer

3. How many cigarettes a day do you smoke now?
   [ ] 10 or less
   [ ] 11-20
   [ ] 21-30
   [ ] More than 30

4. On the days that you smoke, how many cigarettes do you usually smoke?
   [ ] 5 or less
   [ ] 6-10
   [ ] 11 or more

5. In the past 30 days, on how many days did you smoke 1 or more cigarettes?
   [ ] 10 or less
   [ ] 11-20
6. Since you enrolled in the study, have you stopped smoking, for one day or longer because you were trying to quit?

☐ Yes
☐ No
☐ Don’t know / prefer not to answer

7. Have you smoked a cigarette, even a puff, in the last 30 days?

☐ Yes
☐ No
☐ Don’t know / prefer not to answer

8. If you have quit, which statement best describes your smoking behavior since your quit date?

☐ I have not smoked since my quit date
☐ I have smoked rarely since my quit date (for example, less than once per week)
☐ There was a period where I smoked at least once per week for 2 weeks in a row OR there was a period where I smoked 7 days in a row
☐ I have not quit
☐ Don’t know / prefer not to answer

9. How helpful were the weekly motivational emails? (5 means you have found them to be very helpful and 1 means you did not find them helpful at all)

☐ 1  ☐ 2  ☐ 3  ☐ 4  ☐ 5

10. Did you receive 12 weeks supply of the study medication you were assigned to?

☐ Yes [IF YES, GO TO QUESTION #11]
☐ No
☐ Don’t know / prefer not to answer

11. Have you started using the medication?

☐ Yes [IF YES, GO TO QUESTIONS #2.1, #6.1, #6.2, #6.3, #6.4, #6.5]
#6.5, #6.6, #6.7, #6.8, #13, #15

☐ No [IF NO, GO TO QUESTIONS #3.1, #3.2, #3.3, #3.4, #3.5, #12]

When did you start to use the medication? (2.1)

12. If you have not started using the free bupropion/ varenicline, please indicate if any of the following reasons apply by choosing option "yes".

3.1 I haven’t set a quit date:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

3.2 I set a quit date but did not honour it:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

3.3 I quit without bupropion or varenicline:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

3.4 I changed my mind about quitting smoking:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

3.5 Other reason(s): [IF YES, GO TO QUESTION #3.6]
☐ Yes ☐ No

3.6 Please specify other:

13. Are you continuing to use the free bupropion/ varenicline that was mailed to you?

☐ Yes

☐ No [IF NO, GO TO QUESTIONS #5.1, #5.2, #5.3, #5.4, #5.5, #5.6, #5.7, #14]

☐ Don’t know / prefer not to answer

14. If you have stopped using the free bupropion/ varenicline, please indicate if any of the following reasons apply by choosing option "yes".

5.1 Did not find it helpful:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

5.2 Relapsed to smoking:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

5.3 Did not know how to use it:
5.4 Stopped experiencing withdrawal or craving:

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

5.5 Quit smoking and I did not need it anymore:

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

5.6 Experienced side-effect(s):

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

5.7 Other reason(s): [IF YES, GO TO #5.8]

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

5.8 Please specify other reason(s):

15. Have you experienced any of the following side-effects?

6.1 Dry mouth:

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

6.2 Trouble Sleeping:

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

6.3 Vivid dreams:

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

6.4 Rash:

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

6.5 Nausea:

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

6.6 Dizziness:

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

6.7 Fatigue:

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

6.8 Other side-effect(s): [IF YES, GO TO QUESTION #6.9]

☐ Yes  ☐ No  ☐ Don’t know / prefer not to answer

6.9 Please specify other side-effect(s) experienced:
16. Did you use any nicotine replacement therapy (NRT) patch, gum, inhaler or lozenges over the last 4 weeks?

☐ Yes

☐ No

☐ Don’t know / prefer not to answer

17. Over the last 4 weeks, did you puff on an electronic cigarette, also known as an e-cigarette? Please include any e-cigarette with or without nicotine.

☐ Yes [IF YES, GO TO QUESTION #18]

☐ No

☐ Don’t know / prefer not to answer

18. Did you use e-cigarettes to help you to quit or reduce your smoking or to remain smoke free?

☐ Yes

☐ No

☐ Don’t know / prefer not to answer

19. Over the last 2 weeks, how often have you been bothered by any of the following problems?

[SCORE: NOT AT ALL = 0, SEVERAL DAYS = 1, MORE THAN HALF THE DAYS = 2, NEARLY EVERY DAY = 3. PARTICIPANTS ARE PRESENTED WITH a) AND b) FIRST, IF SCORE A SUM OF 3 OR HIGHER FOR a) AND b), GO TO c) – i)]

a). Little interest or pleasure in doing things

☐ Not at all

☐ Several days

☐ More than half the days

☐ Nearly every day

b). Feeling down, depressed, or hopeless
c). Trouble falling or staying asleep, or sleeping too much

- [ ] Not at all
- [ ] Several days
- [ ] More than half the days
- [ ] Nearly every day

d). Feeling tired or having little energy

- [ ] Not at all
- [ ] Several days
- [ ] More than half the days
- [ ] Nearly every day

e). Poor appetite or overeating

- [ ] Not at all
- [ ] Several days
- [ ] More than half the days
- [ ] Nearly every day

f). Feeling bad about yourself, or that you are a failure, or have let yourself or your family down

- [ ] Not at all
- [ ] Several days
More than half the days

Nearly every day

g). Trouble concentrating on things, such as reading the newspaper or watching TV

Not at all

Several days

More than half the days

Nearly every day

h). Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around a lot more than usual

Not at all

Several days

More than half the days

Nearly every day

i). Thoughts that you would be better off dead, or of hurting yourself in some way

Not at all

Several days

More than half the days

Nearly every day

20. Please read this question carefully and pick out the one statement that best describes how you are feeling for the past 2 weeks. If several statements seem to apply equally well, select the one with the highest number:

0: I don’t have any thoughts of killing myself

1: I have thoughts of killing myself, but I would not carry them out
☐ 2: I would like to kill myself

☐ 3: I would kill myself if I had the chance

[IF SCORE 2 OR 3, GO TO QUESTION #1.1]

1.1 Please review your answer to question 20. If not correct, please select the correct option. If you have chosen the correct answer, please choose 'Answer to question 20 confirmed'.

☐ Answer to question 20 confirmed

[IF ANSWER TO QUESTION 22 CONFIRMED, GO TO QUESTION #2]

2. If you scored "2" or "3" on question 20, please discontinue your use of varenicline/bupropion and contact your physician immediately to report this feeling. If your physician is not immediately available, please go to the nearest Emergency Department.
Appendix 14. Week 12 Follow-Up Survey

We would like to ask you some questions about your smoking behaviour. All of your responses will be kept completely confidential and will only be available to the study investigators. The results we report will not identify you. You may refuse to answer any of the survey questions and are free to withdraw from the study at any time and for any reason. If you have questions or concerns regarding the ethics of this study, please contact Dr. Padraig Darby, Chair of Research Ethics Board at the Centre for Addiction and Mental Health at 416-535-8501 ext. 6876 or padraig_Darby@camh.net.

1. At the present time, how often do you smoke cigarettes?
   - [ ] Daily [IF DAILY, GO TO QUESTION #4]
   - [ ] Occasionally / Non-daily [IF OCCASIONALLY / NON-DAILY, GO TO QUESTIONS #5, #6]
   - [ ] Not at all

2. Have you smoked a cigarette, even a puff, in the last 7 days?
   - [ ] Yes [IF YES, GO TO QUESTION #7, #9, #10]
   - [ ] No [IF NO, GO TO QUESTIONS #3, #11, #12, #13, SKIP #4, #5, #6]
   - [ ] Don’t know / prefer not to answer

3. Have you smoked a cigarette, even a puff, in the last 30 days?
   - [ ] Yes [IF YES, GO TO QUESTION #8]
   - [ ] No
   - [ ] Don’t know / prefer not to answer

4. How many cigarettes a day do you smoke now?
   - [ ] 10 or less
   - [ ] 11-20
   - [ ] 21-30
   - [ ] More than 30

5. On the days that you smoke, how many cigarettes do you usually smoke?
   - [ ] 5 or less
   - [ ] 6-10

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6. In the past 30 days, on how many days did you smoke 1 or more cigarettes?

☐ 10 or less
☐ 11-20
☐ 21-30

7. Since you enrolled in the study, have you stopped smoking, for one day or longer because you were trying to quit?

☐ Yes [IF YES, GO TO QUESTION #8]
☐ No
☐ Don’t know / prefer not to answer

8. What is the longest number of days in a row that you went without smoking since you enrolled in the study? ________________________________

9. On a scale of 1 to 10 where 10 means this is the most important thing you have to do and 1 is the least important, how important is it for you to be quitting smoking altogether? ________________________________

10. On a scale of 1 to 10 where 10 means you are very confident that you can quit smoking and 1 means you have very little confidence, how confident are you that you can quit smoking altogether? ________________________________

11. If you have quit, which statement best describes your smoking behavior since your quit date?

☐ I have not smoked since my quit date
☐ I have smoked rarely since my quit date (for example, less than once per week)
☐ There was a period where I smoked at least once per week for 2 weeks in a row OR there was a period where I smoked 7 days in a row
☐ I have not quit
☐ Don’t know / prefer not to answer

12. On a scale of 1 to 10 where 10 means this is the most important thing you have to do and 1 is the least important, how important is it for you to continue to not smoke? ________________________________
13. On a scale of 1 to 10 where 10 means you are very confident that you can quit smoking and 1 means you have very little confidence, how confident are you that you can continue to not smoke? ___________________________

14. How helpful were the weekly motivational emails? (5 means you have found them to be very helpful and 1 means you did not find them helpful at all)

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

15. Did you receive 12 weeks supply of the study medication you were assigned to?

☐ Yes [IF YES, GO TO QUESTION #16]

☐ No

☐ Don’t know / prefer not to answer

16. Have you started using the medication?

☐ Yes [IF YES, GO TO QUESTIONS #2.1, #6.1, #6.2, #6.3, #6.4, #6.5, #6.6, #6.7, #6.8, #18, #20]

☐ No [IF NO, GO TO QUESTIONS #3.1, #3.2, #3.3, #3.4, #3.5, #17]

When did you start to use the medication? (2.1) ___________________________

17. If you have not started using the free bupropion/ varenicline, please indicate if any of the following reasons apply by choosing option "yes".

3.1 I haven’t set a quit date:

☐ Yes ☐ No ☐ Don’t know / prefer not to answer

3.2 I set a quit date but did not honour it:

☐ Yes ☐ No ☐ Don’t know / prefer not to answer

3.3 I quit without bupropion or varenicline:

☐ Yes ☐ No ☐ Don’t know / prefer not to answer

3.4 I changed my mind about quitting smoking:

☐ Yes ☐ No ☐ Don’t know / prefer not to answer

3.5 Other reason(s): [IF YES, GO TO QUESTION #3.6]

☐ Yes ☐ No

3.6 Please specify other:

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18. Have you finished using all of the free bupropion / varenicline that was mailed to you?

☐ Yes

☐ No [IF NO, GO TO QUESTIONS #5.1, #5.2, #5.3, #5.4, #5.5, #5.6, #5.7, #5.8, #19]

☐ Don’t know / prefer not to answer

19. If you did not finish using all of the free bupropion/ varenicline, please indicate if any of the following reasons apply by choosing option “yes”.

5.1 Still using it:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

5.2 Did not find it helpful:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

5.3 Relapsed to smoking:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

5.4 Did not know how to use it:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

5.5 Stopped experiencing withdrawal or craving:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

5.6 Quit smoking and I did not need it anymore:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

5.7 Experienced side-effect(s):
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

5.8 Other reason(s): [IF YES, GO TO QUESTION #5.9]
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

5.9 Please specify other:

20. Have you experienced any of the following side-effects?

6.1 Dry mouth:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

6.2 Trouble Sleeping:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

6.3 Vivid dreams:
6.4 Rash:  
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

6.5 Nausea:  
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

6.6 Dizziness:  
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

6.7 Fatigue:  
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

6.8 Other side-effect(s):  
[IF YES, GO TO QUESTION #6.9]
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

6.9 Please specify other side-effect(s) experienced:

21. Did you use any nicotine replacement therapy (NRT) patch, gum, inhaler or lozenges over the last 4 weeks?

☐ Yes

☐ No

☐ Don’t know / prefer not to answer

22. Over the last 4 weeks, did you puff on an electronic cigarette, also known as an e-cigarette? Please include any e-cigarette with or without nicotine.

☐ Yes  
[IF YES, GO TO QUESTION #23]

☐ No

☐ Don’t know / prefer not to answer

23. Did you use e-cigarettes to help you to quit or reduce your smoking or to remain smoke free?

☐ Yes

☐ No
24. What benefits have you noticed since quitting smoking or reducing how much you smoke? (Check all that apply)

- [ ] More money
- [ ] Breathe easier
- [ ] More energy
- [ ] Increased confidence
- [ ] Feel better about myself
- [ ] I haven’t noticed any benefits
- [ ] Don’t know / prefer not to answer
- [ ] Other
- [ ] Not applicable (I have not quit or reduced my smoking)

25. Have you experienced any of the following symptoms that you think are related to quitting or reducing your smoking after enrolling in the study?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know / prefer not to answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irritable / Cranky</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inability to concentrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hunger / Increased Appetite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other symptom(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Please specify other symptom(s) experienced:

26. Did any of the following make it harder for you to quit or reduce your smoking after enrolling in the study?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know / prefer not to answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cravings:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boredom:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking alcohol:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Being around other smokers:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please specify other:

27. Did you seek any of the following additional resources to help you quit or reduce smoking while participating in the study?

<table>
<thead>
<tr>
<th>Resource</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know / prefer not to answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-help booklets:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers’ helpline (phone, web, or text services):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual counseling:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-session group counseling workshop:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Multi-session group counseling workshops:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

Other:
☐ Yes ☐ No ☐ Don’t know / prefer not to answer

Please specify other:

28. Over the last 2 weeks, how often have you been bothered by any of the following problems?

[SCORE: NOT AT ALL = 0, SEVERAL DAYS = 1, MORE THAN HALF THE DAYS = 2, NEARLY EVERY DAY = 3. PARTICIPANTS ARE PRESENTED WITH a) AND b) FIRST, IF SCORE A SUM OF 3 OR HIGHER FOR a) AND b), GO TO c) – i)]

a). Little interest or pleasure in doing things

☐ Not at all
☐ Several days
☐ More than half the days
☐ Nearly every day

b). Feeling down, depressed, or hopeless

☐ Not at all
☐ Several days
☐ More than half the days
☐ Nearly every day

c). Trouble falling or staying asleep, or sleeping too much

☐ Not at all
☐ Several days
☐ More than half the days
☐ Nearly every day
d). Feeling tired or having little energy

☐ Not at all
☐ Several days
☐ More than half the days
☐ Nearly every day

e). Poor appetite or overeating

☐ Not at all
☐ Several days
☐ More than half the days
☐ Nearly every day

f). Feeling bad about yourself, or that you are a failure, or have let yourself or your family down

☐ Not at all
☐ Several days
☐ More than half the days
☐ Nearly every day

g). Trouble concentrating on things, such as reading the newspaper or watching TV

☐ Not at all
☐ Several days
☐ More than half the days
☐ Nearly every day

h). Moving or speaking so slowly that other people could have noticed. Or the opposite; being so fidgety or restless that you have been moving around a lot more than usual

☐ Not at all
Several days
More than half the days
Nearly every day

i). Thoughts that you would be better off dead, or of hurting yourself in some way

Not at all
Several days
More than half the days
Nearly every day

29. Please read this question carefully and pick out the one statement that best describes how you are feeling for the past 2 weeks. If several statements seem to apply equally well, select the one with the highest number:

0: I don’t have any thoughts of killing myself
1: I have thoughts of killing myself, but I would not carry them out
2: I would like to kill myself
3: I would kill myself if I had the chance  [IF SCORE 2 OR 3, GO TO QUESTION #1.1]

1.1 Please review your answer to question 20. If not correct, please select the correct option. If you have chosen the correct answer, please choose 'Answer to question 20 confirmed'.

Answer to question 20 confirmed  [IF ANSWER TO QUESTION 22 CONFIRMED, GO TO QUESTION #2]

2. If you scored "2" or "3" on question 20, please discontinue your use of varenicline/bupropion and contact your physician immediately to report this feeling. If your physician is not immediately available, please go to the nearest Emergency Department.
Appendix 15. Saliva Sample Collection Instructions

Preparation – BEFORE COLLECTION

1. Remove lipstick and/or lip balm and avoid using any creams or lotions containing steroids 24 hours before collection, if possible.
2. It is preferred that you do not eat or drink and do not brush or floss teeth 30 minutes before collecting the saliva sample.
3. Wash your hands with soap and water and dry them thoroughly.
4. It is also preferred that you proceed with Instructions for collecting saliva in the morning before breakfast and before smoking.

Please wait to collect the saliva sample until you have time to mail it. It is important to mail the saliva sample on the same day it is collected.

Instructions – WHEN YOU ARE READY TO START COLLECTING SALIVA

1. Remove the specimen bag containing small plastic container from the smaller bubble-padded envelope labeled as “Exempt Human Specimen”.
2. Take out the small plastics container out from the plastic bag.
3. To give your saliva sample, please see the instructions on the next page and follow steps 1 - 7.
4. Once you have given your saliva sample, place the container back into the Biohazard Specimen Bag, remove as much air as possible, and seal it (do NOT remove the absorbent sheet).
5. Then, place the specimen bag containing the saliva sample back into the smaller bubble-padded envelope labeled as “Exempt Human Specimen”.
6. Seal the bubble envelope properly and mail it immediately. Postage has already been prepaid.

Remember: It is important to mail the saliva sample on the same day it is collected.

If you have any questions, please contact us:
By e-mail: match.study@camh.ca
By phone: (416)535-8501 ext: 77297
Saliva Collection Container

1. Remove the Inner Container from the Outer Container

2. Remove Cap from Inner Container

3. Remove Cotton Swab from Inner Container

4. Place Cotton Swab under your tongue - hold there for 2 minutes

5. Return Cotton Swab to the Inner Container

6. Replace Cap on Inner Container - Snap on Tightly

7. Place Inner Container into Outer Container - Snap Together Tightly

Completed Saliva Sample Collection Container

Please make sure the Cotton Swab is wet!

On the container label, please write the DATE and TIME you gave your sample.
Appendix 16. Saliva Sample Analysis Protocol

Determination of nicotine, cotinine and 3-hydroxycotinine in biological samples- Maria Novalen- 2011-06

Background

Nicotine is the main constituent of tobacco that is responsible for the addictive properties of cigarettes and other tobacco-containing products. In humans, about 80% of nicotine is metabolized to cotinine, with hepatic CYP 2A6 catalyzing 90% of the reaction. The major metabolic pathways of nicotine are shown in Figure below. The ratio of trans-3`-hydroxycotinine to cotinine is strongly correlated with the oral clearance of nicotine and can be used as a marker of the rate of nicotine metabolism.
Chemicals

Nicotine and cotinine were obtained from Sigma Aldrich, trans-3'-hydroxycotinine and the internal standards nicotine-d₄, rac-cotinine-d₃ and trans-3'-hydroxycotinine-d₃ were purchased from Toronto Research Chemicals.

Specimen

Whole blood, plasma, saliva or urine kept in -30°C prior to analysis.

Calibration curve:

<table>
<thead>
<tr>
<th>Name of standard</th>
<th>Final concentration (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>Nicotine 1000&lt;br&gt;Cotinine 1000&lt;br&gt;3-Hydroxycotinine 1000</td>
</tr>
<tr>
<td>500</td>
<td>Nicotine 500&lt;br&gt;Cotinine 500&lt;br&gt;3-Hydroxycotinine 500</td>
</tr>
<tr>
<td>100</td>
<td>Nicotine 100&lt;br&gt;Cotinine 100&lt;br&gt;3-Hydroxycotinine 100</td>
</tr>
<tr>
<td>10</td>
<td>Nicotine 100&lt;br&gt;Cotinine 10&lt;br&gt;3-Hydroxycotinine 10</td>
</tr>
<tr>
<td>1</td>
<td>Nicotine 1&lt;br&gt;Cotinine 1&lt;br&gt;3-Hydroxycotinine 1</td>
</tr>
</tbody>
</table>

Standards prepared in 0.01 M HCL and stored in -30°C.

The standard curve is calibrated with linear function and 1/x weighing. Coefficient of correlation should be > 0.99. LOQ for nicotine, cotinine and 3-hydroxycotinine = 1 ng/ml.

Internal standards:

Working solution 20 ng/ml of nicotine-d₄, cotinine-d₃ and trans-3'-hydroxycotinine-d₃ prepared in 0.01 M HCl.

Instrumentation

*HPLC system:*
HPLC system (Agilent 1260 LC system): Agilent 1260 Quaternary pump, Agilent 1260 Inifinity Standard Autosampler and temperature-controlled column compartment.

*Column:*
The separation of nicotine, cotinine and 3-hydroxycotinine on Synergi Polar RP column (150 x 4.6 mm I.D.; particle size 4 micron) (Phenomenex). Kept at ambient temperature during analysis.
Flow rate:
0.7 ml/min.

HPLC gradient:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Flow (ml/min)</th>
<th>10 mM ammonium acetate / 0.1% acetic acid in water (A)</th>
<th>10 mM ammonium acetate / 0.1% acetic acid in methanol (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.7</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>6.5</td>
<td>0.7</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>8.0</td>
<td>0.7</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>8.1</td>
<td>0.7</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>13.0</td>
<td>0.7</td>
<td>80</td>
<td>20</td>
</tr>
</tbody>
</table>

Mass spectrometry:
Instrument: Agilent 6430 Triple Quadrupole LC/MS system
Software: MassHunter software.
Acquisition mode: multiple reaction monitoring (MRM)
Ionization: atmospheric pressure ionization (APCI)
Vaporizer temperature: 450°C
Gas temperature: 350°C
Gas flow: 5 l/min
Nebulizer pressure: 40 psi
Capillary voltage: 4500 V
Corona discharge current: 5 µamps
Collision energy: 35 eV for cotinine and cotinine-d₃, 30 eV for 3HC and 3HC-d₃ and 20 eV for nicotine and nicotine-d₄.

SRM transitions monitored:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Transition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>163 (\rightarrow) 84</td>
</tr>
<tr>
<td>Nicotine-d₄</td>
<td>167 (\rightarrow) 84</td>
</tr>
<tr>
<td>Cotinine</td>
<td>177 (\rightarrow) 80</td>
</tr>
<tr>
<td>Cotinine-d₃</td>
<td>180 (\rightarrow) 80</td>
</tr>
<tr>
<td>3-Hydroxycotinine</td>
<td>193 (\rightarrow) 80</td>
</tr>
<tr>
<td>3-Hydroxycotinine-d₃</td>
<td>196 (\rightarrow) 80</td>
</tr>
</tbody>
</table>

Sample preparation – plasma, whole blood and liquid saliva

1. Add 100 µl of sample or calibration curve standard into an eppendorf tube
2. Add 100 µl internal standard solution in 0.01 M HCl (20 ng/ml of cotinine-d₃, trans-3’-hydroxycotinine-d₃ and nicotine-d₄)
3. Dilute with 900 µl HPLC grade water
4. Add 100 µl of 30% perchloric acid to precipitate protein, vortex mix, centrifuge at 2200 g (9000 rpm on small bench top centrifuge).
5. Transfer supernatant into a 13 x 100 mm tube containing 2 ml tripotassium phosphate (50% w/v in water, pH ~ 14)
6. Add 5 ml methylene chloride, vortex mix 5 minutes.
7. Transfer organic layer (bottom) into a 13 x 100 mm tube and add 100 µl of 10% HCl in methanol
8. Evaporate extract under a nitrogen evaporator
9. Re-constitute in 100 µl of buffer (100 mM ammonium acetate in 80/20 water/methanol and 1% acetic acid).
10. Transfer to autosampler vial for LC-MS/MS analysis. Injection volume 50 µl.
11. Use method called “PNAT apci” or “PNAT apci diverted” on LCMS 1 (old) to analyze human blood, plasma, saliva or urine samples for nicotine, cotinine and 3-hydroxycotinine

Sample preparation – saliva in collection tubes with sample adsorbed to a sponge

**Comment:** As saliva contains no significant amount of protein, the protein precipitation step is omitted. See instructions below.

1. Thaw the collection tubes, make sure each tube contains the sponge in the upper compartment. If the part holding the sponge is missing, take it from an un-used tube and put the sponge in it before putting back in the tube.
2. Centrifugate the collection tubes at 3000 rpm for 5 minutes on the floor centrifuge to expel saliva from the sponge. If no saliva is expelled from the sponge, see instructions for specific clinical samples on how to proceed with those samples.
3. Add 100 uL saliva or calibration curve standard, 100 uL internal standard standard solution in 0.01 M HCl (20 ng/ml of cotinine-d₃, trans-3`-hydroxycotinine-d₃ and nicotine-d₄), 900 µl HPLC grade water and 100 µl of 30% perchloric acid to a 13 x 100 mm tube
4. Add 2 ml tripotassium phosphate (50% w/v in water, pH ~ 14)
5. Follow instruction for plasma, whole blood and liquid saliva from step 6 onward.