Evaluating the Real-World Effectiveness of Bupropion
Versus Varenicline for Smoking Cessation: Exploring
the Role of Nicotine Metabolism and Medication Adherence

By

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for the degree of Master of Science

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ABSTRACT

Bupropion and varenicline are effective, first-line prescription-only pharmacotherapies for smoking cessation; however, their real-world use is limited by affordability and accessibility. Using a novel internet-based randomized design, we evaluated the real-world effectiveness of mailed bupropion and varenicline, as well as the roles of nicotine metabolism (NMR) and medication adherence, in a sample of interested smokers using web-based recruitment and follow up. Quit rates at end of treatment (EOT) were significantly higher for varenicline (30.2%) compared to bupropion (19.6%). Quit rates at 6 months (14.0%) and 12 months (12.1%) were not significantly different between bupropion and varenicline. Increased medication compliance significantly improved cessation outcomes at EOT. NMR was associated with nicotine dependence. Varenicline benefited Slow Metabolizers of nicotine whilst bupropion benefited Normal Metabolizers. Even though real-world quit rates were comparable to clinical trials, improving medication compliance and implementing personalized pharmacological and behavioral interventions are promising approaches to increase efficacy of smoking cessation pharmacotherapies.
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1.0 INTRODUCTION

1.1.1. Smoking and its Impact

Smoking is one of the most preventable causes of disease, disability and death. Use of tobacco, the primary component of a cigarette, and smoking-related illnesses contributes to approximately 5 million deaths per year. In other words, one out of every 10 adult deaths is due to tobacco use globally. Additionally, it is estimated that by 2030, tobacco use will be responsible for 8 million deaths annually (WHO, 2011). The World Health Organization (WHO) reported that in 2015, over 1.1 billion people smoked tobacco (WHO, 2016). Tobacco use accounts for 480,000 deaths annually and accounts for approximately 90% of deaths from lung cancer, 60% from pulmonary disease and 30% from heart disease. It is estimated that the accumulated loss of life expected from tobacco use is to reach one billion by the end of the 21st century (World Lung Association, The Tobacco Atlas). Cigarettes are the most commonly used form of tobacco use in the world, although cigars, smokeless tobacco and dual use of tobacco products are increasingly common.

1.1.2. Health Risks of Smoking

Tobacco use is responsible for increased risks of chronic conditions as well as cardiovascular diseases, pulmonary diseases and cancer. There are approximately 7000 chemicals found in cigarettes with over 250 of them proven to be harmful (USDHSS 2010). Additionally, 70 of these chemicals have been proven to be carcinogenic (NTP 2005). Smoking causes the majority of all cases of lung cancer diagnosed and is also linked to a number of other forms of cancer such as oral, kidney, liver, stomach, colorectal, bladder, prostate and breast (Carbone, 1992). The compound responsible for the addictive properties of tobacco is nicotine. Nicotine affects almost every organ in the body and is detrimental to overall health for all individuals (CDC 2011). Numerous studies have shown that smoking increases health risks of stroke, ischemia, peripheral vascular disease, aortic aneurysm and Type II Diabetes (USDHHS, 2011). Additionally, smoking is responsible for several respiratory diseases, such as chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, asthma and pneumonia (USDHHS 2010). Some other potential negative health consequences of smoking include rheumatic arthritis, low bone density, stomach ulcer, and erectile dysfunction (USDHHS, 2014). Additionally, involuntary exposure to tobacco smokes in forms of second-hand smoke and third-hand smoke has deleterious health effects on those exposed (USDHHS, 2006). Smoking also can have different health risks for men and women. For example, tobacco use can damage a woman’s reproductive health; increase risks of ectopic pregnancy, miscarriages, breast cancer, stillbirths and sudden infant death syndrome (SIDS). For men, smoking increases health risks of sexual impotence.
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. In 2002, Rehm and colleagues estimated that total estimated healthcare costs attributable to smoking in Canada was $4.4 billion or 3.8% of the total healthcare costs in Canada. In 2012, the total healthcare expenditures in Canada were estimated at $207.4 billion where $21.3 billion was attributable to smoking related illnesses. In the same report from 2012, of the $50.3 billion of economic burden, approximately $26.5 billion was attributable to male smokers and $23.8 billion to female smokers (Health Canada, 2012). This is a reflection of continuous higher smoking prevalence in men than women (20% vs 15% respectively). Lastly, in Ontario, tobacco use costs the economy $6.1 billion in direct healthcare costs (Rehm, Taylor, & Room, 2006).

1.1.4. Smoking Prevalence in Canada

Fortunately, smoking prevalence in Canada has declined in recent years. In the most recent report, 18% of Canadians aged 12 and over is smoking either daily or occasionally (Statistic Canada 2014). This was a decrease from 2013 (19%) and is the lowest rate since 2001. The percentage of daily or occasional smokers was the lowest for youth aged 12-17 (4.3%) whilst 9.4% of seniors aged 85 and older smokes occasionally. People typically begin smoking during their teenage years. In 2014, 55% of 20-24 year olds have never smoked. Within this age group, there were more females (62%) that had never smoked compared to males (47%). However, recent reports indicate that the prevalence of female smokers has increased in recent years (Health Canada, 2014). Canadian daily smokers aged 15 years and older consumed an average of 13.9 cigarettes per day in 2013, a decrease from reports in 2012. Male daily smokers consumed more cigarettes per day (average of 15.2) than female daily smokers (average of 12.5). Additionally, the percentage of residents who smoked daily or occasionally was lower than the national average of 18% in Ontario (17%) and in British Columbia (14%). The highest rate was in Yukon (26%) and Saskatchewan (20%) (Health Canada, 2016).

1.1.5. Importance of Reducing Smoking Rates

Reducing smoking prevalence is very important to reduce exposure, improve health and decrease economic burden on society. Studies have shown that quitting has both short-term and long-term health benefits. For instance, after only one year of smoking abstinence, the risk of developing coronary heart disease is halved and after 15 years of smoking abstinence, the risk decreases to that of a non-smoker (USDHSS 2010;WHO 2007). After 10 years of smoking abstinence, the risk of lung cancer also drops to half (USDHHS 1990).
Cigarette smoking has been associated with 10 years loss of life and tripled death rate for daily smokers compared to non-smokers (NCI 2014). In a report by Jha et al. (2013), it was shown that quitting smoking before the age of 40 significantly reduces the chances of dying from a tobacco-attributed disease by 90%. Additionally, smoking cessation in adults aged 45 years or older has significant benefits with a potential 6 years gain of life (Jha et al., 2013). Reducing smoking prevalence can prevent millions of future premature deaths expected if youth initiation rates and adult cessation rates are increased (USDHHS 2012).

In Canada, it has been estimated that for every smoker that quits, more than $8000 dollars is saved per year in medical costs (FTCS, 2011). Additionally, over $400,000 is gained through prevention of premature deaths (FTCS 2011). Additionally, the usage of pharmacotherapy for smoking cessation has been reported to save between US$128-US$1,450 per quality-adjusted life years (QALYS), which accounts for both quality and quantity of life lives (Ekpu & Brown, 2015). The use of pharmacotherapies such as varenicline, NRT and bupropion are both clinically effective and cost effective. In conclusion, it is of vital importance to improve smoking cessation rates, resolving one of the biggest health concerns of this generation.
1.2 Statement of Problem and Study Rationale

1.2.1. Challenges of Smoking Cessation

From the previous section, it can be seen that smoking harms both the individual and society as a whole. The key to resolving the burden of smoking is to lower smoking prevalence overall. The main proactive strategies that can be employed to decrease smoking prevalence are prevention and policy. Prevention focuses on decreasing smoking initiation at a population level through public awareness campaigns and education. On the other hand, policy strategies make it increasingly difficult for smokers to smoke in public thereby demoralizing and discouraging the smoking behavior. In contrast, it is also vital to implement strategies to target current smokers to quit. Both proactive and reactive strategies must be employed in conjunction to decrease current smoking prevalence and prevent future increases in prevalence. However, smoking cessation can be challenging since tobacco dependence is multifaceted. Numerous factors contribute to tobacco dependence. These include a combination of pharmacological, psychological, biological, genetic, environmental and social elements (Benowitz, 2010).

Nicotine, the powerful psychoactive substance in cigarettes, is extremely addictive when inhaled via cigarette smoking (Kumar & Lader, 1981). Nicotine reaches the brain almost immediately, binds to nicotinic acetylcholine receptors and activates the brain reward system by releasing dopamine. Dopamine reinforces smoking behaviors (Benowitz, 1999; Dani & Heinemann, 1996). Furthermore, nicotine has a short half-life and thus, in order to maintain pleasurable effects and avoid withdrawal symptoms, smokers need to smoke more frequently. The smoking behavior turns the activity into an overlearned behavior that contributes to tobacco dependence (Benowitz, 2010; Coe et al., 2005; Davis & Gould, 2008; Olausson, Jentsch, & Taylor, 2004). Therefore, in order for smokers to quit, they need to manage both the pharmacological and the behavioral aspects of their nicotine addiction. This complexity can be seen in a survey conducted in a sample of 800,000 smokers where they reported a wide variety of reasons for smoking. Some of these reasons are: enjoyment from smoking, craving for cigarettes, stress and anxiety, weight gain and cost of cessation treatments (UWCTRI, 2005).

1.2.2. Challenges in Intervention’s Efficacy

Clinical interventions are critical to a comprehensive smoking control strategy design (Lancaster, Stead, Silagy, & Sowden, 2000). The first-line pharmacotherapies that are efficacious for smoking cessation are: NRT, bupropion and varenicline (Gonzales et al., 2006; Hughes, Stead, & Lancaster, 2007; Silagy, Lancaster, Stead, Mant, & Fowler, 2004). However, of about 66% of smokers who
have ever made a quit attempt, less than half have used a cessation aid. Even more surprising, 90% of these smokers reported attempting to quit on their own, without getting help from available smoking cessation programs (Health Canada 2007). Additionally, most of these smokers identify that lack of access to adequate and evidence-based information and cost of these smoking cessation pharmacotherapies were the main reasons for not using these cessation aids (Health Canada, 2007).

To overcome these barriers, successful methods for mass-distribution of nicotine replacement therapy have been developed and implemented with high efficacies (Costello et al., 2011; Zawertailo, Dragonetti, Bondy, Victor, & Selby, 2013). However, clinical trials have shown that bupropion and varenicline are more efficacious than NRT and are expected to make a substantial impact if widely distributed to smokers (Cabana et al., 1999; Jiménez-Ruiz, Berlin, & Hering, 2009; Wu, Wilson, Dimoulas, & Mills, 2006). On the other hand, bupropion and varenicline are prescription-only medications and come with unique challenges such as low knowledgeability (ACS, 2014). Health care providers are ideally suited to advise and assist with smoking cessation of their patients (Stead & Lancaster, 2012). However, a survey conducted in Canada demonstrated that discussions related to smoking cessation between physicians and patients are not common (Stevenson, 2005). Specifically, out of 88% of smokers who visited a primary care physician in the past year, only half received any advice on quitting or reducing smoking behaviors (Stevenson, 2005). Other studies have shown that lack of knowledge and confidence on part of the primary health care provider are limiting factors (Cabana et al., 1999; Steinberg, Nanavati, Delnevo, & Abatemarco, 2007). In clinical studies involving bupropion and varenicline, these limitations are in direct relation to smokers’ inaccessibility to these smoking cessation aids in comparison to nicotine replacement products, since bupropion and varenicline are only available through prescription from a licensed practitioner. Additionally, these prescription smoking cessation medications are expensive and with limited coverage by public and private insurance companies (McDonald et al., 2012). This represents another barrier for bupropion and varenicline use, especially for smokers with lower socioeconomic status (Health Canada, 2013). Thus, the population-level impacts of bupropion and varenicline are limited by combinations of lack of knowledge, affordability and accessibility. Addressing these barriers could greatly improve the effectiveness and usage of these smoking cessation medications in real-world settings (Gollust, Schroeder, & Warner, 2008).

Although bupropion and varenicline have been proven efficacious in clinical trials (Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006), there is surprisingly limited evidence available to establish their real-world effectiveness. There are numerous differences between clinical trials and real-world settings, which could potentially affect cessation treatment outcomes. For example,
clinical trials have strict eligibility criteria, excluding light smokers and smokers with certain comorbidities. Thus, participants of these studies are in better health than the general population of smokers. Additionally, treatment with medications in clinical trials is often associated with smoking cessation behavioral counseling, which does not always occur in real-world settings (David et al., 2013; Gonzales et al., 2006; Jorenby et al., 2006; Ramon & Bruguera 2009; Stapleton et al., 2013). All these factors together have the potential to restrict the real-world validity of clinical trial findings. In conclusion, for all the reasons stated above, there is a need to assess the real-world effectiveness of these prescription medications for smoking cessation at the population-level.

1.2.3. Challenges in Preventing Relapse

One of the biggest challenges in treating tobacco dependence is that it is a chronic relapsing disease (Japuntich, Piper, Leventhal, Bolt, & Baker, 2011). Despite efforts in improving smoking cessation interventions, current available treatments have lower efficacy than desired and only a portion of smokers benefit from them. For example, bupropion results in higher quit rates than nicotine replacement therapy at earlier stages of treatment however the portion of smokers who remain abstinent after one year decreases significantly (Gold, Rubey, & Harvey, 2002; Jorenby et al., 1999). The efficacy and relapse prevention profile of varenicline is more promising with a 22% abstinent rate at 1-year post treatment (Gonzales et al., 2006; Jorenby et al., 2006; Ramon & Bruguera, 2009). Due to low long-term success rates of smoking cessation therapies, there is a growing need for optimization of existing treatments. Additionally, it is vital to explore medication compliance in real-life settings since it is a major limiting factor of pharmacotherapy efficacy. Previous studies have shown that compliance rates of bupropion and varenicline are surprisingly low in clinical trials, often using for less time than is optimal (Bansal, Cummings, Hyland, & Giovino, 2004; Fossati et al., 2007; Gonzales et al., 2006; Raupach, Al-Harbi, McNeil, Bobak, & McEwen, 2015). Potential reasons for low compliance are: experiencing adverse side effects, lack of supporting behavioral counselling and smokers prematurely discontinuing medication believing they no longer need it (Balmford, Portland, Hammond & Cummings 2011).

Lastly, smoking is a multifactorial and there are many individual differences in how smokers respond to smoking cessation medications (Phillips et al., 2007; True et al., 1997). There is considerable evidence supporting the role of genetic factors that affect smoking behavior and smoking cessation (Lerman, Schnoll, & Munafò, 2007; Quaak, van Schayck, Knaapen, & van Schooten, 2009). Recently, numerous studies have focused on the role of nicotine-metabolizing enzyme CYP2A6 in smoking cessation. Studies have shown that the rate by which smokers metabolize nicotine influences their responses to smoking cessation medications (Ho et al., 2009; Lerman et al., 2006;
Schnoll et al., 2009). Other previous studies have evaluated the impact of varenicline treatment and bupropion with placebo and NRT (Lerman et al., 2015; Patterson et al., 2008). However, it is still unclear whether the rate of nicotine metabolism affects bupropion and varenicline treatment outcomes in different ways. It is essential to understand how these inherited characteristics could potentially affect treatment responses and thus help tailor nicotine cessation treatments to maximize treatment efficacy. In conclusion, smoking is a complex, recurring chronic addiction that is costly to society. Thus, there is an urgent need for development of effective and sustainable interventions at a population-level.

1.3 Statement of Purpose and Objectives of Study

It has been established that the current prescription-only first line pharmacotherapies for smoking cessation, bupropion and varenicline, are not yet widely used despite their efficacy in clinical trials (Health Canada 2007). There is also very limited data on real-world effectiveness and medication compliance, both short term and long term, of bupropion and varenicline at the population-level. Furthermore, there is evidence that individual response to pharmacotherapy varies, although limited data on the nature and specific effects of these factors are currently available. Therefore, the purpose of this study is to address the aforementioned gaps in knowledge. The specific objectives are as follows:

**Primary Objective:** To evaluate the effectiveness of mailed bupropion and varenicline in a sample of treatment-seeking smokers interested in participating in a randomized controlled trial using patient-driven internet-based recruitment and follow up.

Specific Aims:
- Measure short-term and long-term cessation rates associated with bupropion and varenicline use in a real-world setting.
- Evaluate the practicality of a patient-driven internet-based mass-distribution model for prescription only smoking cessation pharmacotherapy delivery.

**Secondary Objective:** To explore the role of medication compliance and treatment outcomes in a real-world setting.

Specific Aim:
- Assess the real-world medication compliance and its effects on treatment outcomes for bupropion and varenicline.
**Tertiary Objective:** To explore the role of rate of nicotine metabolism/CYP2A6 activity on nicotine dependence and treatment outcomes.

**Specific Aim:**
- Examine the relationship between rates of nicotine metabolism, using the Nicotine Metabolite Ratio (NMR; a phenotypic marker for nicotine metabolism), and gender, cigarettes per day (CPD) and nicotine dependence as measured by the Fagerstrom Test for Nicotine Dependence (FTND).
- Examine the relationship between nicotine metabolism (measured by NMR) and treatment outcomes at end of treatment.

1.4 **Statement of Hypotheses and Rationale for Hypotheses**

1) **We hypothesize that treatment with varenicline will result in higher cessation rates than bupropion at end of treatment (EOT).**

**Rationale:** Two clinical trials have been conducted comparing the efficacies of 12-week treatments of bupropion and varenicline in a head-to-head comparison design using randomized, double-blinded, and placebo-controlled, parallel-group designs. In both phase III clinical trials, varenicline was more effective than bupropion for smoking cessation (Gonzales et al., 2006; Jorenby et al., 2006). In both trials, participants were randomly assigned to receive either 1) varenicline, titrated to 1 mg twice daily 2) bupropion SR titrated to 150 mg twice daily or 3) placebo for the standard 12-week period of treatment. Both clinical trials also had brief behavioral intervention. The cessation outcomes of both studies of head-to-head comparisons of bupropion and varenicline were comparable. 30-Day Continuous Abstinence was defined as not having smoked, not even a puff, in the past 30 days. The 30 Day Continuous Abstinence rates at EOT (12 weeks) were approximately 44% for the varenicline group and 30% for bupropion group and 17% in placebo group. Varenicline was significantly more efficacious than placebo with an odd ratio (OR) of 3.8 with 95% confidence interval (CI) of 2.7-5.5. Bupropion was also significantly more efficacious than placebo with an OR of 1.9 and a 95% CI of 1.4-2.6. Varenicline was significantly more efficacious than bupropion at EOT with an OR of 1.93 with a 95% CI of 1.4-2.7. 7 Day Point Prevalence of Abstinence (7 Day PPA), defined as not having smoked, not even a puff, in the past 7 days, was also examined. At 4 weeks into treatment, 7 Day PPA rate for varenicline was approximately 48% compared to 37% for bupropion treatment. At 8 weeks into treatment, 7 Day PPA rates for varenicline and bupropion were 51% and 36%
respectively. At week 12, varenicline treatment resulted in approximately 50% 7 Day PPA compared to 36% for bupropion treatment. Therefore, we believe the results from our study will be consistent with the results from the two clinical trials and varenicline will result in higher abstinence rates at EOT (12 weeks) than bupropion. We hypothesize a 15% difference will be observed between the medication groups at EOT 30 Day Continuous Abstinence and 7 Day PPA respectively. However, we also hypothesize overall quit rates will be lower in our study than in clinical trials since in real-world settings participants will be self-motivated and will receive little support from a controlled clinical setting.

2) **We hypothesize that long-term quit outcomes for varenicline at 6 months will be superior to bupropion, however, at 12 months, quit rates will be similar between bupropion and varenicline.**

**Rationale:** Two previously conducted clinical trials comparing bupropion and varenicline in a head-to-head manner evaluated long-term abstinence rates for medication groups. The methods were previously described in hypothesis #1. They were randomized, double-blinded, placebo-controlled, parallel-group designs. In both phase III clinical trials, varenicline was more effective than bupropion for smoking cessation (Gonzales et al., 2006; Jorenby et al., 2006). The cessation outcomes of both studies of head-to-head comparisons of bupropion and varenicline were comparable. Continuous Abstinence was defined as abstinence between weeks 9 to 24 (6 months) where quit rates were approximately 30% and 21% for varenicline and bupropion respectively. Varenicline was significantly more efficacious than bupropion for cessation outcome with an OR of 1.63 with a 95% CI of 1.14-2.33. Varenicline was significantly more effective than placebo with an OR of 3.68 and a 95% CI of 2.42-5.60. 7 Day PPA at 6 months was approximately 35% and 26% for varenicline and bupropion respectively. Varenicline was significantly more effective than bupropion with an OR of 1.56 with a 95% CI of 1.11-2.17. On the other hand, at 12 months follow up, continuous abstinence was defined as continuous abstinence from weeks 9 to 52 (12 months). Quit rates were 22% and 16% for varenicline and bupropion respectively. Varenicline was significantly more effective than placebo with an OR of 3.09 and a 95% CI of 1.95-4.91. However, the quit rate in the varenicline group was not significantly different compared to bupropion between weeks 9-52 with an OR of 1.46 and a 95% CI of 0.99-2.17. 7 Day PPA rates at 52 weeks were approximately 31% and 23% for varenicline and bupropion respectively. Therefore, we believe from the results of these studies that varenicline will have higher abstinence rates than bupropion at 6 months but not at 12 months. We hypothesize that a 10% difference in quit rates will be observed between varenicline and bupropion at 6 months for 30-Day Abstinence and 7 Day PPA. However, we
also hypothesize that due to differences between clinical trials and real-world setting, overall quit rates will be lower in our study than clinical trials.

3) We hypothesize that increased medication adherence will result in higher cessation rates at end of treatment (EOT) for bupropion and varenicline.

**Rationale:** In a study conducted by Liberman et al. (2013), the relationship between varenicline adherence and smoking cessation outcomes at EOT was explored in a sample of 1,477 smokers. In this study, 55% of participants completed the 12 weeks varenicline treatment and participants adherent to treatment were twice as likely to succeed in quitting smoking compared to non-adherent participants with an OR of 1.93 and a 95%CI of 1.59-2.33 (Liberman et al., 2013). Another study conducted by Catz et al (2011) explored the relationship between varenicline adherence and quit outcomes at 6 months follow up where quit rates were almost twice as high for adherent participants than non-adherent participants (Catz et al., 2011). However, it is worthy to note that adherence was defined as having used >80% of medication as measured by self-reported pill count. Another study conducted by Leischow et al. (2016) explored the relationship between bupropion adherence and cessation outcome at 6 weeks in a sample of 312 adolescent smokers. Participants were randomized to one of: placebo, 150 mg bupropion or 300 mg bupropion for 6 weeks. Abstinence was biochemically confirmed at CO<10 ppm and by urinary cotinine <50 mg. In this study, quit rates of participants assigned to 150 mg bupropion were 65% for adherent participants and 34% for non-adherent participants (Leischow, Muramoto, Matthews, Floden, & Grana, 2016).

In a study conducted by Hays et al. (2010), adherence was analyzed within the two clinical trials stated previously conducted by Gonzales et al. (2006) and Jorenby et al. (2006). Adherence and cessation outcome at end of treatment was analyzed for participants randomized to bupropion and varenicline. In this study, a significant positive association was seen between adherence and cessation outcome for both bupropion and varenicline groups. The OR for quitting on varenicline vs bupropion was 3.96 [95%CI 2.98-5.25] for adherent individuals whereas OR for quitting on varenicline vs bupropion was 3.69 [95%CI 2.88-4.72] in the overall sample. There was no direct comparison of the predictive ability of adherence and medication assignment, however, the fact that the OR was higher for completers than the overall population suggests that adherence is a very important predictor of cessation outcome. Therefore, we hypothesize that increase adherence will result in higher abstinence rates at end of treatment and that medication adherence will be a superior predictor of treatment outcome than medication assignment (Hays, Leischow, Lawrence, & Lee, 2010).
4) We hypothesize that rate of nicotine metabolism will be positively correlated with CPD but not with nicotine dependence as measured by FTND score.

Rationale: Numerous studies conducted previously have shown a significant relationship between gender and NMR (Benowitz, 2010; Mwenifumbo, Sellers, & Tyndale, 2007). Females generally have higher NMR than men. A previous study conducted evaluated the relationship between NMR and nicotine dependence across sex and race in a sample of 833 smokers (Schnoll et al., 2014). In this study, a significant relationship was found between NMR and CPD. When controlled for sex and race, nicotine dependence was not associated with NMR when using FTND as the measure of dependence (Schnoll et al., 2014). Another study explored the relationship between NMR measured in urine and nicotine dependence measured by FTND in a sample of 73 smokers. Both studies concluded that the association seen between NMR and dependence may be more attributable to the association between NMR and cigarettes per day rather than FTND. Therefore, we hypothesize that NMR will be correlated with CPD but not with nicotine dependence as measured by FTND.

5) We hypothesize that at end of treatment, varenicline and bupropion treatment will benefit normal metabolizers more than slow metabolizers as measured by NMR.

Rationale: A study conducted by Patterson et al. (2008) explored the relationship between NMR and smoking cessation outcome with 10 weeks of bupropion treatment. There were similar quit rates were observed for slow metabolizers at approximately 32% between bupropion and placebo however for normal/fast metabolizers, participants using bupropion had significantly higher quit rates than placebo (34% vs 10%) suggesting bupropion may be more beneficial for fast metabolizers. However, similar quit rates were seen for all metabolizer groups on bupropion (approximately 30%-34%) (Patterson et al., 2008). Another study conducted by Lerman et al. (2015) explored the relationship between NMR and quit rates in normal and slow metabolizers in those treated with 12 weeks of varenicline vs those treated with nicotine patches. In this study, participants were stratified based on their metabolizer status and randomized to treatment (varenicline, patches or placebo). In this study, varenicline was more efficacious for normal metabolizers with quit rates of approximately 39%. The study concluded that varenicline treatment in normal metabolizers was more efficacious than treatment with patches whereas in slow metabolizers, varenicline and patches were equally efficacious (at approximately 28%) (Lerman et al., 2015). However, the overall quit rates between the metabolizer groups were not significantly different. Therefore, we hypothesize that NMR will not be a significant predictor of cessation outcome at end of treatment. We predict that overall quit rates will be similar for
normal metabolizers and slow metabolizers. However, we predict that fast metabolizers will benefit more from varenicline treatment whilst bupropion will benefit slow and fast metabolizers equally.

### 1.5 Existing Literature Review

#### 1.5.1. Neuropharmacology of Nicotine Addiction

#### 1.5.1.1. Nicotine Content in Cigarettes and Nicotine Absorption

Tobacco addiction is a complex chronic order that affects the brain. The primary addictive component of tobacco found in cigarettes has been identified as nicotine (Hukkanen, Jacob, & Benowitz, 2005). Cigarettes are designed to maximize the efficiency of nicotine delivery. Approximately one tenth of the weight of a cigarette is nicotine content. On average, a cigarette contains about 1.0-1.5 mg of nicotine however; only 0.5 mg of nicotine is absorbed systemically per cigarette (Benowitz & Jacob, 1984). It takes approximately 5 minutes and 10 puffs to smoke a cigarette. When a person inhales smoke from a cigarette, nicotine is distilled from the tobacco and is efficiently carried in smoke particles into the lungs where it is rapidly absorbed into the pulmonary venous circulation. The lungs provide a larger surface area for rapid absorption of inhaled compounds. Nicotine then enters the arterial circulation and moves swiftly to the brain where it readily diffuses into the brain tissue to bind to nicotine cholinergic receptors (nAChRs). This process is very rapid, in fact, it takes only 10 seconds for nicotine to be absorbed and reach the brain (Hukkanen et al., 2005). Additionally, since inhaled nicotine reaches the brain before entering systemic circulation, it undergoes little to no first-pass metabolism and thus, a significant amount of unchanged nicotine reaches the brain very quickly. This contributes to the addictive properties of nicotine since a sudden increase in blood concentration of nicotine occurs very rapidly (Benowitz, 1990). Lastly, a distinctive property of nicotine is its short half-life: approximately 1-2 hours. In other words, it takes about 2 hours for 50% of absorbed nicotine to be eliminated from the body. Thus, smokers need to smoke frequently to maintain a constant plasma nicotine concentration.
1.5.1.2. Nicotine Acetylcholine Receptors and Neurotransmitter Release

Nicotine is a tertiary amine consisting of a pyridine and a pyrrolidine ring. (S)-nicotine is the compound found in tobacco which stereoselectively binds to nicotine cholinergic receptors (nAChRs) (Yildiz, Ercal, & Armstrong, 1998). The nAChR is a ligand-gated ion channel receptor. When a cholinergic agonist binds to the outside of the channel, the channel opens to allow entry of cations such as sodium and calcium. The cation then activates voltage-dependent calcium channels to allow further calcium entry. The nAChR is composed of five subunits and is found in the peripheral and central nervous systems (Gotti, Zoli, & Clementi, 2006). In mammalian brains, there are as many as nine α subunits (α2-α10) and three β subunits (β2-β4). However, the most abundant receptor subtypes in human brains are a α4β2, α3β4 and α7 (homomeric) (Benowitz, 2009).

The α4β2 specifically is the receptor subtype predominant in the human brain and is believed to be the main receptor modulating the addictive properties of tobacco dependence (Benowitz, 2009). It is believed that the β2 subunit is responsible for behavioral effects of nicotine in mice (Picciotto et al., 1998). The α4 subunit is thought to be an important determinant of sensitivity to nicotine. In mice, a mutation in the α4 gene region results in a receptor that is hypersensitive to the effects of nicotine (Tapper et al., 2004). Mice with this mutation are more sensitive to nicotine induced reward behaviors and effects on tolerance and sensitization. The α3β4 nAChR is believed to be involved in the cardiovascular effects of nicotine (Aberger et al., 2001). Additionally, the homomeric α7 nAChR is thought to be involved in rapid synaptic transmission and may play a role in learning within nicotine addiction (Levin, Bettegowda, Blosser, & Gordon, 1999). The receptor may include α5, α6 or β3 subunits, and thus, they may affect the sensitivity and function of this receptor in presence of nicotine.

When nicotine is bound to the presynaptic nAChR, modulation of neurotransmitter release occurs. The activity of the presynaptic nAChR commences a direct and indirect intracellular calcium signal that enhances neurotransmitter release. The neurotransmissions released include: dopamine, noradrenaline, acetylcholine, glutamate, GABA, serotonin, opioid peptides and endocannabinoids (Clarke & Reuben, 1996). Consequently, nicotine influences both physiological and psychological processes in the brain. These influences may include: pain perception, anxiety, attention, memory, relaxation, decreased fatigue, feeling of pleasure and mild euphoria (Decker, Brioni, Bannon, & Arneric, 1995; Henningfield, Miyasato, & Jasinski, 1985).
1.5.1.3. The Role of Dopamine on Nicotine Addiction

Nicotine addiction is a chronic brain disorder. Physiologic dependence results from prolonged tobacco use and behavioral reinforcement. Nicotine establishes and maintains tobacco addiction by complex actions, which affects the neurochemistry of the brain. Of all the neurotransmitters affected by nicotine binding, dopamine is the most heavily influenced. Dopamine is crucial to the reward pathway of the brain since it is a neurotransmitter involved in motivation and reinforcement of learned behaviors (Nestler, 2005). When nicotine is bound to the nAChR, dopamine is released in the mesolimbic dopaminergic system. This network projects dopaminergic neurons from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens (NAc) in the limbic forebrain and the prefrontal cortex (PFC). This pathway is crucial for the rewarding effects of nicotine administration and promotes the initial drug seeking behavior in nicotine addiction (Nestler, 2005). In rodent studies, when nicotine is injected, there is an increase in dopamine neurons firing and elevated dopamine concentrations are seen particularly in the NAc (Grenhoff, Aston-Jones, & Svensson, 1986; Pidoplichko, DeBiasi, Williams, & Dani, 1997). The increase in dopamine release in the NAc is thought to mediate reinforcing properties of nicotine and drive the acquisition and maintenance of responding to nicotine administration. There are other studies that suggest that dopamine projections outside of the NAc contribute to different complementary components that drive nicotine dependence (Imperato, Mulas, & Di Chiara, 1986). Overall, dopamine release signals a pleasurable experience in the brain and thus is important in the reinforcing effects of nicotine and other drugs of abuse.

In rodent studies, inducing lesions in dopamine neurons in the brain prevents nicotine self-administration (Cryan, Hoyer, & Markou, 2003) and when intracranial self-stimulation is used as a model for brain reward in rats, nicotine lowers threshold for self-administration (Cryan, Bruijnzeel, Skjei, & Markou, 2003). Thus, through its effects on dopamine release, acute nicotine administration increases brain reward function. Similarly, nicotine withdrawal is associated with significant increases in self-stimulation reward threshold, thus resulting in deficient dopamine release and reduced reward. (Epping-Jordan, Watkins, Koob, & Markou, 1998). This decrease in brain reward function experienced during a period of nicotine withdrawal is an important trait associated with nicotine cessation treatments challenges.

1.5.1.4. Desensitization and Up-Regulation of the nAChRs

As mentioned before, nicotine has a relatively short half-life, and for smokers to maintain its pleasurable effects, they must smoke frequently. With repeated exposure to nicotine, neuroadaptation develops in many smokers (Wang & Sun, 2005). Neuroadaptation, a phenomenon
that occurs in many individuals who abuse drugs, is a process where the body grows accustomed to a drug and requires a higher dose of the drug to elicit the same physiological response, often leading to tolerance, which often leads to increased drug-seeking behavior. Nicotine tolerance is a major barrier for smoking cessation treatment because it often leads to relapse. As a result of neuroadaptation, an increase is seen in the number of nAChR binding sites in the brain. This increase in receptor concentration/density represents an up regulation in response to nicotine-mediated desensitization of receptors.

Desensitization plays a role in nicotine tolerance and dependence. Craving and withdrawal symptoms have both been shown to begin in chronic smokers when previously desensitized (from chronic nicotine use) α4β2 nAChRs are unoccupied and recover to a responsive state during natural periods of abstinence, such as sleeping (Dani & Heinemann, 1996). Craving and withdrawal symptoms manifest themselves in both physical and emotional reactions that in effect are opposites of those experienced when nicotine is present. Some of these undesirable effects experienced in a period of abstinence include: feeling depressed, anxious, restless, irritable, having difficulty concentrating and/or sleeping and increased appetite (Conti et al., 2008; Hughes, Gust, Skoog, Keenan, & Fenwick, 1991). Thus, smokers maintain α4β2 nAChRs in a desensitized state (by smoking) in order to avoid or alleviate these withdrawal symptoms.

The mechanisms involved in the up-regulation of nAChRs in humans is unclear, however, human post-mortem studies results suggest that prolonged exposure to the equivalent of the concentration of nicotine in a smoker increases the binding and possibly the number of excitable nAChRs (Benwell, Balfour, & Anderson, 1988). However, there is variation in how up-regulation occurs between different areas of the brain and between different nAChR subtypes. For example, presynaptic regulation of catecholamine release are enhanced by nAChR up-regulation and this may enhance the responses to subsequent nicotine administration (Barik & Wonnacott, 2009). Paradoxically, it is also hypothesized that nAChR up-regulation contributes to the development of sensitization. In other words, as more nAChRs become available to respond to the same nicotine dose, less nicotine is needed to achieve the same physiological effect (receptor activation). However, continuous exposure to nicotine caused by chronic smoking produces desensitization of particular nAChR subtypes, which may contribute to tolerance so that more nicotine is needed to achieve the same effects since certain nAChRs are unable to respond. During longer periods of smoking abstinence, the up-regulated nAChR recovers from desensitization. Thus, reactivation occurs resulting in an increased population of excitable nAChRs during prolonged abstinence.
1.5.1.5. Other Modulators Affected by Smoking

Other neurotransmitters that are affected by chronic nicotine use include: norepinephrine, acetylcholine, serotonin, γ-aminobutyric acid (GABA), glutamate, and endorphins. When these molecules are released, they could mediate various behaviors of nicotine. Most nicotine mediated neurotransmitter release is affected by modulating presynaptic nAChRs, although direct release of neurotransmitters also occurs (Wonnacott, 1997). Evidence shows that dopamine release is facilitated by nicotine-induced augmentation of glutamate release and with long-term treatment, by inhibition of GABA release (Mansvelder, Keath, & McGehee, 2002). In addition to direct and indirect stimulation of various neurotransmitters, chronic tobacco use reduces brain monoamine oxidase A and B activity. These reductions are expected to increase monoaminergic neurotransmitter levels such as dopamine and norepinephrine, which then result in increasing the effects of nicotine contributing to addiction (Lewis, Miller, & Lea, 2007). Inhibition of MAO has been shown to increase nicotine self-administration in rats, which suggests that MAO inhibition interacts with nicotine to reinforce nicotine dependence (Villéger, Lotfipour, Belluzzi, & Leslie, 2007).

Tobacco withdrawal has been associated with a negative emotional state, which includes anxiety and increased stress, which may represent stimuli to relapse to tobacco use. Previous work suggests that activation of the corticotropin-releasing factor (CRF) and its receptor contributes to the negative affect experienced during nicotine withdrawal (Slawecki, Gilder, Roth, & Ehlers, 2003). CRF activation produces anxiety behavior and pharmacological blockade of the CRF receptors inhibit the anxiogenic effects of nicotine withdrawal. Blocking the CRF nicotine receptor has been shown to decrease nicotine self-administration that occurs during abstinence in rats. Withdrawal from other drugs of abuse, such as morphine, is also associated with activation of the CRF system, which suggests that this is a common mechanism for drug withdrawal symptoms (Lasheras, Laorden, Milanes & Nunez, 2015). Lastly, other components of tobacco smoke, such as sensory and motor elements, may influence the addictive properties of nicotine by altering neural responses to the drug (Rose 2006). In other words, although some compounds are not addictive on their own, they may affect the overall motivational impact of nicotine (Fowler, Arends, & Kenny, 2008). In conclusion, nicotine has both the behavioral and neurobiological properties of an addictive drug; environmental associations and other properties of tobacco smoke alter the severity of tobacco dependence.
1.5.2 Behavioral Pharmacology of Nicotine Addiction

1.5.2.1. Behavioral Aspects of Smoking as a Learned and Reinforced Behavior

Another theory to explain mechanisms of nicotine addiction is that conditioned smoking cues maintain smoking behavior during periods of saturation and desensitization of brain nAChRs (Balfour, 2004; Donny et al., 2003). The powerful addictive properties of nicotine suggest a complex interaction between presence of the drug and the context in which it is delivered. When compared to other addictive drugs such as cocaine, nicotine alone does not seem to be as powerfully addictive in animal models as many smokers perceive it. Thus, researchers have considered the role of cues and smoking as a learned behavior contributing to its addictive properties rather than just nicotine content. Environmental stimuli become conditions cues when they are paired with the unconditioned rewards that result from nicotine usage (Tang et al., 2012). In rodent studies, it has been shown that repeated association of a cue with nicotine administration reinforces the effect of nicotine (Caggiula et al., 2001). In humans, memories associated with certain addictive behaviors could become the internal motivation that drives continual drug usage (Dani & Bertrand, 2007). Learned associations with nicotine occur when nicotine acts locally on memory-related circuits and induces dopamine release from midbrain centers (Tang et al., 2012). Cellular mechanisms underlying this system are the result of the ability of nicotine to alter local GABAergic inhibition and thus enhancing synaptic mechanisms that are responsible for systems-level learning (Tang et al., 2012). Results of these studies suggest that chronic nicotine administration induces a dopamine signal, which increases the likelihood and strength of synaptic potentiation, which is responsible for drug-associated learning. Nicotine acts through the brain and influences the synaptic mechanisms that normally mediate neuronal plasticity involved in learning. Cues associated with smoking lead to neuronal activity in regions linked to attention, memory, emotion and motivation (Smolka et al., 2006). Therefore, nicotine associated cues reinforces nicotine seeking behavior resulting in relapse (Dani & Bertrand, 2007). Decreased dopamine receptor activation shows greater conditioning to smoking-related stimuli and suggests that dopamine has a significant contribution to the associative learning that occurs in drugs of abuse (Tang et al., 2012). Other theories suggest that the behavioral and neuropharmacological effects of nicotine are complementary. In other words, smokers may continue to smoke throughout the day to maintain plasma nicotine levels but also continue to acquire the rewarding effects from the conditioned reinforcements that result from chronic nicotine use (such as taste or feel of the smoke).
1.5.2.2. Personality Traits and Smoking

Another factor that could play a role in tobacco dependence is personality. The Big Five Model or the Five Factor Model (FFM) is a widely used model of personality and has been used to study the relationship between personality characteristics and smoking habits (Rondina et al., 2007). The FFM is composed of the following five traits: extraversion, neuroticism, agreeableness, conscientiousness and openness to experience (Terracciano & Costa, 2004). These five traits are about 50% genetically determined and remain relatively constant throughout the lifetime of an individual ((Costa, Terracciano, & McCrae, 2001). In some studies, current smokers scored significantly higher on neuroticism and significantly lower scores on agreeableness and conscientiousness in comparison to never-smokers. Former-smokers scored intermediate on all the traits above. The relationship between neuroticism and smoking was especially observed in individuals with low conscientiousness, demonstrating an interaction between the two traits (Terracciano & Costa, 2004). One study investigated the correlation between FFM with lifetime cigarette use, smoking progression and smoking persistence in adults in a 10-year time span. Neuroticism and openness to experience was significantly associated with any lifetime cigarette use. Neuroticism was the only trait that accurately predicted likelihood of smoking initiation and smoking progression (Zvolensky, Taha, Bono, & Goodwin, 2015). The association between cessation outcomes and personality was also explored. Cessation outcomes were explored in response to 12 months of combined treatment with cognitive behavioral therapy and medication. After adjusting for nicotine dependence level, a higher relapse rate was observed in men with higher scores on impulsivity. Women were more likely to relapse if they scored higher on sociability (Nieva et al., 2011).

1.5.3 Clinical Components of Nicotine Addiction

1.5.3.1. Clinical Diagnosis of Nicotine Addiction

Drug dependence is a complex disorder but can be readily diagnosed clinically. Drug dependence is characterized by compulsive and repetitive drug-seeking behavior (USDHHS, 2010). There are a series of clear criteria that have to be met to diagnose a substance use disorder. These criteria were set by the World Health Organization in the International Classification of Diseases, tenth revision (WHO, 1992) and the American Psychiatric Association in the Diagnostic and Statistical manual, revision of the DSM-V (APA, 2013). The complete list of criteria can be seen in Appendix XXX. According to the DSM-V, tobacco use disorder is diagnosed by a cluster of two or more symptoms experienced by the individual in a one-year span (APA, 2013). The DSM-V allows for diagnosis of addiction on a continual mild to severe scale. However, substance use disorder is a complicated condition and the DSM-V list alone does not accurately reflect all the factors involved in addiction (Hasin et al., 2013). Another widely used scale to measure nicotine dependence is the Fagerstrom
Test of Nicotine Dependence (FTND) developed by Heatherton, Kozlowski, Frecker and Fagerstrom in 1991. This model primarily measures the level of physical dependence to nicotine on a scale of one to ten. The FTND is a brief six-item questionnaire consisting of six multiple-choice questions. The higher total FTND score indicates a greater dependence to nicotine. The FTND is easy to administer and has consistent internal accuracy. Many studies used this test and have demonstrated that FTND can accurately predict quitting and relapses (Piper, McCarthy, & Baker, 2006).

1.5.3.2. Smoking Cessation Biomarkers

In clinical studies involving smoking, characterizing the smoking status of an individual is vital. Self-reported measures, such as number of cigarettes smoked per day (CPD) are commonly employed in clinical studies. However, there is likely subject bias associated with self-report assessments (Caraballo, Giovino, Pechacek, & Mowery, 2001; Etter & Perneger, 2001). CPD may not be an accurate representation to tobacco exposure since smokers vary with respect to smoking topography characteristics. Examples of topography characteristics include: number of puffs taken per cigarette and puff volume (Lee, Malson, Waters, Moolchan, & Pickworth, 2003). Thus, objective biochemical measures are needed to confirm smoking behaviors. Two most commonly used methods are exhaled carbon monoxide (CO) and cotinine levels in plasma, saliva or urine.

Carbon monoxide (CO) is a low molecular weight gas that is one of the byproducts of tobacco combustion (Ryter & Choi, 2013). CO levels can be easily measured using portable meters (Irving, 1988). People can also be exposed to CO from environmental sources such as coal and gas burning (Zhang et al., 2013). Therefore, CO level cutoff points to distinguish a smoker from a non-smoker may be slightly different depending on the population at hand. Generally, a cut-off point of 5-6 ppm has been accepted to identify non-smokers (Sandberg et al., 2011). Advantages of using expired CO as a measure for smoking behavior include: low cost, non-invasive and immediately shows result (Jarvis, Russell, & Saloojee, 1980). However, expired CO is only sensitive to recent smoking behaviors due to its relatively short half-life of 4 hours (Sandberg, Grunewald, Eklund & Wheelock, 2011). Expired CO is not useful for detecting light smoking since CO levels from smoking are low and are comparable to levels of environmental sources of CO. Lastly, CO measurements are not applicable to smokeless tobacco detection since CO is a combustion product (Benowitz 2002).

Cotinine is another biomarker that is commonly used to characterize smoking status. Cotinine is the primary metabolite of nicotine. It is very chemically stable with a half-life of 16-19 hours. Its concentration is also consistent for a smoker over time (Benowitz, Jacob, Fong, & Gupta, 1994). Cotinine levels can be measured in plasma, urine or saliva (Etzel, 1990). Previous studies have
shown that cotinine is a reliable measure of smoking behavior (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987). Cotinine is also an appropriate method for assessing smoking status using mailed-in saliva samples (Etter, Neidhart, Bertrand, Malafosse, & Bertrand, 2005). There are also individual differences in cotinine production, which depend on the rate of nicotine metabolism, which are affected by genes, gender and race (Benowitz, 2009). From previous studies, an optimal cut-off point for cotinine assessment is a concentration of 15 ng/ml measured in saliva. This cutoff has high sensitivity and specificity to discriminate between smokers and non-smokers (Etter & Perneger, 2001). Additionally, the half-life of cotinine is even longer in slow metabolizers of nicotine and therefore can reflect smoking behaviours for a longer time period than normal or fast metabolizer counterparts. Whilst CO and cotinine are widely used in clinical settings, other biomarkers such as nicotine and anabasine can also be used to reflect smoking behaviors under certain conditions. Nicotine can be measured in biological specimens such as saliva, blood and urine. While it is an excellent marker for tobacco use, it is expensive to measure. Due to the short half-life of nicotine (1-2 hours), nicotine levels are not reflective of tobacco use that occurred more than 8-12 hours previously (Benowitz 2002).

Lastly, anabasine and anatabine, two nicotine-related alkaloids in tobacco, can also be measured. These alkaloids are especially useful for detecting tobacco use in persons using NRT since the compounds are not present in nicotine-containing products. The half-lives of anabasine and anatabine are also relatively long (16 hours and 10 hours respectively) (Jacob et al., 1999). However, use is limited by high assay costs (Benowitz 2002). In conclusion, biochemical validations are reliable measures of smoking status and each biomarker has its own benefits and drawbacks depending on the population and setting.

1.5.3.3. Nicotine Addiction Susceptibility

For most people, smoking a single cigarette will not lead to development of a tobacco use disorder. Smoking develops in three stages: initiation, maintenance and relapse. It has been reported that 80% of smokers generally begin smoking by the age of 18 (Torrens, Lynch, & Bonnie, 1995). Although only two thirds of adolescents try cigarette smoking at some point, 20-25% of them develop into dependent daily smokers by adulthood (CDC, 2011). There are many factors that affect initial tobacco exposure and its progression into dependence. The initiation and transition to daily dependence to nicotine is modulated by a complex combination of biological, psychological, personal and socio-environmental factors (USDHHS, 2000; WHO, 2010).
Studies indicate there are a number of potential biological and genetic factors involved in tobacco dependence sensitivity and response. These factors will predispose an individual to develop tobacco dependence (Quaak et al., 2009). These genetic effects can be categorized into either pharmacodynamics or pharmacokinetic features of tobacco dependence. Variations with the nicotine drug target, such as nAChRs could determine the binding affinity of nicotine mediating its pharmacological effects in the brain reward system (Al Koudsi & Tyndale, 2005). Factors that influence nicotine metabolism can also affect the half-life of nicotine in the body (Caporaso et al., 2001). Smokers regulate their intake of nicotine to maintain a certain level throughout the day to prevent withdrawal symptoms (Rubinstein et al., 2008). Thus, smokers who metabolize nicotine rapidly take in more nicotine per day than those who are slower metabolizers (Rubinstein et al., 2008). Nicotine is metabolized in the liver by the enzyme CYP2A6 to cotinine. People with a genetic predisposition for slow metabolism (certain variants in CYP2A6) generally smoke fewer cigarettes per day than people with faster metabolism (Malaiyandi, Sellers, & Tyndale, 2005). Additionally, proportions of smokers with slower metabolism decreases with increasing age suggesting that slow metabolizer smokers are more likely to quit than their faster metabolism counterparts. Lastly, faster nicotine metabolism is associated with more severe withdrawal symptoms and lower chances of quit success even when using nicotine patch treatment (Lerman et al., 2006; Rubinstein, Benowitz, Auerback, & Moscicki, 2008).

Risk factors for smoking in childhood or adolescence include peer and parental influences, behavioral problems, personality characteristics (rebelliousness, depression and anxiety) and genetic influences. The risk of dependence significantly increases when people begin smoking at an earlier age (Torrens et al., 1995). Animal studies indicate that nicotine can induce permanent brain changes that can lead to addiction. The adolescent rats exposed to nicotine have greater rates of nicotine self-administration in adulthood. This supports the theory that early exposure to nicotine predicts and increases the severity of nicotine dependence (Ali & Dwyer, 2009; Placzek, Zhang, & Dani, 2009). Various factors also contribute to maintenance of smoking behavior. The physiological dependence developed with nicotine addiction results in withdrawal and craving symptoms in the absence of the drug. These symptoms are the major barriers to quitting and lead to relapses. Studies show that higher levels of nicotine dependence increase the risk of future relapse (Cosci et al., 2009). Psychological factors also affect smoking behaviors. Studies suggest that individuals maintain smoking in response to stress, depression and to control their body weight (Leventhal et al., 2007; Pomerleau et al., 2005). Gender has also been shown to affect smoking cessation rates. Women have lower success rates in smoking cessation studies using NRT (Schnoll, Patterson, & Lerman, 2007). This could be because women are more sensitive to non-nicotinic psychological aspects of smoking whereas men are more sensitive to the reinforcing effects of pharmacological
effects of nicotine intake (Pauly, 2008). Quitting success is also affected by the smoker’s intention, motivation and confidence to quit (Caponnetto & Polosa, 2008; Osler & Prescott, 1998).

Lastly, socio-environmental factors may also play a role in smoking behaviors of individuals that are more likely to smoke if it is perceived as acceptable and the norm in their social environment. The perceived “norm” could be affected directly by tobacco advertising or through movies (DiFranza et al., 2006). Parental smoking behaviors can affect the smoking behaviors of teenagers. Peer tobacco use has been shown to strongly correlate with smoking initiation and persistence (Biglan, Duncan, Ary, & Smolkowski, 1995). Therefore, smoking may be initiated by an individual as a method of social-bonding (Krohn, Massey, Skinner, & Lauer, 1983). Additionally, accessibility and availability to cigarettes at low prices could also promote their use (Robinson, Klesges, Zbikowski, & Glaser, 1997). In conclusion, there are numerous variables that influence initiation, maintenance and relapse of smoking behaviors. Altogether, this suggests that in designing smoking cessation treatments, a one-size-fits-all method may not be the most effective.

1.5.4 Smoking Cessation Interventions

1.5.4.1. Smoking Cessation with No Intervention

Tobacco dependence is multidimensional and manifests in both physical and psychological components contributing to smoking as a chronic relapsing disorder. Tobacco dependence is one of the hardest addictions to quit. Studies have shown that success rate is very low in self-quitters with no intervention. About 80% of smokers who attempt to quit relapse within the first month. In fact, only 3-5% of smokers remain abstinent at 6 months after their quit date (Hughes, 2007). On average, it takes 5 to 7 quit attempts before an individual can successfully quit smoking permanently (Hughes, 2000). However, studies indicate that the chance of long-term quitting increases by 50% if a smoker can remain abstinent for at least 3 to 6 months (Gilpin, Pierce, & Farkas, 1997). The biggest barrier to quitting is the long lasting withdrawal and craving symptoms that surface when one quits (Hughes, 1992). Another factor is the strong reinforcing effects of nicotine, especially when inhaled through cigarettes (Benowitz, 1990). Unlike other drugs, nicotine is not intoxicating. In other words, smokers can self-titrate their nicotine uptake by altering the number of cigarettes or duration of puffs or puff volumes. This allows smokers to reach an optimal level of nicotine, which can alleviate their withdrawal and craving but still does not cause any adverse effects (Ashton, Stepney, & Thompson, 1979; Phillips et al., 2007; Strasser, Lerman, Sanborn, Pickworth, & Feldman, 2007).

In summary, many factors contribute to the strong addictive properties of smoking and approaches have been developed to combat them. These approaches include both non-pharmacological (behavioral intervention) and pharmacological treatments (bupropion and varenicline).
1.5.4.2. Behavioral Interventions

Behavioral interventions are commonly employed to treat smoking. These interventions are verbal instructions to help modify a health-related behavior. The goal of behavioral therapy is to provide smokers information on the mechanism of addiction, health consequences of smoking, benefits of cessation and strategies on how to cope with craving and ultimately, how to successfully quit and prevent relapse. They also provide cognitive therapy, which includes changing the way smokers think about quitting and especially identifying socio-environmental cues that trigger the smoking behavior (Kober, Kross, Mischel, Hart, & Ochsner, 2010; Mallin, 2002). Behavioral therapy can range from minimal advice to quit from a clinician to intensive clinical interventions such as individual, group or phone counseling. Minimal behavioral interventions have been shown to have minimal effects in self-quitting rate. However, they can prompt the smoker to seek smoking cessation aids to help them quit (Stead et al., 2013). On the other hand, intensive behavioral interventions have been shown to increase quitting rates substantially (Lancaster & Stead, 2005; Mottillo et al., 2009). Meta-analyses conducted reported significant results for behavioral interventions on long-term quit rates. Group counseling methods were shown to be most effective for cessation outcome (OR=1.75 95%CI: 1.11-2.93) (Mottillo et al., 2009). These behavioral interventions can be used alone or in combination with pharmacotherapies (Stead & Lancaster, 2012). Another meta-analysis included studies combining behavioral with pharmacotherapy where counselling significant improved cessation outcome (RR=1.92, 95% CI:1.66-2.00) (Hartmann-Boyce, Stead, Cahill, & Lancaster, 2013). It has been shown that success rates are improved by 10-25% when four sessions of behavioral support are provided versus when pharmacotherapies were used alone (Stead & Lancaster, 2012). Extended behavioral therapy can also help maintain abstinence after a successful quit attempt (Killen et al., 2008). Additionally, behavioral therapies are especially useful for pregnant smokers since pharmacotherapies are often not safe to use during pregnancy (Cressman, Pupco, Kim, Koren, & Bozzo, 2012).

1.5.4.3. Nicotine Replacement Therapy

For many smokers, behavioral therapy alone is not sufficient for a successful quit outcome. Pharmacological treatment may be required to alleviate the physiological and psychological symptoms of nicotine withdrawal. The most common and widely used pharmacotherapy for smoking cessation is nicotine replacement therapy (NRT). NRT is a first-line non-prescription over the counter smoking cessation medication. The main goal of NRT is to deliver a sustained dose of nicotine to replace the peaks and valleys of nicotine concentrations that smokers normally receive from smoking (Gourlay & McNeil, 1990; Henningfield, 1995). The nicotine from NRT similarly binds to the
nAChRs to relieve withdrawal and craving symptoms. These withdrawal symptoms can be alleviated with relatively low blood levels of nicotine. The nicotine dose from NRT is sufficient to saturate the nAChRs but the lower dose makes smoking less satisfying by desensitizing the nAChRs. Thus, even if a person smokes while using NRT, the behavior will be less rewarding (Benowitz, 2009).

NRTs come in various forms and delivery methods. Nicotine gums were the first type of NRT developed and used in the market. They were formulated in two possible dosages: 2 mg or 4 mg and designed to deliver nicotine through the buccal mucosa in the mouth. Nicotine will then be systematically absorbed and reach the brain to exert its normal therapeutic actions (Russell, Feyerabend, & Cole, 1976). Transdermal patches are another type of NRT widely used. Patches are available in doses of 7 mg, 14 mg and (more commonly) 21 mg. They were designed to be applied over a 24-hour period (Fiore, Jorenby, Baker, & Kenford, 1992). Patches are normally used in 10-week treatment periods, although adherence is low in most smokers (Zhang, Cohen, Bondy, & Selby, 2015). Other forms of NRT include: lozenge, tablet, nasal spray and inhaler. The use of NRT products like gum and lozenges allow smokers to self-dose with nicotine when they have an urge to smoke. Patches, on the other hand, deliver nicotine gradually and result in sustained nicotine levels throughout the day. Therefore, when using patches, the positive reinforcement normally present when one smokes a cigarette, is diminished. Overall, all forms of NRT have been shown to be effective for smoking cessation. Clinical studies have shown that NRT usage significant increases odds of successfully quitting by 2 times compared to placebo [OR=1.77 95%CI: 1.66-1.88] (Silagy et al., 2004). A strong advantage of using NRT is that they are safe and severe side effects with NRT usage is rare (Tonstad, Gustavsson, Kruse, Walmsley, & Westin, 2014). However, side effects such as nausea are commonly experienced. Some individuals have also developed skin irritation and rashes in response to patch usage (Health Canada, 2011).

1.5.4.4. Bupropion

Bupropion hydrochloride (HCL) sustained released, marketed as Zyban, was the first licensed non-nicotine pharmacological therapy for smoking cessation in 1997 (CW, 2015). It was originally used as an atypical antidepressant in the USA and other countries. The development of bupropion for tobacco dependence was based on the random clinical finding that when smokers received bupropion for depression, they reported less desire to smoke and were spontaneously quitting (Aveyard & Dautzenberg, 2010). The generic bupropion SR is identical to Wellbutrin and Zyban in terms of dosage, pharmacokinetic and bioavailability. Thus, they have been proven bioequivalent to the brand name.
1.5.4.4.1. Mechanism of Action of Bupropion

The exact mechanism of action for bupropion in smoking cessation has not been clearly established. Bupropion is a beta-phenylethylamine derivative. Some studies have shown that it preferentially blocks norepinephrine and dopamine re-uptake in the mesolimbic system and the nucleus accumbens (Wilkes, 2008). Thus, bupropion is a dual inhibitor of dopamine and norepinephrine but also, to a weaker extent, serotonin reuptake (Stahl et al., 2004). The actions of bupropion on dopamine reuptake in the nucleus accumbens are the most implicated in its effects as a smoking cessation treatment. Bupropion prolongs the duration of dopamine, and thus prevents withdrawal and craving symptoms that occur in the abstinence of nicotine. Additionally, inhibition of the reuptake of dopamine results in the decrease of dopamine bursts that occurs in response to smoking. Therefore, smoking may not be as reinforcing and pleasurable when using bupropion (Warner & Shoaib, 2005).

The exact role of the effects of bupropion on norepinephrine reuptake inhibition in smoking cessation is unclear. However, norepinephrine release in the hippocampus plays a role in withdrawal (Done & Sharp, 1992). Thus, bupropion potentially could help reduce withdrawal symptoms by inhibiting reuptake of norepinephrine. The effect of bupropion on serotonin reuptake inhibition and smoking cessation is being investigated. It is unclear whether bupropion’s actions are mediated by its effect on serotonin reuptake. Bupropion is also a weak antagonist of the nicotine receptors and blocks the reinforcing effects of nicotine (Ascher et al., 1995; Slemmer, Martin, & Damaj, 2000). Bupropion is metabolized into three active metabolites by cytochrome 2B6. Hydroxybupropion, one of the three metabolites, has been show in recent studies to possibly contribute to the pharmacological effects of bupropion for smoking cessation (Damaj et al., 2004) where a metabolite-response relationship was seen for hydroxybupropion but not for bupropion. Hydroxybupropion could potentially have greater inhibition effects than bupropion (the parent drug) in blocking dopamine, norepinephrine and the nAChRs (Damaj et al., 2010).

1.5.4.4.2. Pharmacokinetics of Bupropion

The approved dosing regimen of bupropion for smoking cessation in clinical practice is titrated 150 mg twice daily. Bupropion is recommended for smokers who smoke 10 or more cigarettes per day. Bupropion reaches steady state in the body after 5-8 days of treatment initiation (Aubin et al., 2004). Thus, smokers are advised to commence bupropion usage 7-14 days prior to their target quit date and continue treatment for a total of 12 weeks (Patel, Feucht, Reid, & Patel, 2010; West, 2003). A single dose of 150 mg bupropion results in a Cmax of 100 ng/ml after approximately 3 hours. The purposes of titrating are to allow for the body to adapt to bupropion and also for stable brain
concentrations of bupropion to be reached (West, 2003). Bupropion is orally administered and is absorbed through the gut, extensively metabolized in the liver and excreted through the kidneys. The elimination half-life of bupropion is approximately 21 hours. Bupropion is extensively metabolized by cytochrome 2B6 (CYP2B6) and CYP2D6 in the liver to its three metabolites: hydroxybupropion, threohydrobupropion and erthrobupropion (Jefferson, Pradko, & Muir, 2005). It is hypothesized that the primary pharmacological effects of bupropion are exerted through its three major metabolites (Warner & Shoabi, 2005). CYP2B6 is a polymorphic enzyme and thus can result in variability in response to bupropion treatment (Lee et al., 2007). Bupropion is also a potent inhibitor of the CYP2D6 enzyme (Kotlyar et al., 2005). Due to this effect, bupropion can result in drug-drug interactions with compounds that are metabolized by CYP2D6. Thus, some antidepressants have been contraindicated for concurrent use with bupropion (Wang et al., 2006; Wilkes, 2008).

1.5.4.4.3. Clinical Efficacy Studies involving Bupropion

Many clinical studies have been conducted to evaluate the efficacy of bupropion for smoking cessation. One large-scale randomized placebo controlled study was conducted in 1997. In this study, participants were randomly assigned to 100, 150 or 300 mg/day of bupropion or placebo for 7 weeks. At end of treatment (EOT), the highest quit rate was observed with subjects treated with 300 mg of bupropion/day. The 7 Day Point Prevalence of Abstinence at EOT for this group was 44% versus 19% for placebo (Hurt et al., 1997). A recent meta-analysis confirmed the superior clinical efficacy of bupropion compared to placebo with an OR of 1.82 and 95%CI: 1.60-2.06. The Cochrane review also showed a risk ratio over placebo of 1.69 (95%CI: 1.53-1.85) (Hughes et al., 2007). Clinical studies with a head-to-head comparison of bupropion to NRT showed equal efficacy (OR=0.99) (Cahill, Stevens, Perera, & Lancaster, 2013). Clinical studies involving long-term smoking abstinence of smokers treated with bupropion have also been conducted. In one of these studies, the OR of being smoking abstinence at 52 weeks (one year after treatment initiation) was 1.46 with a 95% CI: 1.00-2.14 for bupropion compared to placebo. Other studies have confirmed this trend (Evins et al., 2005; Hays et al., 2001). Bupropion dosage can also be personalized to meet different the needs of smokers. In a previous clinical trial study, extended bupropion treatment during pre-quit reduces smoking behaviors and improves short-term abstinence rates (Hawk et al., 2015).

Unfortunately, real-world data on the effectiveness of bupropion is limited. Some studies indicate a similar quit rate with bupropion in real-world settings (Holmes et al., 2004). A cross-sectional study of a multi-national population indicated improved quit outcomes on bupropion compared to not using any cessation aids (Kasza et al., 2013). Studies have also indicated that bupropion may be more efficacious or better tolerated in a population of smokers with comorbidities or certain genetic
polymorphisms (David et al., 2007; Tonstad, 2002). Overall, bupropion is clinically effective for smoking cessation by decreasing nicotine withdrawal symptoms and craving.

1.5.4.4.4. Safety of Bupropion

Bupropion is relatively safe and well tolerated in the general population at its approved dosages. However, due to its multiple pharmacological mechanisms of action, side effects may be experienced. The most common adverse effects associated with bupropion use are: insomnia (24-42%), headache (4-33%), dizziness (2-11%) dry mouth (6-28%), nausea (9-13%) and anxiety (5-9%) (Wilkes, 2008). Allergic reactions, sensitivity have been reported, however infrequently (Boshier, Wilton, & Shakir, 2003; Wilkes, 2008). Altogether, adverse events are only experienced by 50% of patients in the first two weeks of taking bupropion and this rate drops to 6% by 3 months into treatment (Barrueco et al., 2005). Additionally, most of the adverse effects resolve on their own without clinical interventions. It is important to note that many adverse reactions to bupropion are similar to those experienced of nicotine withdrawal symptoms and therefore it is difficult to distinguish them. Bupropion use is contraindicated in patients with history of seizures, bipolar affective disorder, eating disorders, pregnancy and breast-feeding (GlaxoSmithKline 2006). Lastly, 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). This claim was based on a report showing increased risk of reported depression and suicidal behavior with bupropion compared to NRT (Moore, Furberg, Glenmullen, Maltsberger, & Singh, 2011). This claim has now been removed in light of findings from a clinical trial assessing neuropsychiatric safety of varenicline and bupropion where the authors concluded that these medications are safe and should not have black box warnings (Anthenelli et al., 2016).

1.5.4.4.5. Compliance with Bupropion Treatment

The major limitation of bupropion treatment is its low compliance rate. This is partly due to side effects during treatment. Generally, studies have shown that compliance rates drop to approximately 75% by the third week of treatment. The rate further drops to 40% by week 7 and 28% by week 10 into treatment (Kohlenberg, Antonuccio, Hayes, Gifford, & Piasecki, 2004). Another study suggested that approximately 9% of participants discontinued bupropion use at some point during the 12 weeks treatment period. A study conducted comparing bupropion and bupropion with NRT indicated that only 63% of participants were using bupropion 5 days into treatment period (Stapleton et al., 2013). In clinical research settings, bupropion compliance can be validated by self-report measures or biochemically. Nonetheless, although bupropion has been shown to be clinically efficacious, real-world effectiveness of bupropion may be restricted by poor adherence in the treatment period.
1.5.4.5. Varenicline

Varenicline tartate is the second prescription-only approved first-line pharmacotherapy for smoking cessation. In Canada, it is sold under the brand name Champix, manufactured by Pfizer Inc. The compound was originally discovered and synthesized by Jotham Coe, PhD and Brian O’Neil as a novel smoking cessation agent at Pfizer (Coe et al., 2005). After further investigations, varenicline has been approved for smoking cessation use since 2007 (Lam & Patel, 2007).

1.5.4.5.1. Mechanism of Action of Varenicline

Varenicline is a selective partial agonist of the α4β2 nAChR and binds to the receptor with high affinity (Hays, Ebbert, & Sood, 2008; Jiménez-Ruiz et al., 2009). There are currently two proposed mechanism of actions that explains how varenicline aids with smoking cessation. In the first theory, varenicline binds to the α4β2 receptor, which leads to release of dopamine in the brain reward pathway. Varenicline’s effect on dopaminergic neuronal release alleviates the withdrawal and craving symptoms that arise in the absence of dopamine in these regions of the brain during a period of nicotine abstinence. Since varenicline is a partial agonist, it will not elicit a substantial increase in the extracellular dopamine levels. In rodent studies, when a maximum dose of 1mg/kg of varenicline is applied, the dopamine release by varenicline in the nucleus accumbens is only approximately 60% of what is normally maximally produced by nicotine (Coe et al., 2005). Secondly, it has been shown that the affinity of varenicline for the α4β2 receptor is 16 times higher than nicotine. Thus, when nicotine is present, varenicline competes with nicotine for the receptor binding site and had antagonism activity. Although varenicline produces only 50% of the response of nicotine, it can simultaneously block the effects of any nicotine added to the system due to its partial agonist properties. Therefore, when someone smokes in the presence of varenicline, the nicotine-inducing effects of smoking will be blocked (Coe et al., 2005). Another theory suggests that varenicline also has affinity for the serotonin 5-HT3 receptor however; this characteristic seems to be independent of its effects on smoking cessation (Jiménez-Ruiz et al., 2009). In addition to its high affinity for the α4β2 receptor, varenicline has also shown weak affinities for other sub-types of the nAChRs such as α3β2 and α6 containing receptors. Varenicline is also a full agonist at the homomeric α7 nAChR (Mihalak, Carroll, & Luetje, 2006). It is currently unclear whether these additional mechanisms of actions play any role in effects of varenicline on smoking cessation.
1.5.4.5.2. Pharmacokinetics of Varenicline

Clinically, varenicline is prescribed to daily smokers who smoke 10 or more cigarettes per day. Patients are advised to start varenicline one to two weeks prior to their quit date. The standard dose for varenicline is 1 mg twice a day. The dose is titrated to give the body adequate time to adjust and minimize side effects (Lam & Patel, 2007). An important pharmacokinetic characteristic of varenicline is that when orally administered, it is highly bioavailable and is unaffected by the presence or intake of food. A single dose of 1 mg varenicline administered in healthy smokers results in a maximum plasma concentration of approximately 5 ng/ml in about 3-4 hours (Faessel et al., 2010). Also, varenicline undergoes very minimal biotransformation. In fact, more than 90% of orally administered varenicline is excreted in urine in its uncharged form. A small percentage of ingested varenicline undergoes N-carbamoyl glucuronidation and oxidation to produce varenicline N-carbamoylglucuride and N-glucosylvarenicline (Obach et al., 2006). The elimination half-life of varenicline is about 24 hours and it is primarily eliminated in urine by the kidneys (Faessel et al., 2006). Varenicline is also partially cleared by active tubular secretion through organic cation transport OCT2. Thus, polymorphic variations in OCT2 or impaired kidney function could potentially affect the elimination of varenicline and consequently affect the efficacy and safety of varenicline (Bergen et al., 2014; Feng et al., 2008). Additional studies have shown that varenicline does not inhibit or induce any major cytochrome P450 enzymes. Since varenicline is not metabolized by cytochrome P450s, nor do they affect its activity, there is little potential for any interaction between varenicline and other drugs that go through these enzymes (Faessel et al., 2010). Therefore, it could be a suitable choice for smokers with comorbidities, who may be administering multiple medications for treatment of other conditions.

1.5.4.5.3. Clinical Efficacy Studies of Varenicline

Several clinical studies have been conducted on the superior efficacy of varenicline for smoking cessation compared to other available pharmacotherapies, bupropion and NRT (Ebbert et al., 2015; Koegelenberg et al., 2014; Tulloch, Pipe, Els, Clyde, & Reid, 2016). In a pooled-analysis of two Phase III clinical trials by Gonzales et al., (Gonzales et al., 2006) and Jorenby et al., (Jorenby et al., 2006), treatment with 1 mg of varenicline taken twice a day led to significantly higher quit rates than both bupropion and placebo. The continuous abstinence rates at EOT were 44% in subjects 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 in participants treated with varenicline. Thus, varenicline relieved craving once the participants stopped smoking. A recent clinical trial conducted comparing NRT, flexible NRT and varenicline for smoking cessation showed that continuous abstinence rates (weeks 2-52) was
significantly higher for varenicline (36%) than NRT (29%) with an OR of 1.84 and a 95% CI of 0.94-3.58 (Tulloch, Pipe, Els, Clyde, & Reid, 2016). Another recent clinical trial study evaluated the efficacies of varenicline and bupropion for smoking cessation in a sample of 405 individuals over a year. Participants randomized to varenicline had significantly higher quit rates at EOT than bupropion (31% versus 18% respectively). Additionally, by week 52, varenicline still had significantly higher quit rates than bupropion (14% versus 6% respectively) when using 7 Day PPA and Point Abstinence as measures (Benli et al., 2017).

Recent meta-analyses of studies in smoking cessation showed that varenicline was more efficacious than placebo with an OR of 2.88 and a 95% CI of 2.40-3.27. Varenicline significantly increased odds of quitting compared to bupropion with an OR of 1.59 and a 95% CI of 1.29-1.96. Varenicline also increased the odds of quitting compared to any 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 in 2015. This analysis indicated that varenicline quit rates were 49% at weeks 9-12 (EOT) and 22% at week 52 from treatment initiation. The relapse rate in the varenicline group was similar to the group of subjects receiving placebo (55% versus 53% respectively). Nonetheless, overall, a significantly higher percentage of subjects using varenicline were able to quit at one year after treatment initiation (Agboola, Coleman, McNeill, & Leonard-Bee, 2015).

Despite the proven efficacy of varenicline in clinical trials, data on effectiveness of varenicline in real-world settings are limited. One prospective pragmatic intervention study reported biochemically confirmed continuous quit rate of 58.3% at EOT with subjects treated with varenicline combined with behavioral therapy (Ramon & Bruguera, 2009). Another study performed a retrospective chart review of participants with or without psychiatric comorbidities while measuring the real-world effectiveness of varenicline. The quit rate at EOT with varenicline was 33.7%, which was twice the quit of NRT (18.4%) [RR: 1.82 95%CI: 1.22-3.03]. These results were significant after adjusting for a number of baseline and demographic characteristics (Kaduri et al., 2015). However, the knowledge of the real-world effectiveness of varenicline is limited to findings of observational studies. Therefore, a randomized study can provide additional certainty on how varenicline affects quit rates outside clinical trial settings.

1.6.5.6.5. Safety of Varenicline

Varenicline is generally well tolerated. In most cases, occurrences of adverse events experienced by patients are comparable to that of bupropion and placebo. The adverse events are similar across treatments because smoking abstinence leads to similar symptoms and therefore it is difficult to
distinguish smoking cessation indications and adverse events from treatments (Jimenez-Ruiz et al., 2009). The most common side effects associated with varenicline use are nausea (30%), insomnia (18%), headache (15%), abnormal dreams (13%), constipation (30%) and abdominal pain (7%). Other reported symptoms include: sleep disturbance, dizziness, dry mouth, increased appetite and weight gain (Garrison & Dugan, 2009; Lam & Patel, 2007). Generally, these side effects are not serious and only temporarily experienced within the first few weeks of treatment.

1.5.4.5.5. Compliance Rates of Varenicline Treatment

The efficacy of most smoking cessation treatment is limited by low compliance rates. Studies have shown a positive correlation between treatment and quit outcome. 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. In this study, 55.7% of participants never initiated varenicline treatment. Of those who started medication usage, only 54.9% of them finished the full 12 weeks course of treatment. The abstinence rates were also measured where in the full adherent group, 50.7% of participants successfully quit compared to the non-adherent group where only 30% of them became abstinence (Liberman et al., 2013). The results of this study could have been confounded by factors such as motivation to quit. Smokers who remained fully compliant with treatment could have been more motivated to quit and thus more like to be abstinent. In a systematic review, compliance rates of two clinical trials of head-to-head comparisons of varenicline and bupropion were examined. It was shown that adherence to medication is highly correlated with improved tobacco abstinence. The chances of quitting when treated and fully adherent to varenicline was significant higher than placebo with an OR of 3.96 and a 95%CI of 2.98-5.25 (Hays et al., 2010). Overall, varenicline is an effective pharmacotherapy for smoking cessation despite its low compliance rates.

1.5.4.5.6. Clinical Trials Comparing Efficacies of Bupropion versus Varenicline

There are currently only five individual clinical trials comparing bupropion and varenicline in clinical settings when used as smoking cessation pharmacotherapies between 2006 and 2014. As mentioned previously, clinical trials conducted in 2006 by Gonzales et al. (2006) and Jorenby et al., (2006), head-to-head comparisons of bupropion and varenicline showed that quit rates with varenicline was significantly higher than bupropion at EOT (Gonzales et al., 2006; Jorenby et al., 2006). Another clinical trial explored efficacies of varenicline versus bupropion plus intensive smoking cessation counseling. In this study, varenicline use was associated with a significant increase in quit rate at EOT however by 6 months and 12 months, quit rates of varenicline and bupropion were not significantly different (Cinciripini et al., 2013). The most recent clinical trial
conducted in 2014 examined the efficacy of combination varenicline and bupropion therapy compared to varenicline monotherapy. Combination varenicline and bupropion treatment significantly increased quit rates at EOT and at 6 months, however after one year, quit rates of combination varenicline and bupropion therapy and varenicline monotherapy were not significantly different (Ebbert et al., 2014). Additionally, varenicline can be adjusted to meet specific needs of smokers. For example, in clinical settings the dose of varenicline can be reduced in smokers experiencing persistent side effects. Varenicline can be used long-term to maintain abstinence or to prevent relapse (Ebbert, Wyatt, Hays, Klee, & Hurt, 2010). On the other hand, varenicline can also be administered for an extended duration during pre-quit periods to aid smokers reduce smoking behaviors prior to becoming fully abstinent (Ebbert et al., 2015). In conclusion, varenicline is an efficacious smoking pharmacotherapy in clinical settings however, real-world data of varenicline efficacy is limited.

1.5.4.6. Technology-Based Interventions

In the present era of mobile phones and technology, new innovative approaches are necessary to attract smokers who might not respond well to traditional designed smoking programs. Technology has become a crucial part in lifestyles of many people. Technology is widely used and instantly accessible (PEW 2014). Therefore, interventions delivered through the Internet and mobile devices are expected to contribute significantly to behavioral changes such as smoking cessation. To date, there are already cessation aids offered via text messaging services and mobile applications. The appealing aspect of these interventions is that they can be personalized. For example, some mobile applications remind smokers of the progress they have made and aid them to set and achieve reachable goals. Recent studies have shown that these self-help online and mobile-based smoking interventions are effective at increasing quitting success rates compared to no treatment (Civiljak, Stead, Hartmann-Boyce, Sheikh, & Car, 2013; Hartmann-Boyce et al., 2013; Whittaker et al., 2012). A recent study evaluated the efficacy of a video-based intervention on smoking cessation outcomes and found that while it was not more effective than pharmacotherapies in short-term abstinence measures, long-term abstinence rates were higher than pharmacotherapies (Stanczyk, de Vries, Candel, Muris, & Bolman, 2016).
1.5.5 Nicotine Metabolism and Tobacco Dependence

1.5.5.1. Nicotine Metabolism and its Metabolites

As mentioned before, there are many factors that will predetermine the level of nicotine dependence and affect one’s ability to quit smoking successfully. One of these factors is the rate of nicotine metabolism. Nicotine is extensively metabolized in the liver by cytochrome 2A6 (CYP2A6) enzyme (Hukkanen et al., 2005). Approximately 80% of nicotine is metabolically inactivated by CYP2A6 into its major metabolite, cotinine (COT), which has a half-life of 16-18 hours (Benowitz & Jacob, 1994). Cotinine then undergoes further biotransformation to produce 3’-hydroxycotinine (3HC). The biotransformation of cotinine to 3HC is exclusively metabolized by the same enzyme CYP2A6 (Messina, Tyndale, & Sellers, 1997). Figure 1 shows the nicotine metabolism pathway. 3HC has a shorter half-life than nicotine and is eliminated by 50% in about 5 hours. Numerous studies have shown that there is high inter-individual variability in the intrinsic hepatic clearance of nicotine (Raunio, Rautio, Gullstén, & Pelkonen, 2001). In fact, twin studies have demonstrated that 60% of this variation is attributable to genetic factors (Swan et al., 2005). Other than genetic sources of variability, demographic characteristics such as age, gender and ethnicity can also affect enzyme activity. Additionally, it is believed that CYP2A6 activity is influenced by environmental factors including the presence of inhibitors and inducers of the enzyme (M. J. Chenoweth et al., 2014). An example of such an inhibitor is estrogen.

![Figure 1. The Metabolism Pathway of Nicotine into its two main metabolites, cotinine and trans-3’-hydroxycotinine (3HC)(Atoum & Al-Khatib, 2017).](image)

1.5.5.2. Nicotine Metabolism Ratio (NMR)

To quantify an individual’s CYP2A6 enzyme activity, a representation of the genotype should be employed. Unfortunately, genotyping is very expensive and does not provide an accurate measure of nicotine metabolism. A novel biomarker has been developed which takes into consideration all sources of variability, called the Nicotine Metabolite Ratio or NMR. NMR is a representative measure of nicotine metabolism. NMR is a ratio of the 3’-hydroxycotinine (3HC) over cotinine (COT) concentration. NMR is a validated non-invasive phenotypic marker of CYP2A6 activity and can be easily measured in urine, saliva or plasma (Dempsey et al., 2004). NMR has been recognized as a reliable marker of CYP2A6 activity on the basis that the biotransformation of cotinine to 3HC is
almost a direct function of CYP2A6 activity. Although 3HC has a shorter half-life compared to COT, its elimination is limited by COT formation. Therefore, 3HC concentration in biological fluids is directly proportional to its rate of formation. Thus, the ratio of 3HC to cotinine remains constant (Benowitz, Pomerleau, Pomerleau, & Jacob, 2003). Additional studies have shown that there is little to no evidence suggesting any within subject viability of this ratio (Dempsey et al., 2004). Studies have shown that NMR is not affected by the time of sampling and remains relatively constant from day to day in regular or daily smokers. Thus, a single sample can provide an accurate measure of NMR of individuals (Lea, Benowitz et al., 2006).

1.5.5.3. NMR and Smoking Behaviors

Many studies have been conducted to evaluate the association between nicotine metabolism and various smoking behaviors. Studies have used NMR as a marker to study the relationship between nicotine metabolism and smoking behaviors. Nicotine metabolism can be categorized as fast or slow metabolizers by using NMR measures. One study has found that faster metabolizers take deeper puffs of their cigarettes (Strasser et al., 2011). Studies have shown that NMR is positively correlated with number of cigarettes smoked per day (Benowitz et al., 2003). Rapid metabolizers smoke more per day, consistent with the fact that they clear nicotine faster and therefore need to smoke more frequently to maintain a steady level of nicotine in their body (Benowitz et al., 2003). However, another study investigated the same relationship in a sample of African American light smokers and reported no significant correlation between NMR and cigarettes per day (Ho et al., 2009). This suggests that ethnicity may affect nicotine metabolism variations between smokers. There has been a recent interest in nicotine metabolism variations as related to different ethnicities. There are known racial differences in the rate of nicotine metabolism with African Americans on average having a slower rate of nicotine metabolism compared to Whites (Chenoweth et al., 2014). Overall there was a greater step-down, linear type relationship between NMR groups and cotinine or cotinine/cigarette in African Americans, which is consistent with the idea that differences in blood cotinine levels between the African American NMR groups were primarily due to differences in CYP2A6 enzyme activity without titration of nicotine intake among faster nicotine metabolizer (Ross et al., 2016). More recent studies have found an association between higher NMR and increased nicotine dependence (Benowitz et al., 2003; Falcone et al., 2011; Schnoll et al., 2014). The role of nicotine metabolism variation is different in various developmental stages of smoking behaviors. For example, young smokers who are slow metabolizers have been shown in one study to have a 53% increased chances [OR=1.53 95%CI: 1.11-2.11, P=0.009] of developing nicotine dependence compared to normal metabolizers (Olfson et al., 2016). All the evidence indicates that nicotine dependence is a multifactorial trait and is influenced by more than nicotine metabolism. Consistent with these
findings, another study has found that NMR can predict early onset of withdrawal symptoms in the absence of cigarettes (Hendricks, Delucchi, Benowitz, & Hall, 2014).

### 1.5.5.4. NMR and Smoking Cessation Treatment Outcomes

To improve treatment efficacy, many studies have utilized the nicotine metabolism biomarker to identify smokers who would respond better to certain treatments. In these studies, NMR assignment was conducted post hoc. One study found that NMR accurately predicted treatment outcome in a sample of smokers being treated with 8 weeks of open-label transdermal nicotine patch. In this study, smokers were categorized as slow or normal metabolizer on the basis of their baseline 3HC/COT ratio measures (NMR). The odds of quitting differed by 70% between slower and faster metabolizers. When adjusted for nicotine dependence levels, body mass index, ethnicity and gender, these results were still significant. However, NMR levels were not associated with abstinence rates in smokers treated with nicotine nasal spray (Lerman et al., 2006). A similar study validated these findings when controlling for variables such as age, gender, ethnicity and nicotine dependence (Schnoll et al., 2009). Additionally, a study of African American light smokers demonstrated a significant association between CYP2A6 and quitting smoking success. Interestingly, this effect was more pronounced in females (Ho et al., 2009).

CYP2A6 activity has also been shown to correlate with response to non-nicotine pharmacotherapies. The relationship between NMR and bupropion treatment outcome combined with counseling was investigated in a study where smokers were categorized into 4 quartiles based on their NMR value. Abstinence rates were evaluated at end of the 10-week treatment. In this study, slow metabolizers treated with bupropion or placebo had similar quit rates (32%). However, quit rates were very low in fast metabolizers receiving placebo (10%). This quit rate was significantly improved when treated with bupropion (34%) (Patterson et al., 2008). This could suggest that bupropion treatment does not provide additional benefit to slow metabolizer smokers but is beneficial to fast metabolizers. Ergo, NMR can be a promising marker to help prescribe bupropion to those who will benefit the most from it. In addition, this can help avoid unnecessary exposure to those who do not benefit from bupropion treatment but could suffer from possible side effects. A recent prospective study examined the role of NMR in varenicline treatment compared to treatment with the nicotine patch. In this randomized, placebo-controlled clinical trial, treatment-seeking smokers were assigned to placebo, patch or varenicline. EOT 7 Day PPA rates were assessed. Varenicline was more efficacious for normal metabolizers (38.5%) compared to nicotine patch (22.5%). In slow metabolizers, varenicline (38.5%) and nicotine patch (27.7%) resulted in similar abstinent rates. However, slow metabolizers using varenicline reported more severe side effects compared to fast metabolizers (Lerman et al., 2015).
This demonstrates that varenicline does not provide additional benefit to slow metabolizers; it also places them at higher risk of adverse reactions. Studies to date have focused on the role of NMR in treatment response to NRT or placebo versus non-nicotine pharmacotherapy. Unfortunately, no study has compared bupropion and varenicline to evaluate if CYP2A6 activity differentially affects treatment outcome with these two medications. In terms of personalized medication, NMR has the potential to help improve treatment outcomes whilst also minimizing side effects.

1.5.6. **Summary of Objectives and Hypotheses**

It has been demonstrated that tobacco use disorder is a chronic, relapsing and multidimensional condition. It is the single most preventable cause of disease, disability and death worldwide. Thus, reducing smoking prevalence can decrease premature death and reduce the economic burden on the healthcare system. There are currently only two first line prescription-only pharmacotherapies that have been approved for use in Canada: bupropion and varenicline. These pharmacotherapies have been proven efficacious in various clinical trials. Clinical trials assess the efficacy of medication in ideal conditions, which is not what we see in real-world settings. Therefore, the effectiveness of these smoking cessation pharmacotherapies needs to be evaluated in real-world settings. However, the data on real-world effectiveness of bupropion and varenicline are limited. Many factors, such as accessibility, and affordability, limit the use of these medications to less than half of smokers intending to quit. Additionally, there is limited data on real-world medication adherences in real-world settings which might also be a factor limiting the efficacies of these medications. This only highlights the need for methods that address these barriers to increase the use and adherence of these efficacious medications. Even though these medications have been shown to double the chances of successfully quitting smoking, the respective smoking cessation efficacies are far from optimal and relapse to smoking is common. There is also a substantial body of literature reporting on individual differences in tobacco dependence susceptibility and different responses to treatment. One factor to gain attention recently is nicotine metabolism. However, data on whether or not these factors affect bupropion and varenicline treatment outcomes are limited. Altogether, there is a need to assess the real-world effectiveness of bupropion and varenicline using an innovative approach to avoid aforementioned barriers. Additionally, it is vital to explore how individual characteristics affect nicotine dependence and quit outcomes with treatment of bupropion and varenicline. Understanding the roles of such inherited characteristics could potentially more accurately design smoking cessation treatments to maximize medication’s efficacy whilst minimizing adverse reactions. It may also be possible to identify potential targets for new smoking cessation pharmacotherapies/regimen designs.
2.0 METHODS

General Overview

MATCH stands for Medication Aids for Tobacco Cessation Health, and was the product of scientists at the Nicotine Dependence Clinic (NDC) of The Centre of Addiction and Mental Health (CAMH). MATCH was an open label study where participants were randomized to receive one of two study medications: bupropion (Zyban) or varenicline (Champix). Eligible participants received 12 weeks of pharmacotherapy by mail. Participants were also given a chance to participate in the optional Genetic Sub-Study. Weekly motivational emails were sent to each participant for the entire treatment period (12 weeks). Saliva samples were collected at baseline (prior to starting medication) and mid-treatment (4 weeks into medication regimen). Participants who consented to the Genetic Sub-study submitted an additional saliva sample at baseline for DNA extraction and analysis. Follow up surveys were conducted at 4 weeks, 8 weeks, 12 weeks, 6 and 12 months where information regarding smoking status, smoking habits, medication adherence and adverse events were collected. Additionally, saliva samples for confirmation of smoking abstinence were provided by participants who had self-reported being quit at 6 months and/or 12 months.

2.1 General Study Design

MATCH was designed in a patient-driven way. In other words, participants were not approached by study personnel to be recruited into the study. Treatment seeking smokers who found out about the study visited the study website and self-registered. All enrollments and follow-ups were conducted via the Internet. A schematic of the study design can be seen in Figure 2 where initially participants were led to the MATCH study home page (matchstudy.ca). They were instructed to click on a link, which took them to the Online Portal Data Collection Platform (Appendix I). Participants were then instructed to read the Study information (Appendix II) and the consent forms (Appendix III). Once consent was provided by clicking “yes”, the participants answered a series of questions that assessed their eligibility (Appendix IV). The baseline survey included questions regarding basic demographics, smoking behaviors, past/present medication usage and etc. At the end of the questionnaire, participants had the option to participate in the genetic sub-study. If interested, participants were directed to read the Sub-Study information and Consent Forms (Appendix XIV). Consenting individuals completed The Big Five Personality Trait (BFAs) personality test. This 100-item survey was answered with a 5-point scale ranging from Strongly Agree to Strongly Disagree when asked how participants felt about a prompted scenario.
2.2 Study Flow

Participants Assessed (On website)

Ineligible

Eligible Participants Randomized (1:1)

Visits Physician

Did Not Receive Medication

Pharmacy Counseling

Medication Mailed Saliva Collection Kit Mailed

Varenicline

Bupropion

Discontinued Medication

4 Weeks Follow-up Saliva Collection Kit Mailed

8 Weeks Follow-up

12 Weeks Follow-up

6 Months Follow-up Saliva Collection kit Mailed

12 Months Follow-up Saliva Collection kit Mailed

BFAS Test

Recruitment

Randomization

Follow-Up

Weekly Motivational Emails for 12 Weeks

Figure 2 Schematic of Study Flow Chart. General flow of participants through the study.
After submitting the questionnaires, an automated on-screen message appeared to inform whether each participant was eligible or not (Appendix V). If eligible, the online portal system automatically randomized the participant to one of the treatment arms: bupropion or varenicline. At this time, an enrollment email was sent to notify participants of their medication assignment and included important information for future steps to receive medication. The enrollment email contained vital documents, namely: the Letter to the Doctor (Appendix XVIII) and The Standard Script (Appendix XIX) for the medication they were randomized to. The Standard Script and Letter to Doctor were for participants to give to their doctor to complete. The email also included a copy of the Study Information and Consent Form. Participants who had consented to the Genetic Sub-study received a second email with the Genetics Consent Form (Appendix XIV) and Sub-Study information (Appendix XVII). The Study information form contained basic study information for participants to keep for their own records. The Genetic Consent Form was sent for those participants who had consented to the genetic sub-study and was also for their own records.

Participants had a 5-week window in which they could visit their family physician or a licensed physician from a walk-in clinic, bringing the “Letter to the Doctor” and “Standard Script” documents with them. During this visit, the participants discussed with their physician if the randomized medication was suitable for them and if there were any contraindications for using the medication. Participants whose physician did not prescribe the assigned medication still received motivational emails however their data were not included in the main analysis. On the other hand, if deemed appropriate and there were no contraindications, the physician signed the Standard Script and faxed it to the contract mail-order pharmacy. When the prescription was received, the pharmacist conducted a brief 5-minute telephone counseling with the participant to confirm eligibility, medication and mailing address. When completed, the 12-week supply of bupropion or varenicline was courier delivered to each participant.

The pharmacy information was logged in the Pharmacy Online Portal (Appendix XXII) where participant profiles were activated when their medication was dispensed. Once activated, the system automatically started the follow up schedules with activation date as the beginning of treatment period. Participants chose their quit dates within 30 Days of starting medication however, they were advised to start the assigned medication 7-14 days prior to their quit date. During this treatment period, motivational emails were sent (regardless if the participant had decided to use medication or visit a doctor), which included motivational tips and suggestions to aid in the participant’s smoking cessation attempt.
All participants were followed up for the duration of the study. Follow up surveys were conducted online at 4 weeks, 8 weeks, 12 weeks and 6 months and 12 months (Appendix XXIII) where data related to smoking cessation outcome, medication compliance and adverse events was collected. Short-term abstinence was assessed at weeks 4, 8 and 12 (end of treatment) whilst long-term abstinence was evaluated at 6 months and 12 months from commencement of medication. Participants were emailed at various times to complete their follow up surveys where a direct link was attached. Saliva samples were collected and mailed back at baseline, mid-treatment, and conditionally at 6 and 12 months if participants had self-reported abstinence. The samples were used for NMR evaluation, biochemical confirmation of smoking abstinence and biochemical confirmation of medication compliance (Section 2.17.3 NMR analysis). Participants who consented to the Genetic Sub-study also provided a separate saliva sample for DNA extraction and analysis.

### 2.2 Research Ethics Board (REB) and Registration

The MATCH study protocols were approved by standing Research Ethics Board (REB) at the Centre for Addiction and Mental Health under the protocol number 200/2012. This study was reviewed and approved annually. The MATCH study is registered on Clinicaltrials.gov under: NCT02146911.

Additionally, all personnel who were related to the study have completed the following trainings:

- Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans Course on Research Ethic (TCPS)
- Good Clinical Practice (GCP)
- Privacy Fundamentals
- Privacy in Research
- Standard Operating Procedure (SOP)
- Responsible Conduct of Research (RCR)
- CITI Privacy Training

The MATCH study was conducted in accordance with GCP and TCPS guidelines.

### 2.3 Subject Recruitment

Study recruitment began on June 6th 2014 and ended on Jan 10th 2017. The two most efficient methods of study recruitment were by email promotion and Facebook advertisements. Other methods included by word of mouth across Public Health Units, Community Health Centers and Family Health Teams, Smoker’s Help Line, and other social media accounts.
Mass-email Promotion

Three mass email events within the STOP program at the Centre for Addiction and Mental Health occurred for MATCH study promotion. The STOP program is an Ontario-Wide Program with mass Nicotine Replacement Treatment (NRT) distribution for interested smokers who are looking to quit. The program has a research component that is co-investigated by Dr. Zawertailo. As part of the STOP program, a component of the consent procedure included consenting to be contacted regarding other studies within CAMH. During these mass email events, participants who had consented to be contacted were emailed regarding MATCH study enrollment. A database was created each time for smokers willing to be contacted. An email (Appendix VI) with brief study information and instructions for enrollment was sent to participants in this database. Each event’s outreach was approximately 10,000 participants. Participants were then able to self-register by using the link provided in the promotional email.

Facebook Advertisement

Between June 2015 and December 2016, Facebook advertisements were used periodically (non-consistently) to target participants online for participation. Since the MATCH study utilized the Internet as a medium for medication delivery, participants within the online community were targeted for recruitment. The advertisements were formulated to target 1) People who lived in Ontario and 2) People interested in smoking or smoking cessation. The advertisement included picture prompts (Appendix VII) and a brief description of MATCH with a link to access the online portal data collection system. A blog post was also included in the advertisement (Appendix VIII) for more study information. The Facebook advertising system monitored all clicks and views that the advertisement achieved and had high yielding results for recruitment purposes.

Word of mouth

The investigators of the MATCH study had conducted collaborative research as part of the STOP program with health care providers from Ontario Public Health Units, Community Health Centers and Family Health Teams. This network of health care providers efficiently provided a platform to introduce new treatment opportunities to interested smokers. When the study was launched, an email for healthcare providers (Appendix IX) was sent to alert healthcare providers of this new treatment opportunity for their respective patients. In this email, information regarding the study, treatment options and instructions on how to refer interested smokers to the MATCH study website were included. Interested self-motivated smokers were thus directed to the MATCH study website to enroll.
In 2016, another network of health care providers was interested in providing MATCH study promotion. Members of The Ontario Dental Association (ODA) sent an email to their health care providers on the importance of smoking cessation and dental hygiene improvements. In this email, the MATCH study was listed as a potential resource for interested smokers. This email (Appendix X) included brief information about the study, treatment options and instructions for enrollment. Participants were then self-directed to the MATCH study website. Posters for MATCH study promotion were also placed on advertisement boards across Toronto (Appendix XI) periodically. The poster included brief study information and a link for interested smokers to direct them to the MATCH study website.

2.4 Enrollment Process

Study enrollment was completely internet-based and participants completed all questionnaires on the MATCH study website (matchstudy.ca). Once participants clicked on the link for enrollment, an automated unique identifier was given to them in the format: MC-XXXX or MC-XXXXX for confidentiality purposes.

2.4.1 Study Website: matchstudy.ca

The MATCH website home page displayed information such as: brief description of the study purposes, the relationship with CAMH, provided pharmacotherapies and overall study procedures (Appendix I). A Frequently Asked Questions (FAQ) page was provided answering basic questions regarding purpose and study design (Appendix XII). Study contact information was provided in this page directing participants towards Dr. Zawertailo or a student associate with any concerns or potential questions regarding the study. At any point of the study participants were able to email matchstudy@camh.ca to express concerns or ask further questions. Once participants had read through this section of the website, a hyperlink was presented to proceed onto the initial assessment through usage of the Online Data Collection Portal (below).

2.4.2 Inovex Portal: Online Data Collection

An online data collection portal was specifically designed for MATCH (affiliated with CAMH) by Inovex Inc. where all research data was confidentially stored on a secure server housed in Canada. All study survey components and consent forms were completed and stored on the portal, including baseline and all follow-ups. Participants self-entered all collected information. The online system was designed to automatically reject multiple participant enrollments from one email address. This was done to ensure participants could not receive medication more than once. Participants could not alter any of their responses to survey questions once the survey was completed. The system
ensured that participants (or study personnel) could not alter their medication assignments once randomized by the system. The system also ensured maximum security and confidentially since only study personnel had access to the data, which was password protected. The portal outlook can be seen in Appendix XIII.

2.4.3 Study information and Consent Forms

Once participants visited the study Online Portal and Data Collection Platform, participants were provided with the Study Information and Consent Form (Appendix III). Informed consent was provided before any data was collected from participants (Appendix III). Consent was provided by clicking “yes” or “no” at the end of the form. The Consent Forms covered consent for usage of personal information for scientific research in a confidential manner. The form consented to collection and usage of biological samples for analysis. Additionally, participants were asked for consent to be contacted for future study opportunities. If participants had consented to the Genetic Sub-study, a different consent form was presented to cover participation in the sub-study (Appendix XIV). A copy of the Consent Forms was emailed to participants for their own records. Once participants provided consent, they were directed to the next page to complete the baseline questionnaire.

2.4.4 Baseline questionnaire components

The baseline questionnaire was primarily designed to assess for eligibility, collect useful demographics information and other related baseline characteristics. Additionally, baseline co-variants information was collected that could potentially affect treatment outcome. The baseline demographic questionnaire can be seen in Appendix XV. Example of factors that could be included as a co-variates includes: age, gender, smoking habits and nicotine dependence.

Baseline Demographics

The first few sections of the survey collected basic information such as age, gender, location of residency, ethnicity, education, employment status and other socioeconomic factors (Appendix XV).

Smoking Behaviours

Participants were asked regarding their smoking behaviors at baseline. Namely how many cigarettes they smoke per day (Cig/Day or CPD), how often they smoke (Every Day, Occasionally etc.) and previous attempts at quitting. Participants’ importance to quit and confidence to quit were ranked on a scale of 1 to 10 with 10 being most important/confident.
Nicotine Dependence (FTND score)

Nicotine Dependence was assessed using the Fagerstrom Test for Nicotine Dependence (FTND) created by Heatherton et al (1991). The FTND is a six-item questionnaire that measures level of nicotine dependence. The FTND score ranges from 1 to 10 (higher score representing higher dependence). A score of 5-7 corresponds to moderate dependence whereas a score of 8-10 represents highly dependent.

Medical History

This was an important section for assessment to ensure the safety of pharmacotherapy usage. Participants were asked about their mental health conditions (i.e. depression, bipolar disorder, schizophrenia etc.), current medication usage, and other substance use, such as cocaine.

PHQ-9

The Patient Health Questionnaire (PHQ-9) (Spitzer, Kroenke & Williams, 1999) was administered to evaluate baseline depressive symptoms. The PHQ-9 is based on the DSM-IV criteria for screening for major depression and sub-threshold depressive symptoms. This nine-item assessment produced a score, which corresponded to depressive symptoms: a higher score represented more severe depressive symptoms. Once a participant scores past a threshold on the first two items, the other 7 items will appear to be answered. A total score of 0-4 indicates normal, 5-9 indicates minimal depressive symptoms, 10-14 indicates mild major depression, 15-19 indicates moderate major depression and 20 or higher indicates severe major depression. On the other hand, if the participant scores below the threshold for the first two questions, an automated message will appear to inform participants to consider seeking professional help.

2.4.5. On-screen eligibility, drug assignment and enrollment confirmation

If participants had selected “no” to participation in the genetic sub-study, when they completed the baseline survey, an on screen message appeared informing them of their eligibility (Appendix V). Once participants were deemed eligible, the system automatically assigned participants to one of the two pharmacotherapies. The system automatically sent out a study Enrollment Confirmation email to all eligible participants (Email can be seen in Appendix XVI). This email provided participants with a copy of their informed Consent for the study (Appendix XVII), Study Information (Appendix XVII), a Letter to the Doctor (Appendix XVIII) and a Standard Script for the assigned medication (Appendix XIX). The standard Script was pre-filled with participant’s personal information and prescription for
medication that they were randomized to. Participants that wanted the other medication, or did not like the one they were randomized to, were not allowed to switch and given the option to withdrawal from the study. The email also contained important instructions to direct participants to the doctors bringing the correct forms (see Section 2.9 Visit to the Practitioner).

2.4.6. Genetic Sub-Study and BFAs questionnaire

Once the baseline questionnaire was completed, participants were given the opportunity to participate in the genetic sub-study. If interested, they were directed to a second page where Informed Consent was given to participate in the sub-study (the results from this sub-study will not be presented). Once consent was given, participants were directed to the Big Five Aspect Scale (BFAs) questionnaire where personality traits were measured. The BFAs personality test, developed by DeYoung et al (2007), is a self-report test to assess the Big Five Personality traits: neuroticism, agreeableness, and conscientiousness, extraversion and openness/intellect. The BFAs test is a 100-item questionnaire answered on a five-point scale ranging from “Strongly Disagree” to “Strongly Agree”. The instructions for proper completion of the questionnaire and the questionnaire itself are included in Appendix XX. The BFAs questionnaire also breaks down each personality trait into two aspect traits, which has been shown to show genetic and biological predispositions (DeYoung, Quilty, & Peterson, 2007). The aspect traits are: withdrawal & volatility for neuroticism, compassion & politeness for agreeableness, industriousness & orderliness for conscientiousness, enthusiasm & assertiveness for extraversion and intellect & openness for openness/intellect. The traits measured are predominantly genetically predetermined and remain constant throughout one’s life. Once participants have completed the BFAs, an automated Enrollment Confirmation Email was sent with the following forms: Study Information, Informed Consent, Letter to Doctor and Standard Script. A second email was sent with the Sub-Study Information and Consent Forms.

2.5 Eligibility Criteria

Participants included in the MATCH study were daily smokers, currently smoking 10 or more cigarettes per day, aged 19 years or older, residents of Ontario, who wished to quit within 30 days of receiving the assigned medication, did not have any contraindications for bupropion or varenicline, and were not pregnant nor breastfeeding.
2.5.1 Inclusion Criteria

The inclusion criteria were chosen to affirm study objectives and treatment recommendations. For example, this study was designed to evaluate feasibility of an online medication distribution method within Ontario. Varenicline and bupropion are both recommended for daily dependent smokers who smoke 10 or more cigarettes a day (Patel et al., 2010; West, 2003). Participants were required to indicate if they had an intention to quit within 30 days of receiving the study medication. This criterion was chosen because 30 days is the validated standard used in the preparation stage for a behavioral change such as a smoking cessation according to Prochaska Stages of Change Model (Prochaska & DiClemente, 1983). The complete list of inclusion criteria that determines if one was eligible and randomized for the study are:

- Ontario Resident
- Has a valid email address
- 19 years or older
- Current Daily Smoker
- Daily Smoker for the past year
- Smoking 10 or more cigarettes per day
- Intention to quit smoking within 30 days of receiving medication.

2.5.2 Exclusion Criteria

The exclusion criteria were primarily selected based on contraindications stated for the study medications (Pfizer 2011 and Valeant, 2012). Since participants were randomized to medication groups, contraindication with either of the study drugs resulted in exclusion from the study. Individuals were excluded from the study if they met any of the following criteria:

- Pregnant or Breast-Feeding
- Current/history of eating disorder
- Current/history of psychotic disorder (schizophrenia or bipolar disorder)
- Brain Injury
- Seizures
- Allergy or sensitivity to bupropion and varenicline.
- Current usage of varenicline, bupropion, wellbutrin, nonoamine oxidase inhibitors, thioridazine, antidepressants and/or other medications containing bupropion hydrochloride.
- Had already received medication from the MATCH study in the past.
2.6 Randomization Process

Eligible participants were randomly assigned to one of two possible medication groups: bupropion or varenicline. A block randomization procedure was performed. Eligible participants were randomized in a 1:1 ratio in blocks of 100. This process was performed automatically by the Online Data Collection system.

2.7 Interventions

Participants received both pharmacological and behavioral interventions. Participants received either open-label bupropion or varenicline according to their randomization or neither medication if a medical practitioner chose to not prescribe the assigned medication. All participants received weekly behavioral motivational emails regardless of their medication assignment and whether or not they received medication.

2.7.1 Pharmacotherapies for Smoking Cessation

Bupropion hydrochloride (Sustained Release (SR) generic brand: Sandoz Canada, Jules Leger, Quebec. Medication) was dispensed for 12 weeks as one tablet (150 mg) once daily for the first three days then twice daily for the remainder of the 12 weeks medication period. Generic bupropion chloride SR has been shown to be the equivalent to Zyban (Moreira et al., 2009). Approval from Health Canada was given to use the generic brand for this study. Bupropion was purchased through the CAMH pharmacy. Varenicline tartrate (Champix) (Pfizer, Canada Inc., Kirkland, Quebec) was dispensed for 12 weeks as one tablet (0.5 mg) daily for the first three days, then one tablet (0.5mg) twice daily for the next four days, then at 1 mg twice daily for the remainder of the 12 weeks medication period. Pfizer Canada Inc. supplied Champix as an investigational product at no cost and as part of the investigator-initiated research funding.

2.7.2 Behavioral Intervention (Motivational Emails).

All participants, regardless of their medication assignment, received weekly motivational emails to aid them in their cessation attempt. The weekly emails were sent out through the Online Study Portal automatically. The first behavioral email was sent at the start of the treatment period (after participants have received medication by mail). Thus, a total of 12 emails were sent during the treatment period. The emails contained tips and recommendations on a number of behavioral strategies that participants could employ to increase the likelihood of smoking cessation by the end of the treatment period. These emails also provided tips on methods to create an environment that encourages quitting and remaining abstinent. Other tips included advice on how to recognize and battle issues that involve withdrawal symptoms and cravings. They included positive motivational
messages by providing facts on benefits of smoking cessation. The content of the emails varied from week to week. The content of the emails can be seen in Appendix XXI.

### 2.8 Participant’s Visit to their Physician or Licensed Practitioner

All eligible participants who completed the online baseline survey were automatically sent an Enrollment Confirmation Email with instructions to visit their physician or a licensed practitioner to sign their Standard Script for the randomized medication within 5 weeks of their enrollment date. The prescriber could be a licensed physician, a nurse practitioner, or a pharmacist. The participants booked their own appointment with their physicians to review the prescription and ultimately, the physician decided if the medication assignment was appropriate for the participant. Reminder emails were sent out 2 weeks after enrollment date to ensure participants booked an appointment and met with a physician during the 5-week window. During the visit, the participant discussed with their physician their medication history, current medication usage and other concerns they may have regarding the medication they were randomized to. Participants were instructed to bring the Letter to Doctor and Standard Script (that were attached in the Enrollment Confirmation Email) to their visit (Appendix XVIII and XIX respectively). The Letter to Doctor Document (Appendix XVIII) was designed by study investigators to convey important information on the MATCH study and its research purpose to doctors. The Standard Script (Appendix XIX) was prefilled with the participant’s personal information and prescription information on the medication that the participant was randomized to. It was then up to the physician’s discretion to sign the Script, or decide not to prescribe the assigned medication. Physician were asked to fax the signed prescription to the contract mail-order pharmacy (MediTrust Rexall Direct) that later filled the prescription. Participants that did not have a signed Standard Script within the 5 week window did not receive study medication. However, these participants were activated in a similar way on the Online Portal System, received weekly behavioral motivational emails and were followed up in the same manner as participants who did receive medication.

### 2.9 Prescription Fulfillment at the Contract Pharmacy

All eligible participants were instructed to visit a licensed physician to sign a Standard Script for the pharmacotherapy they were randomized assigned to. Once the Standard Script was signed and faxed to the contract pharmacy, the authenticity of the prescriber was verified by the contract pharmacy. Overall, the pharmacy checked for the script’s arrival and to ensure the prescribers were licensed and able to fulfill prescriptions. After the received Script was verified, the pharmacist conducted a brief phone counseling session in accordance to the Ontario Collegiate of Pharmacists’ standard of practice. During the consultation, the pharmacist discussed with participants possible
allergic reactions, concomitant medications and re-confirmed their eligibility to take the assigned medication. Pharmacists informed participants about correct instructions on proper medication use and addressed the participant’s questions or concerns. Participants were generally advised to practice caution while operating heavy machinery and driving large vehicles until they were certain the medication they were taking did not cause drowsiness. Some other information communicated to the participants included the following:

To Bupropion (generic) Participants:
- Pharmacists began the counseling with asking participants if they he/she were currently taking medications such as bupropion, Wellbutrin or Zyban to avoid a duplication of medication usage.
- Participants were instructed they are being sent 12 weeks of generic bupropion (150 mg) tablets. The tablets should be swallowed whole, not chewed or crushed and should be taken after a meal.
- Pharmacists instructed participants to commence the medication 7-14 days prior to their targeted quit date.
- Participants were instructed to take one table daily from day 1 to 3, then twice a day for the remainder of the 12 weeks treatment period.
- Pharmacists instructed participants that bupropion may cause drowsiness and that they should avoid operating heavy machinery until certain that the medication does not affect their mental alertness. Alcohol may potentially enhance this effect.

To Varenicline (Champix) Participants:
- Pharmacists began counseling with asking participants if they have ever used varenicline before and if not, have they heard of it before.
- Participants were instructed to begin taking Varenicline 7-14 days prior to the targeted quit date.
- Pharmacists informed participants that they were being sent a Starter Pack and a Continuation Pack and that they should be starting with the Starter Pack.
- Pharmacists instructed participants to take the Starter Pack on days 1 to 3 (one 0.5 mg tablet once a day), then from days 4 to 7, one 0.5 mg tablet twice a day. The Starter Pack medication was to be taken once in the morning and once in the evening at approximately the same times every day. From days 8 to end of the 12-week treatment period, participants were instructed to take the continuation pack one 1mg tablet twice a day.
- Participants were instructed to take varenicline after a meal.
Pharmacists instructed participants that varenicline may cause drowsiness and that they should avoid operating heavy machinery until certain that medication did not affect their mental alertness. Alcohol may potentially enhance this effect.

Once the prescription was verified and the brief consultation was completed, the contract pharmacy filled the prescriptions and mailed it to the participant's residence by courier. Once the medication had been dispensed, the pharmacists activated the participant's profile on the portal by clicking on an activation button on their profile. The activation of the profile prompted the follow-up surveys to be scheduled automatically by the data collection system. The activation of the participant's profile also notified study personnel that medication has been successfully dispensed by the pharmacy and saliva samples should be promptly sent at this time (see section 2.10 Biological Samples Collection) to ensure baseline collections occurred prior to commencement of medication. Profiles of participants that did not complete a Standard Script were automatically activated when the 5-week window had elapsed. Finally, the dispensed medication was mailed to the participant's mailing address with a tracking number that could be monitored to ensure the participant receives the medication in a timely manner.

2.9.1. Pharmacy Online Portal

Once a Standard Script was faxed to the Contract Pharmacy, pharmacists logged on to the Pharmacy Portal of the Online Data Collection system, which can be seen in Appendix XXII. The Pharmacy Portal allowed pharmacists to update data and have a checklist for their process of verification and activating participants' profiles. This portal was accessible by all study investigators and pharmacy related personnel. Once the Script was received, pharmacists searched for the participant's name on the portal corresponding to the name on the script. This was also a useful checkpoint to ensure no participants had been double enrolled since the same participant could have enrolled with different emails. In selective cases where multiple profiles appeared under the same name, the participant was disqualified from the study and did not receive medication. Once the correct profile was identified, the pharmacist made the appropriate changes on the portal to reflect that the Script had been received. Once the brief phone counseling was conducted, pharmacists updated the system to reflect the date that medication was dispensed and inputted the tracking number for the parcel.

2.10 Follow Up Surveys

Follow-up surveys were conducted at 4 weeks, 8 weeks, 12 weeks, 6 months and 12 months after the beginning of treatment. As mentioned before, surveys were automatically scheduled by the
system once the participants were activated. Technically, the surveys were scheduled at 5 weeks, 9 weeks, and 13 weeks from when the medication was couriered, to allow a week for medication to be successfully delivered. The same scheduling method was employed for 6 months and 12 months follow up. Prior to survey due dates, participants were notified by email that their follow-up dates were approaching. The reminder email included a hyperlink that directed participants to the appropriate follow up survey on the Online Data Collection Portal. Five reminder emails were sent out at 3-day intervals and each survey remained active for 2 weeks after which the survey cannot be assessed anymore. This time point was used to ensure that surveys were completed at the appropriate times. Follow-up surveys were also completed for participants who did not received medication. A copy of the Surveys for 4 weeks, 8 weeks, 12 weeks 6 months and 12 months are available in Appendix XXXIII.

All follow-up surveys attempted to collect participant information on smoking status, changes in smoking patterns, medication use, medication compliance and adverse effects. Certain surveys also collected information on reasons why participants did not visit a physician to sign the Standard Script. Additional data was also collected on co-variates that could alter primary outcomes of the study including use of Nicotine Replacement Therapy (NRT) or Electronic Cigarettes. To ensure the safety of participants in the study, the PHQ-9 was employed in follow-up surveys to measure presence of depressive symptoms. If participants scored high on the question regarding suicidal thoughts, the system automatically sent a message suggesting the participant to seek medical attention to discuss their symptoms. Additionally, the follow-up questionnaire showed if participants experienced any serious adverse events and if so, participants were advised to discontinue medication usage. Long-term abstinence from usage of each medication was evaluated at 6 and 12 months after start of medication period. Similarly, these surveys assessed smoking status and smoking behaviors.

2.11 Outcome Measures

The primary outcome related to the efficacy of each treatment for cessation at end of treatment (EOT). Short-term abstinence was assessed at 4 weeks, 8 weeks and 12 weeks surveys while long-term abstinence was assessed at 6 and 12 months surveys. For short term abstinence, the primary outcome measure variable was 30 Day Continuous Abstinence which was defined as not having smoked, not even a puff, in the past 30 days and lack of relapse during this period. The question asked in the follow-up questionnaire for 30-Day Continuous abstinence was “Have you smoked, even a puff, in the last 30 days?”. 30 Day Continuous Abstinence was only measured for 8 and 12 weeks surveys. The secondary variable to measure the primary outcome is 7 Day Point Prevalence
(PPA) which was measured at weeks 4 weeks, 8 weeks and 12 weeks. 7 Day PPA was defined as not having smoked, even a puff, over the last 7 days. The question asked in the Follow-up questionnaire for 7 Day PPA was “Have you smoked, even a puff, in the past 7 days?” The two quit variables have been widely used in smoking cessation literature as a reliable measure for abstinence (West et al., 2005). Many clinical trials comparing efficacies of varenicline versus bupropion used these measures for abstinence and thus, can be compared to our results. These measures were also recommended by the Society for Research on Nicotine and Tobacco (SRNT) who actively reviews literature on measurement of abstinence. For long term abstinence, 30-Day Continuous Abstinence and 7 Day PPA were evaluated at 6 and 12 months. Both variables were defined as previously mentioned. Biochemical confirmation of self-reported smoking abstinence was evaluated at 4 weeks, 6 months and 12 months.

In the Intent to Treat (mITT) analyses, all participants who were randomized and received medication were included regardless of their survey completion or withdrawal. Complete Case analysis was conducted for participants who had received medication and completed a survey. Additionally, there were approximately equal number of participants randomized to each group and their respective survey completion rates were approximately equal. Participants who had incomplete surveys or not started one were treated as not quit. Chi-Square Test were conducted at significance p<0.05. When regression analyses were conducted, odd ratios were adjusted for age, gender, CPD and FTND (all at baseline). The overall survey completion rate was ~43% at 6 months follow up and ~40% at 12 months follow up. Participants that had self-reported quit at T2 or T3 follow-ups were sent a saliva sample. 137 participants completed and returned a saliva sample at T2 (6 months Follow Up Survey). 97 participants completed and returned a saliva sample at T3 (12 months Follow up). These saliva samples were tested for biochemical verification of smoking abstinence. Saliva cotinine concentrations less than 15 ng/ml were considered abstinent (SRNT guidelines). In these biologically confirmed abstinence analyses, complete case studies were used.

The secondary outcome related to medication compliance and its relationship with cessation outcomes at end of treatment (12 weeks). Self-reported medication compliance was measured at end of treatment (12 weeks) and the relationship between self-reported compliance and smoking cessation was explored in relation to each pharmacotherapy. Furthermore, the relationship biochemical verification of compliance at mid-treatment (4 weeks) and cessation outcomes at EOT were also explored in relation to each pharmacotherapy.

The tertiary outcome was related to pharmacogenetics factors that could affect treatment efficacy for smoking cessation. The variable was CYP2A6 enzyme activity, as measured by Nicotine Metabolite
Ratio (NMR) described previously. The relationship between NMR and smoking cessation outcomes was explored in relation to each pharmacotherapy intervention. Additionally, the association between NMR and age, gender and nicotine dependence was explored.

2.12 Biological Sample Collection

The MATCH study was an Internet-based study with no in-person interaction between participants and study investigators. Thus, all biological samples were self-collected and mailed back by participants. Saliva samples were collected at baseline, mid-treatment (4 weeks) and conditionally at 6 and 12 months if participants had self-reported abstinence on the Online Data Collection Portal System at 6 and 12 months respectively. Therefore, in total, potentially 4 saliva samples could be collected from participants. If participants had consented to the Genetic Sub-study, a genetic sample was also collected at baseline.

2.12.1 Saliva Sample Collection

Samples were collected using Salivette Tubes purchased from the Med Store at the University of Toronto. The tubes were labeled with the MC-XXXX identifier number associated with each participant, had a return stamp and packaged according to The Transport of Dangerous Goods (TDG) for Exempt Human Specimen by a trained TDG individual. The packages were then delivered by courier or by Canada Post to the participants' mailing addresses. A form was included with all the sample preparations, sample collection and mailing instructions for return of the saliva sample (seen in Appendix XXIV). The packages were mailed back to the MATCH study mailing address (pre-printed on a label) by using the prepaid stamps on the envelopes.

The first saliva sample kit was sent at baseline upon activation of the participant on the online pharmacy portal. The sample was collected prior to commencement of medication and then returned to the MATCH study site. The primary purpose of obtaining a baseline sample was to measure and confirm participants’ smoking habits since biochemical confirmation of smoking status was not possible. Saliva samples were tested for cotinine content, the primary hepatic metabolite of nicotine in the body (Allenby, Boylan, Lerman, & Falcone, 2016) and 3’-Hydroxycotinine, a metabolite of cotinine. These concentrations were used to evaluate the Nicotine Metabolite Ratio (NMR), which is the most reliable non-invasive marker for CYP2A6 hepatic activity in the body (Dempsey et al., 2004).

The second saliva sample kit was sent at mid-treatment, or 4 weeks since commencement of treatment. The purpose of obtaining this sample was to measure drug levels to assess and validate
medication compliance. This sample was also used to measure levels of cotinine to biochemically confirm or reflect smoking status at this time point. The third and fourth saliva sample kits were sent out conditionally at 6 and 12 months after commencement of treatment. Saliva samples were sent to participants who had completed a survey and were self-reported abstinent at 6 months or 12 months. Participants who had not completed a survey or were not self-reported abstinent, did not receive these saliva kits. These samples were analyzed for cotinine concentrations to confirm quit or reflect smoking status.

2.12.2 Saliva sample storage

Upon arrival of the saliva samples to the MATCH study site, they were logged and stored in an -80 Celsius freezer. The freezer was equipped with an alarm that would go off in case of freezer malfunction. Daily checks were performed to ensure an optimal temperature for biological sample storage.

2.12.3 Genetic Sample Collection

Participants who had consent to the sub-study were mailed an Oragene Saliva Collection Kit for DNA analysis in collaboration with Dr. Kennedy of Centre for Addiction and Mental Health. The samples were sent with a participant ID sheet and instructions for sample collection (Appendix XXV and XXVI respectively). However, the results from the DNA analysis will not be discussed in this thesis.

2.12.4 Sample Analysis

Saliva samples were analyzed at the lab of Dr. Rachel Tyndale at The University of Toronto using Liquid Chromatography-Mass Spectrometry (LC-MS). Batches of saliva samples were transferred to Dr. Tyndale’s lab periodically by MATCH study personnel. A transfer form was signed at each transfer. Saliva samples collected at baseline were analyzed for cotinine and 3’- Hydroxycotinine according to the protocol in Appendix XXVII. For mid-treatment analyses, samples were additionally analyzed for the three major metabolites of bupropion (3OH BUP, TERT-BUP and E-BUP) and varenicline according to the protocol in Appendix XXVIII. The three metabolites of bupropion were analyzed since bupropion undergoes extensive metabolism in the body whereas varenicline undergoes little to none. 6 and 12 months saliva samples were analyzed for cotinine content only (<15 ng/mol was considered quit). The mid-treatment saliva samples (collected 4 weeks after starting medication) were analyzed for medication compliance and cotinine concentrations (for confirmation of smoking abstinence). Meanwhile biochemically confirmation of medication compliance was at past detection concentrations. Dry samples were re-dissolved with 1mL of 0.1
HCL. The dry samples could not be used to measure quantitative compounds but can be included in NMR analyses since it is a ratio of two metabolites and therefore was not affected by true concentrations. An excel sheet of sample analyses was then emailed to the MATCH study investigators.

2.12.5 Compensation for Submission of Biological Samples

For compensation, participants received electronic Amazon gift cards that could be redeemed at any time. Participants with saliva samples that were completed and returned were compensated for as follows: $10 for completion of baseline saliva sample, $25 for completion of the optional Genetic sample, $25 for mid-treatment samples and $25 for each of 6 months and 12 months if applicable.

2.13 Medication Compliance

Medication compliance was assessed by both self-reported questionnaires and by biochemical data. Data gathered by these methods explored the role of medication adherence of prescribed medication and how they might affect treatment efficacy. Surveys completed at 4 and 8 weeks evaluated self-reported medication usage and intention of continual medication usage. Follow-up surveys completed at 12 weeks (EOT) measured if participants had used the full treatment course. Reasons for discontinuation were included in these surveys. At end of treatment (12 week follow-up), medication compliance analyses were conducted for self-reported (SR) compliance. Participants were classified as either finished medication or still using medication. The relationship between SR medication compliance and cessation outcomes, measured by 30 Day Continuous Abstinence and 7 Day PPA, were explored. For the purposes of this analysis, complete case was used. Furthermore, participants who had discontinued medication in each medication group were included in compliance analysis to investigate if any association exists between discontinuation and cessation outcomes at EOT. 380 participants completed a saliva sample at T1 (4 weeks follow up).

For biochemical confirmation of medication compliance at mid-treatment (4 weeks), the procedure has already been discussed in section 2.12.1 Saliva Sample Collection. The relationship between biochemical medication compliance and treatment outcomes was explored. In these analyses, complete case analysis was used. For biochemically confirmed abstinence, a past detection concentration of either medication was treated as compliant. Concentrations of bupropion and its three major metabolites (BUP-OH, TERT-OH and E-OH) and varenicline (parent drug) were quantified by HPLC.
2.14 Adverse Events

Occurrences of adverse events were evaluated at follow-up surveys conducted at 4 weeks, 8 weeks and 12 weeks. The questions that evaluated adverse events were “yes” or “no” answers in response to experiencing any of the following events:

- Dry Mouth
- Trouble Sleeping
- Vivid Dreams
- Rash
- Nausea
- Dizziness
- Fatigue
- Irritability
- Inability to concentrate
- Depression
- Restlessness
- Increased appetite
- Trouble sleeping
- Anxiety

Participants were given the opportunity to include any events not stated above. Participants were advised to discontinue medication use in rare cases of severe adverse events. When participants did stop using medication for adverse events, they were withdrawn from the study (although participants could withdraw at any time during the study).

2.15 Data Management

All data collected from participants was stored in an electronic secure format on a password-secured protected server and managed by the Online Data Collection system (Inovex Inc). Participants were only identifiable by their unique identification ID and no connection could be made between the ID and personal information. Participants’ data was strictly used for scientific purposes and kept confidential and only available to study personnel involved. For saliva and genetic samples, identifier IDs was strictly used. There were also no physical copies of any participant information for record keeping.
2.16 Sample Size and Power Analysis

The *a priori* sample size calculation was based on two similar clinical trials conducted in the same head-to-head manner of treatment comparison of bupropion to varenicline. Sample size calculation was also based on a non-pragmatic feasibility study conducted previously. In these previously conducted head-to-head comparisons of bupropion versus varenicline, the 30-Day continuous abstinence (weeks 9-12) rate was approximately 44% and 33% in varenicline and bupropion respectively. The reported 7-Day PPA for the two clinical trials at end of treatment (12 weeks) was approximately 50% and 36% for varenicline and bupropion respectively (D. Gonzales et al., 2006; Jorenby et al., 2006). More importantly, results from the pilot of the MATCH study showed 7-Day PPA rates of varenicline versus bupropion to be 55% and 30% respectively. Therefore, similar trends in effect size were to be expected based on the results of the feasibility study. Using G Power analysis program, a sample size of 174 participants per medication group was required to achieve 80% power to detect a difference between the groups at alpha level 0.05 of significance (Faul, Wald, Rutland-Brown, Sullivent, & Sattin, 2007).

A *post-hoc* test was performed for the actual sample size obtained for the primary outcome measure. A total of 964 participants had intent to treatment (mITT) outcome measures in which 465 had received bupropion and 499 had received varenicline. Using the G power analysis program, a calculated power of 99% was present to detect a statistically significant difference at an alpha level of 0.05 between the two medication groups. Thus, we were sufficiently powered to conduct analyses based on these data.

2.17 Data Analysis Plan

All statistical analyses were performed using SPSS statistical software version 24.0 (IBM, 2016). Baseline characteristics of participants were compared between those randomized to bupropion versus those randomized to varenicline. Baseline characteristics of participants that have received medication were compared between the treatment groups. BFAs characteristics were compared between each medication group. Lastly, baseline characteristics were compared between participants who received medication vs. not received medication for each medication group. For analyses of independent continuous variables such as age, two-tailed Student T-tests for independent variables were used at significance of p<0.05. For analyses of categorical variables, such as gender, Pearson Chi-Squared tests were used at significance of p<0.05. Baseline variables that differed significantly between the medication groups were used as covariates in subsequent analyses.
Analysis of participant data was based on a modified intent-to-treat (mITT); in other words, all eligible participants who have been randomized and completed steps to receive medication regardless if they used medication or not were included in the final analysis. This included participants that had not finished medication or did not complete follow up surveys. Unlike traditional ITT analyses where everyone randomized is included, only randomized participants that had received medication were included. The modified intent-to-treat model was employed to avoid any potential bias as a result of dropout differences, completion differences that could affect initial randomization results between the medication groups. This approach to data analysis has been shown to have high validity in numerous clinical trials. The data of all participants have been randomized shall be included in analyses of quit outcomes. The denominator for quit rate calculation included all randomized participants that completed the steps to receive study medication. Participants that withdrew, or had incomplete follow-up surveys were included in the numerator of quit rate analyses as “not quit”. Both short-term and long-term abstinence rates were analyzed on an ITT basis. At each follow up, multivariate binary logistic regression models were used to determine the odds ratio for cessation with bupropion at the reference. Traits that were different between medication groups at baseline were inputed as covariates in the model. Additional resources used such as NRT and counseling, were also added to the model as covariates of predicting quit success. Complete case analysis of quit outcomes was conducted on participants who responded to EOT surveys. Complete case analysis was analyzed in the same way as ITT analysis described above. Complete case analyses were also used for self-reported medication compliance and side effects analyses.

2.17.1 Analysis of Treatment Outcomes (Short and Long-Term Abstinence)

Quit measures, specifically the 7 Day Point Prevalence of Abstinence and 30 Day Continuous Abstinence rates, were determined at each follow up survey. Quit was measured as a categorical variable (yes or no) and was compared between medication groups at each follow up using the Pearson Chi-Square test. For each medication group, the McNemar’s repeated measure test was used to explore change over time in quit outcomes between follow up time-points. The McNemar test is similar to the Chi Square test but for paired measures to account for within subject variations. This test assesses for significant differences in dependent dichotomous variable measured at two different follow up time points. This was done from 4 weeks to 8 weeks, 8 weeks to 12 weeks and between 4 weeks to 12 weeks.
For analysis of the primary objective, comparison of quit outcomes at end of treatment for each medication group was achieved using the Chi-square Test for statistical difference with quit outcome measured as 30-Day Continuous Abstinence or 7-Day PPA. To explore the effectiveness of the two medications on cessation outcome, logistic regression analysis was used. Logistic regression model was employed since smoking outcome was a dichotomous variable. Quit rate (Yes or No) was entered as the dependent variable and the medication group was the independent variable with bupropion used as the reference group. The regression model was adjusted for any factors that could be potentially different between the two medication groups. These factors were entered as covariates. The same analysis plan was used on complete case analyses at 12 weeks. A separate binary logistic regression was performed to explore the above relationship adjusting for each additional cessation aid (NRT, counseling) that the participants reported using during the 12 weeks treatment period. Also, independent variables such as age, gender, FTND, BFAs personality and alcohol usage were run alone for smoking cessation predictability accuracy.

For complete case analyses, only participants who had completed a survey were included. Additionally, there were approximately equal number of participants randomized to each medication group and their respective survey completion rates were approximately equal. Chi-Square Tests and McNemar Tests were conducted at significance of p<0.05. When multivariate regression analyses were conducted, the bupropion group was used as the reference group. Regression models were adjusted for age, gender, CPD and FTND. Gender was chosen because there was gender differences found at baseline (Table 8). Age, CPD and FTND were chosen because at baseline, there were potential differences between the groups with differences approaching significance (P values ranging from 0.1 to 0.3). The overall survey completion rate was ~70% at 4 weeks, ~60% at 8 weeks and ~50% at 12 weeks (EOT). Comparison of long-term quit outcomes for each medication group was achieved using binary logistic regression analysis with quit outcomes measured at either 6 months or 12 months. In short, the same steps were taken as short-term abstinence analyses (above). Biochemically confirmed abstinence were analyzed between medication groups using the Chi-Square Test. Lastly, comparisons were made between participants who had self-reported abstinence and those who were biochemically verified abstinence at 4 weeks follow up. Using the McNemar Test, quit rates were compared between self-reported quit and biochemically confirmed quit at 4 weeks follow up for each medication group.

2.17.2 Analysis of Medication Compliance and Adverse Effects

Complete case analysis was used in analyses of medication compliance and adverse events. In these cases, only participant data with completed surveys were included in the final analysis. Medication compliance was assessed as both self-reported and biochemically confirmed data. For
self-reported data, 12 week surveys were analyzed. Participants were then categorized into three groups: finished the full 12 weeks, still using and discontinued. Quit outcomes at 12 weeks were compared between each medication compliance group for each treatment group. The linear regression slope analysis was used to look for any association between self-reported medication compliance and quit outcomes and to test for significance of the linear trend line. Analysis of biochemical confirmation of medication compliance was conducted on mid-treatment saliva samples. Concentrations of bupropion and its metabolites and varenicline (parent drug) were measured and participants who had detectable amounts of each compound were considered compliant. Regression models were then used to explore whether biochemical verified medication compliance was a superior predictor of smoking cessation outcome compared to self-reported compliance at EOT. The goal of these analyses was to identify if any association exists between biochemical medication compliance and quit outcomes and also if compliance differs between medication groups. Both analyses used binary logistic regression to explore whether biochemical verified medication compliance was a superior predictor of smoking cessation outcome compared to self-reported compliance at EOT. The goal of these analyses was to identify if any association exists between biochemical medication compliance and quit outcomes and also if compliance differs between medication groups. Both analyses used binary logistic regression to investigate medication compliance as a predictor of smoking cessation outcome. Self-reported adverse events were assessed for each medication group at different follow up times: 4, 8 and 12 weeks. Adverse events were compared between the bupropion group and the varenicline group using a Chi-Square test to investigate if any differences exist between occurrences of adverse events between the two medication groups.

2.17.3 Saliva Sample Analysis: Roles of Nicotine Metabolism Ratio on Treatment Outcomes

For the analysis of the role of NMR in smoking cessation, participants were categorized into two metabolizer groups: Slow Metabolizers (SM) or Normal Metabolizers (NM) based on measured baseline NMR levels. Participants with NMR values below the 25th percentile were considered slow metabolizers (SM) and remaining participants were considered normal metabolizers (NM) similar to previous study (Patterson et al., 2008). Baseline characteristics were compared between SM and NM between each treatment group. The characteristics that differed significantly between the metabolizer groups were included as covariates in the analysis looking at NMR as a predictor of quit outcome.

The Spearman bivariate correlation test was used to look at the association between baseline NMR and gender, CPD and FTND. Spearman is a nonparametric correlation test that does not make any assumptions about distribution of data and nature of variables to report a general monotonic relationship between two continuous variables. The Spearman’s rank correlation coefficient (rs) was obtained for each relationship indicating the strength and reaction of the association. The coefficient can range from -1 to 1, where 1 indicates a strong positive association. The relationship between
NMR and age (at baseline) was explored using Pearson Correlation test since age is a continuous variable.

To explore the effect of nicotine metabolism on quit outcomes, the binary logistic regression analysis was used where ITT end of treatment abstinence outcome was used as the dependent variable and the status of nicotine metabolism (Slow or Normal Metabolizer) was entered as the independent variable. Baseline demographic variables between the metabolizer groups were analyzed and those that were significantly different from each other were considered as covariates in regression analysis for NMR as a predictor of cessation outcome at end of treatment. The goal of these analyses was to determine if any association exists between metabolizer groups and cessation outcome for the two medication groups. Similar to treatment outcome analyses, logistic regression models was used to investigate which metabolizer group more accurately predicts cessation outcome at end of treatment when adjusted for potential covariates found at baseline.
3.0 RESULTS

3.1 Participant Flow

The MATCH study began recruitment on June 6th 2014 and ended on Jan 21st 2017. By the end of recruitment, 964 participants had received medication. The participant flow chart can be seen in Figure 3a & b. Overall, 4974 participants had visited the MATCH study website, of which 779 had failed to complete the baseline survey. Amongst these 779 participants, 62% of them did not provide consent. 4055 participants completed the survey with 2456 deemed eligible and 1599 participants deemed ineligible. The most common reason for ineligibility was current use of antidepressants (contraindicated for both bupropion and varenicline) (42%). The second most common reason for ineligibility was not smoking every day for the past year (13% of ineligible participants).

Amongst the 2456 eligible participants, 130 of participants asked to be withdrawn from the study at various times. The primary reason for withdrawal was due to loss of interest in the study when participants did not receive medication (not visiting a doctor in time or did not want to take the randomized medication). Participants who had withdrawn were offered the option to continue receiving motivational emails for the treatment period. Nineteen hundred and four of eligible participant consented to the Genetics Sub-study of which 1869 of participants completed the Big Five Personality (BFAS) questionnaire. Within eligible participants, randomization to each medication group was approximately equal (1245 randomized to bupropion and 1216 randomized to varenicline). Approximately 40% of eligible and randomized participants visited a physician and received medication (n=964). The remaining 1061 participants did not visit a physician within the allowed 5-week time period. Forty-two percent of the 1061 eligible participants reported that they did not have a family physician. The proportions of participants that had visited a physician did not differ between the medication groups when a Chi-Square Test was conducted at p<0.05. At the time of analysis, 465 participants received bupropion and 499 participants received varenicline. There were approximately 50 prescriptions that were not filled. The main reason for incomplete prescriptions was that the contract pharmacy could not reach them for completion of brief counseling.

Of the 964 eligible participants who received medication, 916 were emailed the 4-week follow up survey (325 randomized to bupropion and 384 randomized to varenicline) of which completion rate was 69%. Participants were not emailed follow up surveys if they requested to be withdrawn from the study. The 8-week survey was emailed for 962 participants (464 randomized to bupropion and 498 randomized to varenicline) where the completion rate was 65%. The 12-week survey (EOT) was emailed for 854 participants (408 randomized to bupropion and 446 randomized to varenicline)
where completion rate was 60%. The 6 month follow up survey was emailed to 845 participants (407 randomized to bupropion and 438 randomized to varenicline) where completion rate was ~45%. Lastly, the 12 month follow up survey was emailed to 614 participants (294 randomized to bupropion and 320 randomized to varenicline) where completion rate was ~40%. The number of non-responders for each follow up time did not differ significantly between the medication groups using Chi-Square Tests ($p>0.8$).

Table 1 shows information regarding saliva samples collected at baseline and various follow up times. There were 64 dry baseline samples that were diluted with 0.1 mol HCL. Samples diluted with HCL could be used for NMR analysis but not for analysis involving true concentrations of compounds. NMR is a ratio of two concentrations and therefore is not affected by dilution. Thus, there were 32 dry samples at T1 that were not used for cotinine analysis. At T2 there were 3 dry samples and at T3 there were 2 dry samples. These samples were not included in cotinine confirmed abstinence analyses.
Figure 3a. Participant Flow from Enrollment to Randomization and Receiving Medication.
Figure 3b. Participant Flow from Enrollment to Randomization and Receiving Medication. Modified Intent to Treat (mITT) numbers are shown throughout the study. Numbers included in mITT analysis changes throughout study since follow ups have yet to be scheduled/due for some participants.

Table 1. Returned Saliva Samples throughout study.

<table>
<thead>
<tr>
<th></th>
<th>Bupropion Group</th>
<th>Varenicline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Returned</td>
<td>Expected</td>
</tr>
<tr>
<td>Baseline Saliva Samples</td>
<td>282</td>
<td>465</td>
</tr>
<tr>
<td>Included for analysis:</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td>Genetic Samples</td>
<td>228</td>
<td>366</td>
</tr>
<tr>
<td>Included for analysis:</td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>4 Week Samples</td>
<td>158</td>
<td>465</td>
</tr>
<tr>
<td>Included for analysis:</td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>6 Months Samples</td>
<td>20</td>
<td>55</td>
</tr>
<tr>
<td>Included for analysis:</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>12 Months Samples</td>
<td>11</td>
<td>34</td>
</tr>
<tr>
<td>Included for analysis:</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
3.2 Demographic Distribution of Participants

Geographical distribution of all eligible MATCH participants was explored in Figure 4 and Table 2 where it can be seen that this method of internet-based medication delivery was effective in reaching both rural and urban parts of Ontario. Most eligible participants (34%) however, were from Southern Ontario where population density is higher. There were 13% from Toronto, 17% from Eastern Ontario and 10% from Northern Ontario.

![Map of Ontario showing dot distribution of MATCH participants](image)

**Figure 4. Dot Distribution of eligible MATCH participants across Ontario.** The distribution map shows that the MATCH study was able to have a wide outreach of participants across Ontario, but especially within Southern Ontario. Each dot represents an eligible participant.

**Table 2. Breakdown of MATCH Study Participants Across Regions of Ontario.** Breakdown of geographical regions where eligible MATCH participants were located. The percentages reflect the corresponding population density. MATCH was effective recruiting in both urban and rural areas of Ontario. No significant differences in each geographical distribution between medication groups were found at p<0.05 when Chi-Square Tests were performed.

<table>
<thead>
<tr>
<th>Geographical Distribution of Eligible MATCH Participants</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern Ontario</td>
<td>433 (11%)</td>
</tr>
<tr>
<td>Eastern Ontario</td>
<td>713 (18%)</td>
</tr>
<tr>
<td>Central Ontario</td>
<td>714 (19%)</td>
</tr>
<tr>
<td>Toronto</td>
<td>527 (14%)</td>
</tr>
<tr>
<td>Southern Ontario</td>
<td>1442 (36%)</td>
</tr>
</tbody>
</table>
3.3 Baseline Demographics of Participants

Four thousand and fifty five participants completed a baseline survey. Generally speaking, participants interested in the MATCH study were middle aged, more than half female, white and highly motivated to quit. There were no significant differences of all baseline characteristics between eligible and ineligible participants when Chi-Square Tests were conducted at \( p<0.05 \) (not shown).

3.3.1 Baseline Demographics of all Eligible and Randomized Participants

Table 3 shows baseline demographics of the 2456 eligible and randomized participants where comparisons between the two medication groups were made with Chi-Square Tests and Two Sample T-tests at \( p<0.05 \). All the traits were not significantly different between the two medication groups and thus it shows that the randomization process was successful and unbiased. Generally, the eligible participants were middle-aged (approximately 45), mostly female (62%), smoke 11-20 cigarettes a day, white and highly motivated to quit. The average age of first cigarette for both groups was \(~15\) years and age of daily smoking was \(~17\) years. Nicotine Dependence was also recorded and participants were overall moderately dependent with a FTND score of 6 out of 10. There were also more Caucasian participants were in the varenicline group than in the bupropion but this was ultimately not significant \( (p=0.15) \).
Table 3. Baseline demographics for all eligible and randomized participants. Baseline demographics were measured and were not significantly different between the two medication groups when using Chi-Square Tests and Comparative Means both at p<0.05

<table>
<thead>
<tr>
<th>Baseline Demographics</th>
<th>Bupropion (n= 1310)</th>
<th>Varenicline (n=1255)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%Male)</td>
<td>39.5%</td>
<td>40.0%</td>
<td>0.960</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>44.5 ± 11.6</td>
<td>44.9 ± 11.7</td>
<td>0.439</td>
</tr>
<tr>
<td>Cigarettes Per Day</td>
<td></td>
<td></td>
<td>0.774</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>9.8%</td>
<td>10.9%</td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>47.8%</td>
<td>45.8%</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>36.3%</td>
<td>37.7%</td>
<td></td>
</tr>
<tr>
<td>&gt;31</td>
<td>6.1%</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>Age of First Cigarette (mean ± SD)</td>
<td>14.7 ± 3.5</td>
<td>14.7 ± 3.4</td>
<td>0.831</td>
</tr>
<tr>
<td>Age of Daily Smoking (mean ± SD)</td>
<td>16.7 ± 3.9</td>
<td>16.8 ± 3.9</td>
<td>0.788</td>
</tr>
<tr>
<td>Importance to Quit (mean ± SD)</td>
<td>9.4 ± 1.1</td>
<td>9.4 ± 1.1</td>
<td>0.580</td>
</tr>
<tr>
<td>Confidence to Quit (mean ± SD)</td>
<td>7.3 ± 2.0</td>
<td>7.3 ± 2.0</td>
<td>0.512</td>
</tr>
<tr>
<td>Fagerstrom Test of Nicotine Dependence (mean ± SD) max. 10</td>
<td>6.01 ± 2.0</td>
<td>6.0 ± 2.0</td>
<td>0.590</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td>0.229</td>
</tr>
<tr>
<td>High School</td>
<td>27.4%</td>
<td>22.8%</td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>54.8%</td>
<td>53.9%</td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>16.7%</td>
<td>17.0%</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td>0.150</td>
</tr>
<tr>
<td>Caucasian</td>
<td>83.8%</td>
<td>84.9%</td>
<td></td>
</tr>
<tr>
<td>African Descent</td>
<td>1.5%</td>
<td>0.4%</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>1.2%</td>
<td>1.0%</td>
<td></td>
</tr>
<tr>
<td>Don’t know</td>
<td>5.4%</td>
<td>6.3%</td>
<td></td>
</tr>
</tbody>
</table>

3.3.2 Participation in the Genetic Sub-Study and BFAs

A thousand nine-hundred and six of the 2456 eligible participants consented to participation in the genetic sub-study of which 1869 had completed the Big Five Personality Assessment (BFAs). Table 4 shows the five personality traits that were measured at baseline. There were no significant differences between the traits between medication groups. Generally speaking, participants had high scores in agreeableness (~4.0 out of 5) and openness to experiences (~3.7 out of 5) in both medication groups. In both medication groups, participants scored the lowest on neuroticism (~2.6 out of 5). When stratified by gender, significant differences between the genders were found in both medication groups (seen in Table 5). Females had significantly higher scores in agreeableness than men (~4.0 vs ~3.8 respectively) in both medication groups (p<0.0001). Females also had significantly higher scores in conscientiousness than men (3.6 vs 3.5 respectively) but only in the bupropion group (p<0.0001). There was a trend of females having higher scores in neuroticism in
both medication groups but it was not significant. Within bupropion users, this effect was nearing
significance at p=0.09. All other traits were not significantly different between genders.

Table 4. BFAs of eligible participants who have consented to the Genetics Sub-Study. The
descriptive statistics of the Big Five Personality Traits for 1869 participants that completed the
assessment. No significant differences were found between the medication groups at p<0.05

<table>
<thead>
<tr>
<th></th>
<th>Medication Group</th>
<th></th>
<th></th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bupropion (n=971)</td>
<td>Varenicline (n=898)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroticism (mean ± SD) max 5</td>
<td>2.61 ± 0.65</td>
<td>2.60 ± 0.63</td>
<td>0.755</td>
<td></td>
</tr>
<tr>
<td>Agreeableness (mean ± SD) max 5</td>
<td>3.96 ± 0.52</td>
<td>3.95 ± 0.52</td>
<td>0.822</td>
<td></td>
</tr>
<tr>
<td>Conscientiousness (mean ± SD) max 5</td>
<td>3.57 ± 0.54</td>
<td>3.59 ± 0.53</td>
<td>0.397</td>
<td></td>
</tr>
<tr>
<td>Extraversion (mean ± SD) max 5</td>
<td>3.60 ± 0.54</td>
<td>3.58 ± 0.54</td>
<td>0.389</td>
<td></td>
</tr>
<tr>
<td>Openness to experience (mean ± SD) max 5</td>
<td>3.70 ± 0.51</td>
<td>3.67 ± 0.50</td>
<td>0.139</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. BFAs of eligible participants who have consented to Genetics Sub-Study split by
gender. The descriptive statistics of the Big Five Personality Traits for 1869 participants that
completed the assessment stratified by gender. Females had significantly higher scores in
agreeableness than men in both medication groups (both at p<0.001). Females had significantly
higher scores in conscientiousness than men only in the bupropion group at p=0.04.

<table>
<thead>
<tr>
<th></th>
<th>Medication Group</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males (n=351)</td>
<td>Females (n=620)</td>
<td>P Value</td>
<td></td>
</tr>
<tr>
<td>Neuroticism (mean ± SD) max 5</td>
<td>2.56 ± 0.61</td>
<td>2.63 ± 0.68</td>
<td>0.093</td>
<td></td>
</tr>
<tr>
<td>Agreeableness (mean ± SD) max 5</td>
<td>3.79 ± 0.51</td>
<td>4.06 ± 0.50</td>
<td>0.000*</td>
<td></td>
</tr>
<tr>
<td>Conscientiousness (mean ± SD) max 5</td>
<td>3.50 ± 0.54</td>
<td>3.61 ± 0.53</td>
<td>0.04*</td>
<td></td>
</tr>
<tr>
<td>Extraversion (mean ± SD) max 5</td>
<td>3.62 ± 0.50</td>
<td>3.59 ± 0.56</td>
<td>0.145</td>
<td></td>
</tr>
<tr>
<td>Openness to experience (mean ± SD) max 5</td>
<td>3.67 ± 0.50</td>
<td>3.72 ± 0.52</td>
<td>0.319</td>
<td></td>
</tr>
</tbody>
</table>

3.3.3 Baseline Characteristics of Participants that Received Medication

Of the 2456 eligible and randomized participants, 964 had received medication. 465 were
randomized to bupropion and 499 were randomized to varenicline. Baseline demographics of
participants who received medication can be seen in Table 6. There were no significant baseline
characteristic differences between the medication groups. Overall, participants were middle aged (~46), mostly female (~64%), smoked 11-20 cigarettes a day, moderately dependent (FTND ~6), white and highly motivated to quit. These traits were similar to Table 4 and showed that there were no major baseline characteristic differences between participants who received medication and those who were eligible when Chi-Square Tests were conducted at p<0.05. There was also a trend of participants who were randomized to varenicline smoking more cigarettes per day than those randomized to bupropion however this effect was not significant.

Table 6. Baseline demographics for all participants who received medication. Baseline demographics were measured for participants who received medication and they were not significantly different between the two medication groups at p<0.05.

<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=465)</td>
<td>Varenicline (n=499)</td>
</tr>
<tr>
<td>Gender (%Male)</td>
<td>42.9%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>45.99 ± 11.32</td>
<td>46.96 ± 11.83</td>
</tr>
<tr>
<td>Cigarettes Per Day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10</td>
<td>11.2%</td>
<td>9.7%</td>
</tr>
<tr>
<td>11-20</td>
<td>46.8%</td>
<td>44.9%</td>
</tr>
<tr>
<td>21-30</td>
<td>34.1%</td>
<td>40.4%</td>
</tr>
<tr>
<td>&gt;31</td>
<td>7.9%</td>
<td>5.0%</td>
</tr>
<tr>
<td>Age of First Cigarette (mean ± SD)</td>
<td>14.61 ± 2.95</td>
<td>14.75 ± 3.59</td>
</tr>
<tr>
<td>Age of Daily Smoking (mean ± SD)</td>
<td>16.54 ± 3.36</td>
<td>16.69 ± 3.83</td>
</tr>
<tr>
<td>Importance to Quit (mean ± SD)</td>
<td>9.41 ± 1.10</td>
<td>9.48 ± 1.03</td>
</tr>
<tr>
<td>Confidence to Quit (mean ± SD)</td>
<td>7.37 ± 2.03</td>
<td>7.21 ± 1.96</td>
</tr>
<tr>
<td>Fagerstrom Test of Nicotine Dependence (mean ± SD) max. 10</td>
<td>5.96 ± 1.94</td>
<td>5.98 ± 2.00</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>31.1%</td>
<td>27.2%</td>
</tr>
<tr>
<td>College</td>
<td>52.2%</td>
<td>54.1%</td>
</tr>
<tr>
<td>University</td>
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<td>18.1%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
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</tr>
<tr>
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<td>84.7%</td>
</tr>
<tr>
<td>African Descent</td>
<td>1.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Indian</td>
<td>2.4%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Don't know</td>
<td>4.3%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

Table 7 shows the same baseline demographics for participants who received medication split by gender since gender differences were detected for BFAS subscales (Table 5). Females had significantly lower FTND score than men in both medication groups. This suggests that males were more tobacco dependent than females. Within the varenicline group, females smoked significantly
fewer cigarettes per day than men and had significantly higher education status than men. These trends were also present for the bupropion group but did not reach statistical significance. Within the bupropion group, males had significantly higher age of first cigarette than females (15 vs 14 respectively) and also significantly higher age of daily smoking (17 vs 16 respectively). These trends were not present in the varenicline group; in fact, they were reversed. Females in the varenicline group had higher age of first cigarette and higher age of daily smoking than females in the bupropion group. All other traits were not significantly different between the genders in both medication groups.

Table 7. Baseline demographics for eligible participants who have received medication split by gender. Baseline demographics of participants who received medication were compared between medications groups split by gender.
3.3.4 Comparison of Participants who Received vs Did Not Receive Medication

Comparisons of baseline demographics of participants who received medication were made versus those who did not. Participants who received medication were approximately 3 years older than those who did not receive medication for both medication groups. There was also an imbalance between the groups since there were more participants who did not receive medication. All other traits were not significantly different between receiving medication and not receiving medication within medication groups. Additionally, there were no significant differences between the number of participants that did not receive medication in each medication group when Chi-Square Tests were conducted.

3.4 Short Term Treatment Outcomes

Short-term smoking cessation treatment outcomes were explored by analyzing self-reported (SR) cessation rates at weeks 4, 8 and 12 between the two medication groups. In the modified Intent to Treat (mITT) analyses, all participants who were randomized and received medication were included regardless of their survey completion or withdrawal. Participants who had incomplete surveys or not started one were treated as not quit. Data was not available from participants that did not finish the entire survey.

3.4.1. Self-Reported Treatment Outcome at End of Treatment (12 weeks Follow Up)

The primary outcome was self-reported quit measured as 30 Day Continuous Abstinence and 7 Day PPA at EOT between the two medication groups and shown in Figures 5a and 5b. There were 408 bupropion participants and 446 varenicline participants included in analyses. Participants randomized to varenicline had significantly higher continuous abstinence rates than bupropion (25% vs 16%; p<0.0001) and 7 Day PPA (30% vs 20%; p<0.0001). Table 8 shows multivariate regression analyses for 30 Day Continuous Abstinence rates of the two medication groups at EOT. Participants randomized to varenicline were more likely to achieve continuous abstinence at EOT compared to bupropion with an OR of 1.81 [95%CI: 1.26-2.62 p<0.001] after adjusting for age, gender, CPD and FTND score. The ORs of varenicline were higher at EOT than at both 4 week and 8 week follow up times and P values were lowest at EOT. When adjusting for age, CPD and FTND alone, these effects were not present and the OR did not change significantly. Table 9 shows multivariate regression analysis of 7 Day PPA rates of the two medication groups at EOT. Participants randomized to varenicline were more likely to achieve 7 Day PPA at EOT compared to bupropion with an OR of 1.89 [95%CI: 1.34-2.68 p<0.001] adjusting for age, gender, CPD and FTND score.
Figure 5a. 30 Day Continuous Abstinence of bupropion and varenicline at 12 weeks follow up time (EOT) (Intent to Treat (mITT)). Participants randomized to VAR had significantly higher 30 Day Continuous Abstinence (25%) than those randomized to BUP (16%) ($X^2 = 13.9$). The VAR group was more likely to achieve continuous abstinence than the BUP group with an OR of 1.81 [95% CI: 1.26-2.62 p=0.001] when adjusted for age, gender, CPD and FTND score (at baseline).

5b. 7-Day Point Prevalent Abstinence (7 Day PPA) of bupropion and varenicline at 12 weeks follow up time (EOT) (Intent to Treat (mITT)). Participants randomized to VAR had significantly higher 7 Day PPA (30%) than those randomized to BUP (20%) ($X^2 = 14.1$). Similar to Figure a, The VAR group was more likely to achieve 7 Day PPA than BUP with an OR of 1.89 [95% CI: 1.34-2.68 p<0.0001] when adjusted for age, gender, CPD and FTND score (at baseline).

Table 8. 30 Day Continuous Abstinence of participants randomized to bupropion and varenicline group at 12 week follow up regression analysis. The effect of medication group on continuous abstinence at EOT was explored adjusting for age, gender, CPD and FTND score (at baseline). The varenicline group were more likely to achieve smoking cessation after adjusting for these variables at p<0.001.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio of study Group</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Study Group (BUP as reference)</td>
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<td>1.26-2.58</td>
<td>0.001*</td>
</tr>
<tr>
<td>Adjusted for:</td>
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<td></td>
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<tr>
<td>Age</td>
<td>1.84</td>
<td>1.28-2.63</td>
<td>0.001*</td>
</tr>
<tr>
<td>Gender</td>
<td>1.78</td>
<td>1.24-2.55</td>
<td>0.002*</td>
</tr>
<tr>
<td>Cig/Day</td>
<td>1.84</td>
<td>1.28-2.65</td>
<td>0.001*</td>
</tr>
<tr>
<td>FTND</td>
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<td>1.27-2.62</td>
<td>0.001*</td>
</tr>
<tr>
<td>All of the Above</td>
<td>1.81</td>
<td>1.26-2.62</td>
<td>0.001*</td>
</tr>
</tbody>
</table>
Table 9. 7 Day PPA of participants randomized to bupropion and varenicline group at 12 week follow up regression analysis. The effect of medication group on 7 Day PPA at EOT was explored adjusting for age, gender, CPD and FTND score (at baseline). The varenicline group were more likely to achieve 7 Day PPA after adjusting for these variables at p<0.001.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio of study Group</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1.35-2.67</td>
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<tr>
<td></td>
<td>Age</td>
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<tr>
<td></td>
<td>Gender</td>
<td>1.87</td>
<td>1.32-2.63</td>
</tr>
<tr>
<td></td>
<td>Cig/Day</td>
<td>1.92</td>
<td>1.36-2.71</td>
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<tr>
<td></td>
<td>FTND</td>
<td>1.91</td>
<td>1.37-2.69</td>
</tr>
<tr>
<td>Adjusted for:</td>
<td>All of the Above</td>
<td>1.89</td>
<td>1.34-2.68</td>
</tr>
</tbody>
</table>

3.4.2. Self-Reported Treatment Outcome at EOT for Complete Case Analysis

Quit outcomes for bupropion and varenicline were explored in complete case analysis as seen in Figure 6a & 6b. There were in total of 473 participants who had completed a 12 week follow up survey, of which 215 were randomized to bupropion and 258 to varenicline. Overall, the varenicline group had significantly higher cessation rates than bupropion measured by both 30 Day Continuous Abstinence and 7 Day PPA (40% vs 25% and 47% vs 30% respectively; p<0.001 for both). When a multivariate regression model was used, the varenicline group was more likely to achieve cessation as measured by 30 Day Abstinence (p<0.001) and 7 Day PPA (p<0.0001) when adjusted for age, gender, CPD and FTND. Accordingly, overall cessation rates were higher in complete case analysis than ITT analysis since non-responders were excluded and the assumption of not-quit was eliminated. In conclusion, when complete case analysis was used, the varenicline group remained more likely to achieve abstinence than bupropion at EOT.
3.5 Predictors of EOT Quit Outcome

3.5.1. Gender

In Table 10 when the OR for varenicline predicting smoking cessation was adjusted for gender alone, the OR and p value both increased suggesting gender having a contributing role for cessation outcome prediction. When used alone as a predictor for smoking cessation outcome at EOT, females were less likely to quit at EOT than males with an OR of 0.729 [95% CI: 0.263-2.02 p=0.543].

3.5.2. Nicotine Dependence (measured by FTND)

Since nicotine dependence and smoking cessation success are related, dependence can also be used as a predictor of cessation outcome. When used alone as a predictor for smoking cessation, there was no effect of FTND score on quit outcome with a p value of 0.711 [OR= 0.955; 95% CI: 0.748-1.219].
3.5.3. Personality Traits

When using personality as a predictor for smoking cessation abstinence at EOT, higher conscientiousness score was the best predictor for cessation, however this effect was not significant at p value of 0.174 [OR 1.99; 95% CI: 0.738-5.362]. Similar trends were observed with neuroticism and extraversion ([OR 0.623; 95%CI: 0.294-1.320] and [OR 0.548; 95%CI: 0.206-1.457] respectively). In Table 6, there were gender differences in personality traits at baseline and therefore they could play a role in using personality as a predictor of cessation outcome (perhaps traits were more predictive for females than for males). However when the OR for all the traits was adjusted for gender, they were still not significant. Personality traits potentially affect chances of a person becoming abstinent however, when used alone as a predictor, it was not significant.

3.5.4. Alcohol Use at Baseline

Alcohol consumption has been linked previously to decreasing likelihood of smoking abstinence. There was a trend of higher alcoholic beverages per day resulted in lower quit rates at EOT for bupropion and varenicline users. Varenicline still was more effective for smoking cessation outcome prediction than bupropion in all beverage groups however not significantly. When used alone as a predictor of smoking cessation outcome, alcoholic beverages was not a significant predictor of outcome at EOT [OR: 0.880 95%CI: 0.089-8.66 p=0.913]. Alcohol consumption could be a factor that affects smoking cessation outcome however on its own, it was not significant.

3.5.5. Receiving Medication

Approximately 40% of eligible participants received medication. Participants who did not receive medication still received motivational emails and could have used other products (NRT, e-cigarettes, etc.) to aid them in their quit attempt. Participants that did not receive medication resulted in much lower odds of quitting with a p value of 0.001 [OR 0.390 95% CI: 0.226-0.674].

3.6 Additional Resources Used by Participants at End of Treatment

Participants were not forbidden from using other resources during the treatment period to aid them in their quit attempt. Between the medication groups, when Chi-Square Tests were conducted, the bupropion group had significantly higher use of NRT (22%) than the varenicline group (10%) (p<0.0001), while use of other resources were not significantly different between the medication groups (Table 10). Using regression analysis, when the OR of study group (predicting cessation outcome at EOT) was adjusted for these factors in Table 11, the OR remained unchanged and still significant. In other words, the varenicline group was more likely to achieve abstinence even when
adjusted for all additional resources used by participants at EOT. However, when only NRT use was included in the model, the OR increased and the p-value increased.

Table 10. Additional resources used by participants at end of treatment (EOT) for Bupropion and Varenicline. There were no significant differences in percent usage of additional resources at EOT for bupropion and varenicline (p<0.05) with exception of NRT usage. Participants randomized to bupropion used significantly more NRT than varenicline at EOT (22% vs 10%) p<0.001.

<table>
<thead>
<tr>
<th>Additional resource used at 12 weeks Follow up (EOT)</th>
<th>Medication Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bupropion (n=215)</td>
</tr>
<tr>
<td>Nicotine Replacement Therapy</td>
<td>21.99%</td>
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<td>E-Cigarettes</td>
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<td>Self-help Booklets</td>
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<td>Individual Counseling</td>
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<tr>
<td>Smoker’s Helpline</td>
<td>10.99%</td>
</tr>
<tr>
<td>Other Resource</td>
<td>4.96%</td>
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</tbody>
</table>

Table 11. Medication predicting smoking cessation outcome (30 Day Abstinence) at EOT adjusted for additional resources used.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
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<td>Study Group (ref = bupropion group)</td>
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<td>Nicotine Replacement Therapy</td>
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<td>1.23-2.54</td>
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<td>E-Cigarettes</td>
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<td>Individual counseling</td>
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<td>Smoker’s Helpline</td>
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<tr>
<td>Other Resource</td>
<td>1.84</td>
<td>1.28-2.64</td>
<td>0.001*</td>
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</table>

3.7 Self-Reported Treatment Outcomes at 4 Weeks Follow up

At 4 weeks follow up, Modified Intent to Treat (mITT) analysis was conducted where self-reported smoking status and 7 Day PPA rates of bupropion and varenicline were compared. Point Abstinence was used instead of 30 Day Continuous Abstinence since participants had only started using medication for 4 weeks. There were 964 participants included of which 465 were randomized to bupropion and 499 were randomized to varenicline. Participants randomized to varenicline had significantly higher Point Abstinence rates than bupropion (32% vs 20% respectively) and higher 7
Day PPA (22% vs 15% respectively) when Chi-Square Tests were conducted (both at p<0.003). Adjusted binary logistic regression analysis showed the varenicline group were more likely to achieve abstinence measured by both Point Abstinence and 7 Day PPA ([OR: 1.95 95%CI: 1.43-2.63 p=0.000] and [OR: 1.69 95%CI: 1.21-2.37 p=0.002] respectively) when adjusted for age, gender, CPD and FTND score.

3.8 Self-Reported Treatment Outcomes at 8 Weeks Follow Up

At 8 weeks follow up, there were 464 participants randomized to bupropion and 498 participants randomized to varenicline included in the analysis. Modified Intent to Treat (mITT) analysis was conducted where 30 Day Continuous Abstinence and 7 Day PPA rates were compared between the medication groups. Varenicline had significantly higher 30 Day Continuous Abstinence than bupropion (19% and 12% respectively) and 7 Day PPA (29% and 17% respectively) when Chi-Square Tests were conducted (both p<0.05). The difference in 7 Day PPA rates between bupropion and varenicline was larger at 8 week follow-ups (12%) than at 4 weeks (7%). When regression analysis was used, participants randomized to varenicline were more likely than bupropion participants to achieve abstinence at 8 weeks follow up measured by continuous abstinence [OR: 1.72 95%CI: 1.18-2.53 p<0.005] and measured by 7 Day PPA [OR: 2.04 95%CI: 1.45-2.87 p<0.0001].

3.9 7 Day PPA Trends During Treatment Period

The mITT analyses of 7 Day PPA rates throughout the treatment period (4-12 weeks) were analyzed between each medication group as seen in Figure 7. Varenicline had significantly higher 7 Day PPA rates than bupropion at 4 weeks (22% vs 15% respectively), 8 weeks (29% vs 17% respectively) and at 12 weeks (EOT) (30% vs. 20% respectively) when Chi-Square Tests were conducted. When using regression analysis, participants randomized to varenicline were more likely to achieve smoking cessation outcome compared to participants randomized to bupropion, at all the follow up times at p<0.001 when adjusted for age, gender, CPD and FTND. The effect of varenicline on cessation outcome was more pronounced at EOT (p<0.0001) than at 8 weeks or 4 weeks as reflected by lower p-values. In Figure 7, using the McNemar's test, it was seen that varenicline participants’ 7 Day PPA increased significantly from week 4–8 weeks (p=0.016) whereas bupropion’s did not (p=0.331). Between weeks 8–12, quit rates did not differ significantly for neither bupropion (p=0.849) nor varenicline (p=0.664). However, between weeks 4 to 12 weeks, quit rates for the varenicline group increased significantly (p<0.0001) from 22% to 30%. The same was true for the bupropion group between weeks 4-12 (p<0.0001) from 15% to 20%. Figure 7 shows linear regression models for both
medication groups where it can be seen that the varenicline group’s 7 Day PPA increased 3.99% per follow up whilst the bupropion group increased by only 2.38% per follow up.

**Figure 7. 7 Day PPA Abstinence rates of Bupropion and Varenicline between 4-12 weeks follow up time (EOT) (Intent to Treat (mITT) analysis).** Participants randomized to VAR had significantly higher 7 Day PPA than those randomized to BUP at all follow up times (p<0.05) using Chi-Square Test. The VAR group was more likely to achieve abstinence compared to the BUP group at 4, 8 and 12 weeks follow up (all at p<0.05) when adjusted for age, gender, CPD and FTND score (at baseline). Quit rates increased significantly from 8-12 weeks (p<0.01) and 4-12 weeks (p<0.01) for the VAR group whilst in the BUP group, quit rates increased significantly from weeks 4 - 12 (p<0.005) when McNemar Tests were conducted.

### 3.10 Long Term Treatment Outcomes

Long term smoking cessation treatment outcomes were explored by analyzing the relationship between cessation outcome at 6 and 12 months between the two medication groups.

#### 3.10.1. Self-Reported Treatment Outcomes at 6 Month Follow Up

Treatment outcomes were compared at 6 months follow up, specifically comparing 30 Day Continuous Abstinence and 7 Day PPA rates between bupropion and varenicline. 407 participants were included for mITT analysis in the bupropion group and 438 participants were included in the varenicline group. At the time of thesis analysis, there were still 90 participants whose 6 months follow up survey were not scheduled yet. In Figure 8a & 8b it can be seen that continuous abstinence of
varenicline was significantly higher than bupropion (15% vs 11% respectively) when Chi-Square-Tests were conducted (p=0.047) whereas 7 Day PPA rates were not significantly different (p=0.16). Overall, 7-Day PPA rates for bupropion and varenicline were not significantly different whereas continuous abstinence was. This suggests that when using the measure of 30 Day Continuous Abstinence, varenicline was more effective at smoking cessation however when using the 7 Day PPA measure, bupropion and varenicline were equally effective This could potentially suggest that around 6 months follow up, more participants randomized to varenicline were relapsing to smoking relative to bupropion. Or another possibility could be participants randomized to bupropion are achieving abstinence at 6-months follow up (NRT usage could be a factor) and this was not controlled for in the randomization design.

![Figure 8a](image_url)  
**Figure 8a. 30 Day Continuous Abstinence of Bupropion and Varenicline at 6 months Follow Up (mITT analysis).** Participants randomized to VAR had higher 30 Day Continuous Abstinence than BUP participants (16% vs 11% respectively) ($X^2_1=3.95$). The VAR and BUP group were equally likely to achieve continuous abstinence with an OR of 1.17 [95% CI: 0.75-1.82 p=0.484] when adjusted for age, gender, CPD and FTND. The unadjusted OR was significant at p=0.048.

![Figure 8b](image_url)  
**Figure 8b. 7 Day PPA of Bupropion and Varenicline at 6 months follow up (mITT analysis).** Participants randomized to VAR had higher 7 Day PPA of 18% versus BUP's rate of 14% ($X^2_1=1.98$). OR 1.00 [95%CI: 0.65-1.52 p=0.613] when adjusted for age, gender, CPD and FTND score.

In Table 12, the unadjusted OR for the effect of varenicline on continuous abstinence was significant at p<0.05. However, when adjusted for gender, this effect was no longer significant suggesting gender plays a role in cessation outcomes at the 6-month mark. When adjusting for age, CPD and FTND score, the OR remains relatively unchanged at ~1.40 and p<0.05. However, when adjusted for age,
gender CPD and FTND, the two medication groups were equally likely to achieve abstinence at 6 months follow up (p=0.484). When adjusting for gender, the OR had a noticeable increase (0.97). In other words, when adjusting for gender, varenicline and bupropion’s 7 Day PPA rates became less significantly different and medication group made no difference in smoking cessation outcome. After adjusting for age, gender, CPD and FTND, the OR for the effect of varenicline on continuous abstinence was 1.00 (p=0.994) with gender making the biggest difference in OR for adjustment. Upon further investigation, quit rates were not significantly different between males and females for each medication group (p=0.8915 and p=0.793 respectively) and males and females both have similar quit rates (approximately 25%).

**Table 12. 30 Day Continuous Abstinence of participants randomized to bupropion and varenicline group at 6 months follow up regression analysis.** The relationship between medication group and smoking outcome at 6 months follow up was explored adjusting for age, gender, CPD and FTND score. The VAR group were more likely to quit with an unadjusted OR (p=0.048) however this effect was not significant when adjusted for age, gender, CPD and FTND (p=0.484). The most influential factor was adjusting for gender where the OR was 1.15 [95%CI: 0.74-1.77 p=0.536] suggesting medication’s predictive role was affected by gender.

<table>
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<tr>
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<th>95% CI</th>
<th>P Value</th>
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<td>1.00-2.23</td>
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<td>Gender</td>
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</tr>
<tr>
<td>All of the Above</td>
<td>1.17</td>
<td>0.75-1.82</td>
<td>0.484</td>
</tr>
</tbody>
</table>

**3.10.2 Biochemically Confirmed Abstinence at 6 months Follow up**

Participants who reported abstinence at the 6 months follow up surveys were asked to complete a saliva sample for confirmation of smoking abstinence using cotinine as a biomarker. There were 402 participants who had completed a survey and 137 of them had self-reported quit. 137 samples were sent and 137 samples were completed and returned at the time of analysis. Participants randomized to varenicline had higher cotinine confirmed abstinence compared to bupropion. As seen in Figure 9, 48% of participants randomized to varenicline whom had cotinine confirmed quit whilst 39% of participants randomized to bupropion had cotinine confirmed quit. When a Chi-Square Test was conducted, the cotinine confirmed abstinence rate was not significantly different between the two medication groups (p=0.281).
3.10.3 Self-Reported Treatment Outcomes at 12 month Follow-Up

At 12 months follow up, there were 614 participants included for mITT analysis (294 bupropion and 320 varenicline) when comparing 30 Day Continuous Abstinence and 7 Day PPA rates between the medication groups. At the time of analysis, there are still 178 participants awaiting 12 months follow up. Figure 10a & 10b shows 30 Day Continuous and 7 Day PPA rates for bupropion and varenicline at the 12 months follow up. Varenicline and bupropion had approximately equal continuous abstinence rates (12% vs. 11%) and 7 Day PPA (12% vs 11.6%). Using the Chi-Square Test, both continuous abstinence and 7 Day PPA rates were not significantly different between bupropion and varenicline at 12 months follow up (p>0.4). However, the trend remains that varenicline had slightly higher quit rates compared to bupropion. Regression analyses of 30 Day Continuous Abstinence and 7 Day PPA were conducted for bupropion and varenicline (not shown). Both medication groups were equally likely to achieve abstinence at 12 months with an OR of 1.17 [95%CI: 0.75-1.82 p=0.484]. Also, medication group was not a predictor of 7 Day PPA rates when adjusted for age, gender, CPD and FTND with an OR of 1.00 [95%CI: 0.65-1.52 p=0.994].
Participants who’ve reported abstinence on the 12 months follow up surveys were asked to complete a saliva sample for biochemical confirmation of smoking abstinence. 251 participants completed a survey and 103 of them had self-reported quit. There were a total of 103 participants who were sent a saliva sample. 25 samples were completed and returned at the time of analysis. Participants randomized to varenicline had slightly higher cotinine confirmed abstinence rates compared to bupropion. As seen in Figure 11, 26% of participants randomized to varenicline (who had SR quit) had cotinine confirmed quit whilst 22% of participants randomized to bupropion had cotinine confirmed quit. When a Chi-Square Test was conducted, the quit rates between medication groups were not significantly different (p=0.721). Similar to self-reported quit trends at 12 months follow up, varenicline and bupropion were approximately equally efficacious at achieving smoking cessation at 12 months follow up. However, similar to self-reported abstinence data, varenicline and bupropion were equally effective.

**3.10.4 Biochemically Confirmed Abstinence at 12 months follow-up**

Participants who’ve reported abstinence on the 12 months follow up surveys were asked to complete a saliva sample for biochemical confirmation of smoking abstinence. 251 participants completed a survey and 103 of them had self-reported quit. There were a total of 103 participants who were sent a saliva sample. 25 samples were completed and returned at the time of analysis. Participants randomized to varenicline had slightly higher cotinine confirmed abstinence rates compared to bupropion. As seen in Figure 11, 26% of participants randomized to varenicline (who had SR quit) had cotinine confirmed quit whilst 22% of participants randomized to bupropion had cotinine confirmed quit. When a Chi-Square Test was conducted, the quit rates between medication groups were not significantly different (p=0.721). Similar to self-reported quit trends at 12 months follow up, varenicline and bupropion were approximately equally efficacious at achieving smoking cessation at 12 months follow up. However, similar to self-reported abstinence data, varenicline and bupropion were equally effective.
3.11 Overall 7 Day PPA for all Follow Up Time Points (mITT)

The intent to treat (mITT) analysis was conducted on 7 Day PPA rates at week 4, 8 and 12 weeks, 6 months and 12 months as seen in Figure 11. Using Chi-Square tests, at week 4, varenicline had significantly higher 7 Day PPA than bupropion (p<0.05). The same significant trends were seen at weeks 8 and week 12 with each time point’s p value decreasing, becoming more significant (peak at EOT) (p<0.001). When the McNemar’s test was conducted, it was seen that the distribution of 7 Day PPA of participants randomized to varenicline between 4 to 8 weeks was significantly different at p<0.05. However, in the varenicline group, between weeks 8 to 12, 7 Day PPA was not significantly different from each other (p>0.5). Meanwhile, the bupropion group did not have a significant increase of 7 Day PPA between 4 to 8 weeks (p>0.5) nor between weeks 8 to 12 (p>0.5). During the treatment period (4-12 weeks), the slopes of the linear trend lines reveal that the 7 Day PPA rate in the varenicline steadily increased from each follow up time to the next by an average of 3.99% whereas for bupropion, the slope did not change as significantly nor dramatically (2.4%) (Figure 12). Regression analysis showed significantly higher quit rates for varenicline at weeks 4, 8 and 12 compared to bupropion (overall p<0.005). At EOT, varenicline had the highest OR when adjusted for age, gender, CPD and FTND. Adjusting for all four factors did not change the significance of this relationship. Further analysis shows that the highest 7-Day PPA rates for bupropion and varenicline participants occurred at the 12 week (EOT) follow up. At the 6 months mark, there were no significant differences between 7 Day PPA rates of both medication groups (14% vs 17%). In fact, bupropion rates were slightly higher than varenicline at this time point. By 12 months follow up, the quit rates were ~12% for both groups. Varenicline had higher quit rates at this time however this was not significant.
The complete case analysis of 7 Day PPA trends throughout the study can be seen in Figure 12. While the trend was similar to Figure 11, there were distinct differences in trends at the 6 months and 12 months follow up time. The 7 Day PPA rates were significantly higher for varenicline than bupropion at 8 weeks (45% vs 26%) [p<0.05] and 12 weeks (48% vs 27%) [p<0.001]. At 4 weeks, varenicline 7 Day PPA rates was higher than bupropion (30% vs 21%) however this was not significant (p>0.05). At 6 months follow-up, the rates of 7 Day PPA were almost the same for bupropion and varenicline (~33%). At all other time points of the study, varenicline had been more effective for smoking cessation with the exception of 6 months follow up. According to complete case analysis, the highest 7 Day PPA rate occurred at EOT for the varenicline group whereas the highest rate for the bupropion group occurred at 6 months follows up. This could possibly be due to increased use of NRT or additional resources used by the bupropion group for smoking cessation.

The biggest difference between Figure 12 and Figure 13 is that 7 Day PPA rates were overall higher in Figure 13. This is mostly due to loss of follow up and assumption of non-quit for incomplete surveys. As expected, 7 Day PPA rates were higher at all follow ups compared to mITT analysis. When the McNemar tests were conducted, quit rates between weeks 4 to 8 were significantly different for both medication groups and rates from week 4 to week 12 were also significant at p<0.05 for both.
medication groups. When regression analyses were conducted, varenicline was a superior predictor of smoking cessation outcome at weeks 8 and week 12 (both p<0.001) when adjusted for age, gender CPD and FTND.

3.13 Medication Compliance

3.13.1. Self Reported Medication Compliance and Treatment Outcomes at EOT

Self-reported medication compliance was assessed at 12 weeks follow up survey (EOT) for 541 participants that had received medication (242 randomized to bupropion and 299 randomized to varenicline) who had completed a survey. Of the 381 participants who had not finished the medication, 195 indicated they are still using (84 randomized to bupropion and 111 randomized to varenicline) whilst 186 indicated they discontinued medication use (84 randomized to bupropion and 102 randomized to varenicline). The most common reason for medication discontinuation was achieving abstinence, unwanted adverse side events and having relapsed. Other reasons include: not finding it helpful, stopped having cravings for cigarettes and believing they did not need it anymore. Compliance rates were not significantly different between the two medication groups (p>0.5).

3.13.2. 30 Day Continuous Abstinence and Medication Compliance at EOT

The relationship between medication use and complete case EOT outcomes can be seen in Figure 14. The figure shows 30 Day Continuous Abstinence rates associated with each compliance group by

Figure 13. 7 Day PPA Abstinence rates of Bupropion and Varenicline throughout study (weeks 4-52) (Complete Case Analysis). Participants randomized to VAR had significantly higher 7 Day PPA than those randomized to BUP at 4, 8 and 12 weeks (p<0.001). At 6 months follow up, quit rates for both medication groups were approximately equal (~30%) whilst at 12 months follow up, 7 Day PPA rates were higher for VAR than BUP however not significantly (p=0.613).
medication groups. Overall, for participants that had finished medication, varenicline had higher quit rates (56%) than bupropion (36%). There was a clear positive relationship between compliance and quit outcomes at EOT. However, this trend seems to be more pronounced for varenicline participants where full compliance with medication resulted in higher quit outcomes than bupropion users who also finished the medication. When the Chi-Square Test was conducted, 30 Day Continuous Abstinence rates for bupropion were significantly lower for participants still using medication compared to participants who had finished medication (p<0.0001). The same is true for varenicline participants at p<0.0001. Bupropion participants experienced an 11% increase in continuous abstinence per increase in medication compliance whilst varenicline participants increased a 20% increase per increase in medication compliance.

![Bar chart showing 30 Day Continuous Abstinence rates for participants still using and finished medication with varenicline and bupropion](image)

**Figure 14. 30 Day Continuous Abstinence Rates of bupropion and varenicline according to medication compliance at 12 weeks follow up (EOT).** 30 Day Continuous Abstinence was analyzed for each medication group stratified by medication usage at 12 weeks follow up. 60% of participants had completed the medication for each medication group

### 3.13.3. 7 Day PPA and Medication Compliance at EOT

The overall 7 Day PPA for participants that had completed medication was 60% and 42% for bupropion and varenicline respectively. Figure 15 shows the relationship between medication compliance and 7 Day PPA for both medication groups. Quit rates were significantly different when Chi-Square Tests were conducted in both compliance groups. When Chi-Square Tests were conducted, it was found that 7 Day PPA significantly increased between still using and finished
medication groups in the bupropion group (p<0.001). Similarly, in the varenicline group, 7 Day PPA significantly increased between participants still using medication and participants who had finished medication (p<0.00001) (Figure 15). The bupropion group experienced a 12.6% increase in 7 Day PPA per increase in compliance class whilst varenicline group experienced a 16.8% increase.

![Figure 15. 7 Day PPA Rates of bupropion and varenicline according to medication compliance at 12 weeks follow up (EOT).](image)

7 Day PPA was analyzed for each medication group stratified by medication usage at 12 weeks follow up. 60% of participants had completed the medication for each medication group.

### 3.13.4. Medication Compliance & Discontinuation and 7 Day PPA of Bupropion and Varenicline

Medication compliance was defined as still using or finished medication in the above analyses; however, there were 182 participants that discontinued medication use at EOT. Thus, the relationship between medication compliance and 7 Day PPA was explored including participants who had discontinued medication. Figure 16a & 16b shows the relationship between compliance status and 7 Day PPA for bupropion and varenicline respectively. Analysis was conducted to investigate if discontinuation time point was associated with treatment outcome. At EOT, there were 102 participants randomized to varenicline who had discontinued medication whilst 84 participants randomized to bupropion discontinued medication. Discontinued bupropion participants had a quit rate of 16% whereas varenicline discontinued participants had 28% quit at EOT. Bupropion compliance was associated with an increased 7 Day PPA. From Figure 16a, it can be seen that 7 Day PPA increased 13% per compliance class for the bupropion group. Increased varenicline compliance
was associated with increased 7 Day PPA. From Figure 16b, it can be seen that per increase in medication compliance class, 7 Day PPA increased by 16% for the varenicline group at EOT.

**Figure 16a.** 7 Day PPA Rates of bupropion according to medication compliance including discontinuation at EOT. Participants either discontinued medication, was still using or finished medication at EOT. 42% of BUP participants that finished medication were abstinent at EOT. Abstinence rates increased by 13% per increase in compliance class.

**Figure 16b.** 7 Day PPA rates of varenicline according to medication compliance including discontinuation at EOT. Participants randomized to VAR who had finished medication had the highest 7-Day PPA of 60% at EOT. Abstinence rates increased by 16% per increase in compliance class.
Medication compliance was evaluated at mid-treatment (4 weeks follow up) by measuring varenicline and bupropion content of participants who completed and returned a saliva sample. The limit of detection was 1ng/ml. Thus, all participants with bupropion or varenicline concentrations below the limit detection were considered non-compliant. At T1, 156 participants randomized to bupropion returned a saliva sample whilst 224 randomized to varenicline returned a sample. Varenicline and total bupropion concentration was quantified. Past detection values of either medication was considered compliant. Overall, more participants were compliant to bupropion (95%) than varenicline (70%). This could be potentially due to participant achieving abstinence sooner whilst using varenicline and discontinue medication use. Figure 17 shows quit rates at EOT of each compliance group (defined at T1). Surprisingly, 55% of varenicline non-compliant participants quit at EOT. However, upon further investigation, this could be because 70% of participants non-compliant to varenicline had already quit by T1. On the other hand, none of the participants non-compliant to bupropion quit by EOT. Amongst compliant participants, varenicline resulted in higher quit rates than bupropion (23% vs 21% respectively) (Figure 17).

Figure 17. End of Treatment (EOT) Quit Rates of Bupropion and Varenicline split by Biochemically Confirmed Compliance at T1 (4 weeks Follow Up). 30 Day Continuous Abstinence Rates were compared between each medication group split by biochemically confirmed medication compliance at T1. Within compliant participants, quit rates of BUP and VAR at EOT were similar (~22%). Within noncompliant participants, none of the participants randomized to BUP quit at EOT and 55% of participants randomized to VAR SR quit at EOT. This difference was significant when Chi-Square Tests were performed (p<0.0001).
3.14 Adverse Events

Participants were asked at various follow up times if they had experienced any adverse events during the treatment period. The rate of self-reported side effects remained relatively stable over follow up times. Table 13 shows prevalence of the most common adverse effects of each medication throughout the treatment period compared using the Chi-Square Test. Most noteworthy were participants randomized to varenicline experienced significantly higher instances of vivid dreams, fatigue and nausea compared to bupropion (all at p<0.001). These findings reflect side effects typically experienced by varenicline users. Additionally, participants randomized to varenicline showed higher occurrences of dry mouth at the 4 week follow up survey. Overall, these medications were relatively safe since there were no serious adverse events nor instances where participants required immediate physician attention.

Table 13. Self-reported adverse events experienced by all participants throughout the treatment period (12 weeks). Participants randomized to VAR showed significantly higher occurrences of vivid dreams, fatigue and nausea (all at p<0.001) at all follow up times whilst participants randomized to VAR showed higher occurrences of dry mouth (p<0.001) at 4 week follow up only.

<table>
<thead>
<tr>
<th>Follow Up Time</th>
<th>4 Week</th>
<th>8 Week</th>
<th>12 Week (EOT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BUP n=430</td>
<td>VAR n=490</td>
<td>P Value</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>48.14%</td>
<td>34.14%</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Trouble Sleeping</td>
<td>51.11%</td>
<td>42.38%</td>
<td>0.099</td>
</tr>
<tr>
<td>Vivid Dreams</td>
<td>37.40%</td>
<td>57.01%</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Rash</td>
<td>6.67%</td>
<td>5.49%</td>
<td>0.158</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37.78%</td>
<td>49.39%</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Nausea</td>
<td>20.74%</td>
<td>52.74%</td>
<td><strong>0.000</strong></td>
</tr>
<tr>
<td>Dizziness</td>
<td>27.01%</td>
<td>18.90%</td>
<td>0.236</td>
</tr>
<tr>
<td>Other</td>
<td>24.07%</td>
<td>19.20%</td>
<td>0.149</td>
</tr>
</tbody>
</table>
3.15 The Role of Nicotine Metabolism on Smoking Cessation

3.15.1 NMR Distribution of all Participants and Baseline Characteristics

670 saliva samples were returned of which 663 were usable for biochemical analysis. There were 10 samples that had NMR values beyond normal acceptable ranges (NMR>1000). These 10 samples were excluded from analyses. Figure 18 shows the NMR frequency distribution for all participants at baseline. The mean of NMR values was 0.594±0.41 (SD). The NMR values range from 0.018 to 4.20. The 25th percentile of NMR was 0.322 based on previous literature (Ho et al., 2009, Lerman et al., 2006, Strassser et al., 2011) to distinguish between Slow (SM) and Normal Metabolizers (NM) of nicotine. Overall, 162 participants were Slow Metabolizers (SM) and 447 were Normal Metabolizers (NM). Additionally, males had significantly lower NMR than females (0.55 vs 0.63 respectively) at p=0.03. When a Spearman's bivariate correlation test was performed, a significant relationship between NMR and gender (p=0.002) was seen. NMR frequency distribution was also compared between bupropion and varenicline at baseline. Overall, there were no significant differences between mean NMR values between the medication groups. However, NMR values for bupropion group were slightly higher than those randomized to varenicline. In Table 16, baseline characteristics were compared between the two metabolizer groups. Normal metabolizers were significantly older than Slow Metabolizers when a Two Sample T-test was conducted (p<0.001). Normal Metabolizers also smoked significantly more cigarettes per day than Slow Metabolizers. All other baseline characteristics were not significantly different at baseline between metabolizer groups.

Figure 18. Frequency Distribution of Measured Nicotine Metabolite Ratios.
The NMR of all participants at baseline ranged between 0.018 to 4.20. The mean was 0.594±0.41. The 25th percentile was 0.322 (the red line), which separated participants into slow or normal metabolizers. Overall, 162 participants were SM and 447 were NM.
Table 14. Baseline demographics of participants classified as Slow Metabolizers and Normal Metabolizers of Nicotine. Age was significantly higher in Normal Metabolizers compared to Slow Metabolizers at p<0.05. Slow Metabolizers also smoke significantly fewer cigarettes per day than Normal Metabolizers at p<0.05. Lastly, there were significantly more participants randomized to varenicline in the SM group compared to the NM group. All other traits were not significantly different between metabolizer groups.

<table>
<thead>
<tr>
<th>Mean and Proportion within column</th>
<th>CYP2A6 Metabolizer Group</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slow (n= 162)</td>
<td>Normal (n=447)</td>
</tr>
<tr>
<td>Medication Group (% Bupropion)</td>
<td>63 (39%)</td>
<td>218 (48%)</td>
</tr>
<tr>
<td>Gender (%Male)</td>
<td>47.3%</td>
<td>40.9%</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>43.0 ± 11.12</td>
<td>49.0 ± 11.24</td>
</tr>
<tr>
<td>Cigarettes Per Day</td>
<td></td>
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</tr>
<tr>
<td>&lt; 10</td>
<td>11.5%</td>
<td>11.0%</td>
</tr>
<tr>
<td>11-20</td>
<td>53.4%</td>
<td>42.5%</td>
</tr>
<tr>
<td>21-30</td>
<td>33.1%</td>
<td>36.6%</td>
</tr>
<tr>
<td>&gt;31</td>
<td>2.0%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Age of First Cigarette (mean ± SD)</td>
<td>14.92 ± 3.81</td>
<td>14.52 ± 3.17</td>
</tr>
<tr>
<td>Age of Daily Smoking (mean ± SD)</td>
<td>16.89 ± 4.04</td>
<td>16.39 ± 3.38</td>
</tr>
<tr>
<td>Importance to Quit (mean ± SD)</td>
<td>9.35 ± 0.89</td>
<td>9.43 ± 1.15</td>
</tr>
<tr>
<td>Confidence to Quit (mean ± SD)</td>
<td>7.03 ± 1.99</td>
<td>7.35 ± 2.04</td>
</tr>
<tr>
<td>Fagerstrom Test of Nicotine Dependence (mean ± SD) max.</td>
<td>5.71 ± 1.96</td>
<td>6.02 ± 1.97</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>21.6%</td>
<td>28.0%</td>
</tr>
<tr>
<td>College</td>
<td>58.8%</td>
<td>52.8%</td>
</tr>
<tr>
<td>University</td>
<td>18.9%</td>
<td>18.6%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European/Caucasian</td>
<td>86.5%</td>
<td>85.7%</td>
</tr>
<tr>
<td>African Descent</td>
<td>0.00%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Indian</td>
<td>2.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Don’t know</td>
<td>3.4%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>
3.15.2 Relationship between NMR and age, gender, CPD and FTND

Relationship between Age and Nicotine Metabolite Ratio (NMR)

To explore the relationship between NMR and age at baseline, the Pearson bivariate correlation test was performed where there was significant relationship between age and logNMR (correlation coefficient = 0.27, p<0.0001). LogNMR was used to normalize the data. Increasing age at baseline was correlated with increasing NMR values as seen in Figure 19.

![Figure 19. Age at baseline and Nicotine Metabolite Ratios (NMR).](image)

Relationship between Nicotine Dependence and Nicotine Metabolite Ratios

To explore the relationship between NMR and nicotine dependence, measured by FTND score, the Spearman bivariate correlation test was performed. LogNMR was used to normalize the data. There was a weak but significant correlation between nicotine dependence and NMR with a coefficient of 0.08 and a p value of 0.05. The graphical representation of this relation can be seen in Figure 20.

![Figure 20. Nicotine Dependence (FTND score) and Nicotine Metabolite Ratios.](image)
Relationship between Cigarette Consumption and Nicotine Metabolite Ratios

To explore the relationship between cigarette consumption per day and NMR, a Spearman test for bivariate correlation was conducted where a weak but significant relationship was seen between increasing CPD and logNMR with a coefficient of 0.096 and p value of 0.019 (Figure 21). LogNMR was used to normalize the data.

![Figure 21. Cigarette per day and Nicotine Metabolite Ratios.](image)

3.15.3 Metabolizer Class and Cessation Outcome at EOT

The role of Nicotine Metabolism (measured by NMR) at end of treatment (EOT) for Modified Intent to Treat treatment (mITT) outcomes was assessed. A total of 609 samples were assessed for intent to treat (mITT) analysis in which 147 were Slow metabolizers (SM) and 447 were Normal Metabolizers (NM). Overall, SM had mITT 30 Day Continuous quit rate of 28% whereas NM had overall quit rate of 21%. 7 Day PPA, on the other hand, was 31% for SM and 26% for NM. When Chi-Square Tests were conducted, there were no significant differences between quit rates for both metabolizer groups. NMR, when used alone, was not a significant predictor of cessation outcome at EOT [OR=0.66 95%CI: 0.43-1.03 p=0.067] when adjusted for medication group, age and CPD (the three factors significantly different between metabolizer groups (not shown). Although not significant, a trend was observed where NM had lower quit rates at EOT than SM. The same analysis was conducted for 7 Day PPA [OR=0.73 95%CI:0.48-1.10 p=0.13] when adjusted for medication group, age and CPD. Results from these analyses (not shown) concluded that NMR was not a significant predictor of continuous or 7 Day PPA when adjusted for medication group, age and CPD.
3.15.4 Interaction Between NMR and Treatment Outcomes at EOT

To investigate if different NMR affected quit outcomes with the two medications, participants were categorized into four possible groups: SM receiving bupropion, SM receiving varenicline, NM receiving bupropion or NM receiving varenicline. Of the 162 participants classified as SM, 66 were randomized to bupropion and 96 randomized to varenicline. Of the 447 participants classified as NM, 217 were randomized to bupropion and 230 were randomized to varenicline. Figure 22a shows 30 Day Continuous Abstinence rates at EOT for the four different groups mentioned. When Chi-Square Tests were conducted, SMs randomized to varenicline had significantly higher 30 Day Continuous Quit rates than bupropion (37% vs 19%) \( p<0.05 \). The same holds true in NMs, where the varenicline group had significantly higher continuous abstinence than the bupropion group (26% vs 16% respectively). Figure 22b shows 7 Day PPA for bupropion and varenicline split by metabolizer groups at EOT. When Chi-Square Tests were conducted, varenicline had significantly higher quit rates than bupropion for both SM (44% vs 19%) and NM (31% vs 21%).

Figure 22a. 30 Day Continuous Abstinence of Bupropion and Varenicline at EOT split by NMR metabolizer group. Participants randomized to VAR had significantly higher 30 Day Continuous Abstinence when a Chi-Square test was used for SM \( \chi^2_1=5.3 \) and NM \( \chi^2_1=7.2 \). VAR participants were significantly more likely to achieve continuous abstinence for SM [OR =3.21 95%CI: 1.48-6.94 \( p=0.003 \)] and NM [1.86 95%CI: 1.16-2.98 \( p=0.01 \)]. NMR was a significant predictor of cessation outcome for VAR group only [OR=0.57 95%CI: 0.34-0.99 \( p=0.047 \)].

Figure 22b. 7 Day PPA of Bupropion and Varenicline at EOT split by NMR metabolizer group. For both SM and NM, participants randomized to VAR had significantly higher 7 Day PPA rate than BUP at \( p<0.05 \) \( \chi^2_1=3.1 \) and \( \chi^2_1=2.8 \) respectively. VAR participants were more significantly likely to achieve 7 Day PPA for SM [OR=4.16; 95%CI: 1.93-8.96 \( p=0.0001 \)] and NM [OR=1.63; 95%CI: 1.06-2.52 \( p=0.028 \)]. NMR was a superior predictor of cessation outcome for the VAR group only [OR=0.53; 95%CI: 0.32-0.91 \( p=0.02 \).
To further explore the relationship between NMR and treatment outcomes, bivariate regression analyses were performed comparing treatment effect within each group of metabolizers as seen in Table 15. Participants randomized to varenicline were significantly more likely to achieve continuous abstinence than the bupropion group at EOT for both SM and NM when adjusted for age and CPD (at baseline) with OR=3.21 [95%CI: 1.48-6.94 p=0.003] and OR=1.86 [95%CI: 1.16-2.98 p=0.01] respectively. Participants randomized to varenicline were also significantly more likely to achieve 7 Day PPA at EOT for both SM and NM (when adjusted for age and CPD) with OR=4.16 [95%CI: 1.93-8.96 p=0.0001] and OR=1.63 [95%CI: 1.06-2.52 p=0.028] respectively. Lastly, the binary regression analyses were performed exploring NMR metabolizer group effect within each medication group for cessation outcome as seen in Table 16 adjusting for age and CPD. For continuous abstinence within the varenicline group, Normal Metabolizers had significantly lower quit rates than SM [OR=0.57 95%CI: 0.34-0.994 p=0.047]. The same was observed for 7 Day PPA where NM had significantly lower quit rates than SM in the varenicline group [OR=0.53 95%CI: 0.32-0.91 p=0.02].

Table 15 Odd Ratios of End of Treatment Outcomes by Medication Group (ref=bupropion) in each of the NMR groups. The odd ratios for the medication groups are presented within each of the NMR groups. For all four groups, the VAR group were significantly more likely to quit at p<0.05 when adjusted for age and CPD (at baseline).

<table>
<thead>
<tr>
<th>Quit Outcome</th>
<th>Metabolizer</th>
<th>Odd Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Day Continuous</td>
<td>Slow Metabolizer</td>
<td>3.21</td>
<td>1.48-6.94</td>
<td>0.003*</td>
</tr>
<tr>
<td>Abstinence</td>
<td>Normal Metabolizer</td>
<td>1.86</td>
<td>1.16-2.976</td>
<td>0.010*</td>
</tr>
<tr>
<td>7 Day PPA</td>
<td>Slow Metabolizer</td>
<td>4.16</td>
<td>1.93-8.96</td>
<td>0.000*</td>
</tr>
<tr>
<td></td>
<td>Normal Metabolizer</td>
<td>1.63</td>
<td>1.06-2.52</td>
<td>0.028*</td>
</tr>
</tbody>
</table>

Table 16. Odd Ratios for End of Treatment Outcomes by Metabolizer group (ref=slow) in each of the Medication groups. The odd ratios for the NMR categories are presented within each treatment group. Metabolizer group was only a significant predictor of cessation outcome within the VAR group measured by 30 Day Continuous Abstinence and 7 Day PPA (both at p<0.05) when adjusted for age and CPD (at baseline).

<table>
<thead>
<tr>
<th>Quit Outcome</th>
<th>Medication</th>
<th>Odd Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Continuous</td>
<td>Bupropion</td>
<td>0.822</td>
<td>0.388-1.739</td>
<td>0.608</td>
</tr>
<tr>
<td>Abstinence</td>
<td>Varenicline</td>
<td>0.57</td>
<td>0.338-0.994</td>
<td>0.047*</td>
</tr>
<tr>
<td>7 Day PPA</td>
<td>Bupropion</td>
<td>1.207</td>
<td>0.57-2.55</td>
<td>0.623</td>
</tr>
<tr>
<td></td>
<td>Varenicline</td>
<td>0.53</td>
<td>0.319-0.905</td>
<td>0.02*</td>
</tr>
</tbody>
</table>
3.15.5 Self-Reported quit versus Biochemically Confirmed Quit Rates for Different Metabolizer Groups

Self-reported abstinence was used as the primary measure of quit outcome for Treatment Outcome analyses. However, Self-reported quit is susceptible to reporter bias. Saliva samples collected at T1 (4 weeks Follow Up) measured cotinine concentrations as confirmation of smoking behavior. To explore if any discrepancy exists between self-reported abstinence and cotinine confirmed abstinence within the two medication groups, the two quit measures were compared as seen in Figure 23a and 23b. The McNemar Test was used to compare if proportions of SR abstinence and cotinine abstinence within each group was significantly different from each other at p<0.05.

From Figure 23a, it can be seen within the bupropion group, self-reported abstinence and cotinine confirmed abstinence rates were approximately the same at 26%. However, for NM, participants had lower SR abstinence compared to cotinine confirmed abstinence. This suggests that NM randomized to bupropion under-report “true” abstinence at T1 (4 weeks follow up). When McNemar Tests were conducted, SR abstinence and cotinine abstinence were not significantly different in both SM and NM.

Figure 23b shows the relationship between SR abstinence and Cotinine Abstinence for SM and NM for participants randomized to varenicline at T1 (4 weeks Follow Up). Participants randomized to varenicline overall under-reported “true” abstinence. In SM, cotinine confirmed abstinence was higher than SR abstinence (52% vs 45%). The same trend was seen in NM, where cotinine confirmed abstinence was 43% vs 35% SR abstinence. Additionally, under-reporting abstinence was more prominent in the NM group. When the McNemar Test was conducted, cotinine confirmed abstinence rate was significantly higher than SR for the NM group. In both measures of abstinence, varenicline was more beneficial for SM to achieve smoking abstinence at T1.
Figure 23a Cotinine Confirmed Abstinence rates and Self-Reported (SR) Abstinence rates of SM and NM randomized to bupropion. SR abstinence and cotinine confirmed abstinence were equal for SM (26%) whilst in NM; SR abstinence (21%) was lower than cotinine confirmed abstinence (23%). This suggests NM randomized to BUP under-reported abstinence at T1. 23b Cotinine Confirmed Abstinence rates and Self-Reported (SR) Abstinence rates of SM and NM randomized to varenicline. SR abstinence was lower than cotinine confirmed abstinence for both SM (45% vs 52%) and NM (35% vs 53%). Both SR quit rate and Cotinine confirmed abstinence rate was highest for SM. Overall, participants randomized to VAR under-reported abstinence for both
4.0 DISCUSSION

4.1.1. Summary of Findings

To date, MATCH is the first study to evaluate the real-world effectiveness of varenicline and bupropion for smoking cessation through an innovative internet-based medium. The primary finding of this study was that participants randomized to varenicline treatment had significantly higher 30 Day Continuous Abstinence and 7 Day Point Prevalence Abstinence than those randomized to bupropion treatment at end of treatment. Using intent-to-treat analysis, whereby participants who did not respond to follow-up surveys were assumed to still be smoking, the overall quit rate observed at end of treatment was 25% for varenicline and 16% for bupropion. In terms of long-term abstinence, participants randomized to varenicline had similar quit rates to those randomized to bupropion at 6 months (16% vs 11%) and at 12 months (12% vs 10%). When cotinine confirmed abstinence analyses were conducted, varenicline had slightly higher quit rates than bupropion at 6 months and at 12 months however this was not significant. Participants randomized to varenicline generally under-report true abstinence (SR abstinence vs COT confirmed abstinence) compared to participants randomized to bupropion.

The secondary finding was that self-reported medication compliance was a significant predictor of quit outcomes for both medication groups. In fact, medication compliance was as strong a predictor for cessation as medication assignment. When biochemically confirmed compliance was assessed, participants randomized to varenicline had significantly lower compliance than participants randomized to bupropion. Of participants randomized to varenicline that had discontinued medication use, 72% of them had already quit by the mid-treatment mark and thus discontinued medication use, indicating reverse causation. Both self-reported and biochemically confirmed compliance were significant predictors of cessation outcome at end of treatment.

As the tertiary objectives, the role of nicotine metabolism and baseline characteristics were explored. Nicotine Metabolite Ratio was significantly associated with age, gender and cigarettes per day but not with nicotine dependence as measured by FTND. NMR was also not a significant predictor of cessation outcome at end of treatment. However, at end of treatment, slow metabolizers of nicotine had higher self-reported 30 Day Continuous Abstinence than normal metabolizers but this effect was not significant. In both slow and normal metabolizers, participants randomized to varenicline had significantly higher continuous abstinence than participants randomized to bupropion. However, when NMR x Medication Effects was explored, varenicline treatment benefited slow metabolizers whilst bupropion treatment benefited normal/fast metabolizers. In conclusion, these findings suggest that this method of mass pharmacotherapy distribution by using the Internet as a medium was highly
effective for cessation outcomes seen by quit rates of bupropion and varenicline at end of treatment that are comparable to traditional clinical trials with these medications. These findings are discussed in more detail in the following sections.

4.1.2. Baseline Characteristics

Overall, there were no significant differences in baseline characteristics of eligible participants randomized to bupropion and varenicline as well as those who received bupropion and varenicline. This indicates that the randomization procedure was effective. Specifically, our study sample consisted of mostly white, middle aged, more than half female smokers who smoked on average between 11-20 cigarettes per day and were moderately nicotine dependent. However, when further analysis was conducted, there were gender differences found in baseline characteristics of eligible participants who received medication. Female participants smoked significantly fewer cigarettes per day than men, had higher nicotine dependence (measured by FTND) and higher education than men. The gender differences within smoking behaviors and dependence has been well documented. The literature suggests that women smoke less than men however they are more nicotine dependent. Men seem to be more affected by the pharmacology-related effects of smoking while women are more affected by behavioral aspects of smoking (McKee, Smith, Kaufman, Mazure, & Weinberger, 2016; Perkins & Scott, 2008; Piper et al., 2010). This difference could also contribute to the gender differences seen in smoking behavior and dependence observed in our study. Lastly, females have significantly higher education than men in our study and this is reflected in Statistic Canada reports that indicate females on average are more educated than men (Statistics Canada 2015).

Although 4055 participants were eligible for the study, only 964 visited their prescriber, had the prescription signed and then faxed and filled by the contract pharmacy. When comparing baseline characteristics of these two groups of participants, the only significant difference found was that participants who received medication were on average 3 years older than those who did not receive medication. This difference was probably due to older smokers being more motivated to quit smoking probably from onset of smoking related health problems (Gilbert, Sutton, & Sutherland, 2005). This effect is supported by studies that show older smokers are more likely to use cessation aids than younger ones due to their inherent lower incidences of successful quit rates (Fidler, Ferguson, Brown, Stapleton, & West, 2013). There were also comparisons made between other traits that differed between participants who are eligible and those who received medication, for example, reason for not receiving medication. There were no compelling reasons for participants not receiving medication other than lack of a family physician or not enough time to see a doctor. This was an unexpected occurrence since it is estimated that only 15% of Canadians do not have a family doctor (Statistics Canada 2014). More than half of eligible participants did not have a signed prescription in our study.
indicating that this may not be entirely due to a shortage of family doctors but rather participants lost their motivation to continue with the study even with the impetus of free medication. However, there were no significant differences between numbers of participants who did not receive medication in the bupropion group versus the varenicline group. Since participants who did not like the assigned medication had the option of dropping out from the study, there is a potential for selection bias. This is also attributable to the fact that the study was designed in a non-blinded method.

Lastly, baseline NMR levels were analyzed for participants who returned a saliva sample (63%). The 25th percentile value in our sample was 0.322, which was used to distinguish between slow and normal metabolizers of nicotine. This cut-off was slightly higher than those used by previous studies looking at NMR (Lerman et al., 2015) in which 0.31 was used as the cut-off. The observed higher NMR cut-off in our study could be due to differences in participant demographics. For example, there were more females and more Caucasians in our sample than in the published study. Both female sex and Caucasian race have been associated with higher NMR values (M. J. Chenoweth et al., 2014). When baseline characteristics were compared between slow and normal metabolizers, there were distinct differences. Normal metabolizers smoked more cigarettes per day than slow metabolizers. These trends are supported by literature that indicate normal metabolizers of nicotine smoke more than slow metabolizers and therefore find it more difficult to quit (Malaiyandi et al., 2005; Schoedel, Hoffmann, Rao, Sellers, & Tyndale, 2004; Tyndale & Sellers, 2001). This is because fast metabolizers of nicotine have lower nicotine serum levels throughout the day and therefore to maintain the reinforcing effects of nicotine, they smoke more cigarettes per day. Slow metabolizers of nicotine generally smoke less and thus have higher chances of maintaining smoking abstinence even when controlling for factors that could potentially affect NMR (Chenoweth, Appleton, Allen, & Rundle, 2015).

Normal Metabolizers were also significantly older than slow metabolizers. This finding was replicated in a previous study that showed older smokers have higher NMR than younger smokers (Johnstone et al., 2006). However, other studies have found that nicotine metabolism was faster in younger smokers (Molander & Lunell, 2001). Meanwhile, other studies have found no differences in nicotine metabolism between adults and adolescents (Al Koudsi & Tyndale, 2005; Gourlay & Benowitz, 1996). Despite these inconsistent findings, it’s been well accepted that smoking slows the metabolism of nicotine by CYP2A6 (Benowitz & Jacob, 1994). The same has been shown for in between subject comparisons (when smoking compared to not smoking) (Benowitz, Lake, Keller, & Lee, 1987). A potential reason to explain the inconsistent literature is that the relationship between cigarettes per day and CYP2A6 metabolism could be confounded by age. As mentioned previously, increased age is significantly associated with increased CYP2A6 activity whilst smoking decreases CYP2A6 activity. Thus, even
though smokers in the NM group smoke more, they were also significantly older than SMs suggesting perhaps, age impacts CYP2A6 activity more significantly than smoking behaviors.

There are also other differences between Slow and Normal Metabolizers that could be explained by nAChR up regulation seen in some smokers. Chronic stimulation of nAChR by an agonist, such as nicotine, induces up regulation of this receptor by mechanisms independent of increased gene expression in adults (Melroy-Greif, Stitzel, & Ehringer, 2016). Previous studies show evidence that different nAChR subtypes show different up regulation mechanisms in response to nicotine throughout the brain (Court & Clementi, 1995). Specifically, regulation of nAChR availability in the thalamus has been associated with nicotine metabolism variations. SM of nicotine exhibit reduced nAChR availability in the thalamus after a period of abstinence compared to normal metabolizers (NM). The difference in nicotine elimination could also explain differences in nicotine binding which alters nACHR availability in smokers (Dubroff et al., 2015).

When personality traits were analyzed between the bupropion and varenicline group, there were no significant differences in the five traits between the groups. However, when stratified by gender, there were significant differences in agreeableness. In particular, females had significantly higher scores in agreeableness than men in both bupropion and varenicline groups. This effect is supported by the literature (Costa et al., 2001). This difference in agreeableness could potentially affect compliance rates with each medication. The other four traits were not significantly different between males and females for both medication groups. Overall, participants had low scores in neuroticism and extraversion.

4.1.3. Treatment Outcomes

4.1.3.1. Varenicline, the Superior Pharmacotherapy for Smoking Cessation

The primary outcome of this study was smoking cessation rates between bupropion and varenicline as measured by both 30 Day Continuous Abstinence and 7 Day Point Prevalence Abstinence. In all follow up times during the treatment period, varenicline was superior at achieving smoking abstinence than bupropion. At end of treatment, participants randomized to varenicline had 25% continuous abstinence and 30% 7 Day PPA. On the other hand, participants randomized to bupropion had 16% continuous abstinence and 20% 7 Day PPA. These findings are similar to other clinical trials with head-to-head comparisons of bupropion and varenicline were EOT quit rates were on average 46% for varenicline and 33% for bupropion (Cincirpini et al., 2013; D. Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006). Quit rates from our study were lower than those observed in clinical trials.
mainly due to methodological differences between real-world and clinical settings (Section 4.1.3.2. Real-World Quit Rates Versus Clinical Trials).

Overall, varenicline was more effective than bupropion at EOT with superior cessation outcomes. The difference in efficacies between the two medications is mainly explained by different actions of bupropion and varenicline. Initially, when treatment is used, both bupropion and varenicline can alleviate nicotine withdrawal symptoms by increasing dopamine release in the nucleus accumbens of the brain reward system. Varenicline achieves this by releasing dopamine via partial agonism of the nicotinic acetylcholine receptor and bupropion achieves it by increasing the duration of action of dopamine by inhibiting its reuptake (Coe et al., 2005; Wilkes, 2008). However, previous studies have shown that the effect of bupropion plateaus shortly into treatment and quit rates of bupropion from week 4 to 12. Additionally, bupropion is extensively metabolized by the highly polymorphic CYP2B6 enzyme. It’s also possible that the main pharmacological effects of bupropion are mediated by its primary metabolite, hydroxybupropion (Zhu et al., 2012) and thus the efficacy of bupropion is affected by CYP2B6 metabolizer class. Therefore, for slow CYP2B6 metabolizers, optimal levels of this metabolite are achieved later on in treatment and thus takes longer for participants to quit whilst using bupropion (Lee et al., 2007).

Varenicline, on the other hand, has dual effects that contribute to its higher efficacy for smoking cessation. Firstly, varenicline is a partial agonist at the nicotinic acetylcholine receptor and therefore activates the receptor to relieve withdrawal symptoms. Secondly, varenicline has a high affinity for the α4β2 nicotinic acetylcholine receptor and therefore blocks the reinforcing effects of nicotine (Coe et al., 2005). In other words, participants might smoke whilst on varenicline and not receive the reinforcing effects. This may explain why quit rates of varenicline increases more significantly than bupropion towards end of treatment. When using bupropion, the reinforcing effects of nicotine can still be achieved when participants smoke whilst varenicline might help participants quit later on in treatment since reinforcing effects are not achieved. Another theory is that at higher concentrations of varenicline, it acts as an antagonist at the nicotinic acetylcholine receptor due to its high affinity for the receptor. In fact, the affinity of varenicline for the receptor is higher than that of nicotine. Therefore, when people smoke whilst using varenicline, varenicline acts as an antagonist and blocks nicotine binding at the receptor (Fagerstrom & Hughes, 2008). It’s believed varenicline has a wide range of interaction with different nicotinic acetylcholine receptors with various affinities. Even though the receptor implicated in smoking is the α4β2, activation of the other subunits could also contribute to its superior efficacy seen in traditional clinical trials. For example, varenicline has been shown to have a higher affinity for the α4β4 receptor than the α4β2. The α4β4 receptor is believed to maintain
cholinergic function after chronic exposure to nicotine and thus could contribute to the addictive properties of smoking (Arias et al., 2015).

4.1.3.2. Real-World Quit Rates Versus Clinical Trials

Overall, quit rates of our study were comparable to ones found in clinical trials however they were generally lower. As expected, 30 Day Continuous Abstinence and 7 Day PPA were lower in our study at all follow up times than clinical trials involving bupropion and varenicline. A modified Intent to Treat analysis was used since randomized participants had the option to drop out of the study for various reasons and their data would not be included in analysis. The self-reported mITT analysis 30 Day Continuous Abstinence and 7 Day PPA was 16% and 20% for bupropion and 25% vs 30% for varenicline. Compared to clinical trials, these same outcomes were 30-36% for bupropion and 40-50% for varenicline (Gonzales et al., 2006; Jorenby et al., 2006). The reason for this discrepancy is primarily due to inherent differences in designs and settings of clinical trial vs real world. A specific example would be inclusion of weekly behavioral counseling in most clinical trials. However, in the MATCH study, there were weekly motivational emails that mimicked counseling in real-world settings. Lastly, drop-out rates and incompletion rates were higher in real-world settings compared to clinical trials. Survey completion rates were only approximately 60% at end of treatment surveys compared to the 75% that is seen in clinical trials. Thus, these factors contributed to the higher observed quit rates in clinical trials. Additionally, in these clinical trials, modified intention to quit analyses were conducted where participants who had missed a clinic visit but reported abstinence at the next visit were considered abstinent for the entire period (Gonzales et al., 2006). Altogether, our intent to treat analysis was robust and increased the denominator of smokers in quit rate calculations and consequently resulted in lower quit rates compared to clinical trials.

As a result of this discrepancy, complete analyses were conducted at end of treatment for participants who had completed a survey. The observed quit rates were higher in this analysis with 30 Day Continuous Abstinence rates and 7 Day PPA rates of 25% and 30% for bupropion and 40% and 47% for varenicline. These rates were on par with results of clinical trials and indicate that when survey incompletion was excluded as an assumption, our results mimic those of clinical settings. This was an important finding to confirm the feasibility of this medication delivery method since it achieves similar findings to clinical trials. In general, real-world effectiveness of bupropion and varenicline are lower than what has been shown in clinical trials. Even though the MATCH study was designed to evaluate real-world effectiveness of pharmacotherapies, it may not adequate reflect true real-world conditions. For example, in the real-world, pharmacotherapy would not be free of charge, medication assignment would not be random and there would be no behavioural support in conjunction with pharmacotherapies. Thus, even though the trial mimicked real-world settings as much as possible,
there are still differences between real-world effectiveness studies and pharmacotherapy in the real world. These differences should be taken into consideration in future study designs.

4.1.3.3. Predictors of Cessation Outcome at End of Treatment

Other factors were also evaluated as potential predictors of cessation outcomes at end of treatment. Specifically, nicotine dependence, sex, personality traits, and alcohol consumption were explored as predictors. While these factors alone were not significant predictors of cessation outcome; previous studies have identified these variables as playing a role in smoking behaviors and cessation outcomes. Higher FTND score has been significantly associated with poorer abstinence rates (Fagerström, 2012). However, in our study, FTND score was not an independent predictor of cessation outcome even when controlling for medication group. Previous studies have shown that the validity of FTND as a predictor is inconsistent depending on cessation interventions (Baker et al., 2007; Caponnetto & Polosa, 2008). Therefore, our results are consistent with the literature.

Gender and cessation outcomes have been investigated in several previous studies indicating that men are more successful at quitting compared to women (Blake et al., 1989; Caponnetto & Polosa, 2008; Murray & Luepker, 2011; Smith et al., 2016; Wetter et al., 1999). However, in our study gender was not a significant predictor of cessation outcome. There is conflicting data on gender’s role in smoking cessation pharmacotherapy efficacy studies. Previous bupropion efficacy studies identified no evidence of greater efficacy in men (Scharf & Shiffman, 2004). However, in a meta-analysis, varenicline treatment was found to have greater efficacy in women (McKee et al., 2016). This will be further explored in “The Role of Nicotine Metabolism and Treatment Outcomes” section. When using age as a predictor of smoking cessation, previous studies have identified a positive relationship between age and abstinence rates. In other words, younger smokers have lower abstinence rates than older smokers when treated with varenicline or bupropion. This is due to decreases in renal and hepatic function alters the efficacy of pharmacotherapy (Scholz et al., 2016).

Alcohol use at baseline was also explored as a predictor of successful cessation outcome. Although alcohol use was not a significant independent predictor of cessation outcome at end of treatment, participants reporting more drinks per occasion were less likely to quit. This is supported by similar trends in studies involving comorbidities of smoking and alcohol consumption (Grant et al., 2015; McKee et al., 2013). Heavy alcohol consumption has been associated with reduced odds of quitting (Augustson et al., 2008; Dollar, Homish, Kozlowski, & Leonard, 2009; Kahler, Spillane, Metrik, Leventhal, & Monti, 2009) and greater risks of smoking cessation failure in clinical trials (Humfleet (Humfleet, Muñoz, Sees, Reus, & Hall, 1999). This comorbidity is evident because are interactions between alcohol consumption and smoking at electrophysiological, pharmacological, genetic and
neurochemical levels (Gonzales & Crews, 1988; Larsson & Engel, 2004; Löf, Olausson, Stomberg, Taylor, & Söderpalm, 2010). The reinforcing effects of alcohol are thought to be mediated also by the dopamine release in the nucleus accumbens (NA) in the ventral tegmental area (VTA) similar to smoking (Gonzales & Crews, 1988). Thus, alcohol use may produce mesolimbic activation by its effects on the central nACHRs. Thus, treatment of smoking cessation pharmacotherapy targeting this receptor may improve alcohol consumption in addition to its smoking cessation abilities (McKee et al., 2013). This would be useful to include in future pharmacotherapy regimen designs when smokers display this comorbidity.

4.1.3.4. Personality Traits and Cessation Outcome

Personality traits were also explored as a predictor of cessation outcome. Previous studies have concluded that neuroticism and openness to experiences were both associated with higher lifetime smoking history and thus lower cessation success (Zvolensky et al., 2015). Even though in our study, neuroticism was not a significant predictor of cessation, there was a trend observed between higher neuroticism scores and lower cessation success. This can be explained by differences in emotion regulation by smoking behaviors and how individuals cope with negative affect or stress (Kassel, Stroud, & Paronis, 2003). Additionally, this trend suggests that the tendency to experience negative affect could trigger stress, which leads to formative smoking behavior and persistency over a long period of time. In our study, higher consciousness scores was negatively associated with superior cessation scores and was the most predictive personality amongst the five. This is supported by previous studies where lower scores on consciousness are predictive of smoking behaviors (Kubicka, Matejcek, Dytrych, & Roth, 2001; Malouff, Thorsteinsson, & Schutte, 2006). Conversely, participants with higher scores on consciousness are less reluctant to take health risks. Thus, smoking cessation interventions that reinforce consciousness (self-discipline, impulse control etc.) may be useful to increase intervention efficacy (Zvolensky et al., 2015). Lastly, there were gender differences in personality traits that could potentially cessation outcomes. For example, males have been seen to have highest cessation success with low scores on impulsivity whilst in women, schizoid patterns (pattern of social detachment) were significantly predictive of cessation success (Piñeiro, López-Durán, Fernández Del Río, Martínez, & Becoña, 2013). However, participation in this questionnaire was optional and thus limited the power needed to detect a significant effect of personality traits.

4.1.3.5. Long Term Efficacy of Bupropion and Varenicline

When long-term abstinence rates of bupropion and varenicline were explored, quit rates were similar at both 6 months follow up and at 12 months follow up. At 6 months follow-up, self-reported quit rates of bupropion and varenicline were at approximately 13% and 15% respectively. Continuous
abstinence was significantly higher for the varenicline group than those the bupropion group however 7 Day PPA rates were not. As predicted, participants randomized to varenicline had slightly higher quit rates at 6 months treatment than bupropion, mirrored in clinical trials discussed previously in which quit rates were on average 25-30% for varenicline and 20-25% for bupropion (Ebbert et al., 2009; Gonzales et al., 2006; Jorenby et al., 2006).

Quit rates observed in our study were lower than clinical trial findings, reasonably due to loss of follow up and low survey completion rates. When comparing quit rates between EOT and 6 months, the varenicline group had higher relapse rates than the bupropion group. It is also noteworthy that participants randomized to varenicline did not have significantly different 7 Day PPA compared to bupropion. This could suggest that either participants using varenicline were starting to relapse or that participants using bupropion are achieving abstinence by perhaps use of other cessation aids at 6 months follow up. From previous analyses, participants using bupropion used significantly more NRT than varenicline at end of treatment surveys. NRT use could potentially be a contributing factor for the increase in quit at 6 months follow up in the bupropion group. When the OR for varenicline’s effects on 6 months cessation outcome was adjusted for gender only, the effect became insignificant suggesting a role of gender in cessation prediction at 6 months follow up. Quit rates at 6 months follow up were not significantly different for neither medication group however in the varenicline group; the p-value was lower. In fact, female participants randomized to varenicline had higher quit rates than males. Although quit rates were not significantly different between males and females, previously work has suggested that females have inherently lower quit rates than males (McKee et al., 2016; Scharf & Shiffman 2004; Wetter, Smith, Jorenby & Baker, 1999). In our study, varenicline treatment has positive effects on long-term female quit rates similar to findings from a recent meta-analysis of sex differences in varenicline efficacy (McKee et al., 2016).

When 12 months cessation rates were compared between bupropion and varenicline, self-reported quit rates were approximately equal at 12% for both bupropion and varenicline groups. Neither varenicline nor bupropion was a superior predictor of cessation outcome. 30 Day Continuous Abstinence and 7 Day PPA showed almost identical trends between the medication groups. This mirrors previous studies where at end of the year, relapse rates contributed to the equal quit rates seen between the medication groups. Biochemically confirmed quit rates of both medication groups showed the same trends. These findings reflect the major challenge for smoking abstinence; the high rates of relapse after treatment. Many studies indicate that most smokers will relapse to smoking within the first year of attempting to quit (Kenford et al., 1994). Our observed quit rate (12%) supports the claim that even with use of evidence based pharmacotherapy for smoking cessation, long-term success rates are only 13%-35% (Fiore & Jaén, 2008). Thus, quit rates from our study were
comparable to long-term pharmacotherapy efficacy studies illustrating the need for improvement of long-term quit maintenance even with use of pharmacotherapy.

4.1.3.6. The Reliability of Self-Reported Abstinence Versus Biochemically Confirmed Abstinence

The reliability of self-reported smoking abstinence measure was also compared to cotinine confirmed abstinence measure at mid-treatment. Although self-reported abstinence measures are widely used in clinical settings, biochemically confirmed abstinence is normally conducted in traditional clinical trials either using cotinine or carbon monoxide. When self-reported abstinence is used, there is an assumption that non-responders or incomplete surveys are non-quits. Self-reported abstinence is also subject to reporter bias and recall bias, which could affect treatment outcomes. However, previous studies have identified self-reported abstinence as a reliable measure of true abstinence by comparing self-reported rates and cotinine confirmed abstinence rates in different populations (Barrueco et al., 2005; Gerritsen et al., 2015). As expected, in our study, both varenicline and bupropion users over-reported abstinence. However, participants in the varenicline group over-reported by more than 10% compared to the bupropion, which only over-reported by a few percent. A potential reason for this discrepancy is participants using varenicline are achieving abstinence sooner than bupropion and thus are more motivated to complete surveys. Nonetheless, cotinine confirmed abstinence rates at 6 months and 12 months follow up showed the same trends as self-reported abstinence data suggesting the over-reporting effect might be consistent throughout the study and affects both medication groups equally. However, it’s worthy to note that one study suggests that under-reporters of abstinence have greater craving and higher cotinine levels but this was in relation to smokeless tobacco (Jain et al., 2015). Cotinine confirmed abstinence is considered the gold standard for evaluation of clinical outcomes (Benowitz 2002). However, regardless of abstinence measure, the trends for both self-reported and cotinine confirmed abstinence are comparable and support each other. Given these findings, biochemically confirmed abstinence may not always be necessarily used over self-reported abstinence, since biochemical tests are expensive and troublesome in clinical settings.

4.1.3.7. Bupropion and Varenicline Combinational Treatment

In conclusion, short-term abstinence rates were higher for participants randomized to varenicline than participants randomized to bupropion, however long-term rates were approximately the same for both medication groups. This supports the superior efficacy of varenicline, the partial agonist, for smoking cessation. The trends observed in the MATCH study confirm clinical trial findings supporting the use varenicline as the first-line pharmacotherapy for smoking cessation. However, long-term cessation
rates remain relatively low and suggest that regardless of medication assignment, relapse is still a major barrier for treatment. Numerous studies have begun new regimens of combination pharmacotherapy to improve these rates. For example, combination treatment of varenicline and bupropion has been explored in a clinical trial where combination treatment was significantly more efficacious than monotherapy for smokers that have higher dependence and low response to initial nicotine replacement therapy (Rose & Behm, 2014). Another study confirmed these findings where combination varenicline and bupropion treatment significantly improved short-term abstinence but not long-term abstinence (Ebbert et al., 2014). In both clinical trials, the combinational treatment was well tolerated and there were no contraindications for use of both medications. Lastly, long-term cessation outcomes (measured at 6 months post-treatment) were higher with combinational treatment in two clinical trials than monotherapy with quit rates ranging from 25% to 50% (Rose & Behm, 2014; Ebbert et al., 2009). A systematic review published recently investigated the efficacy of combinational bupropion and varenicline therapy compared to varenicline monotherapy where EOT abstinence of combination therapy had superior quit rates [OR=1.89; 95%CI: 1.07-3.35 and OR=1.49; 95%CI: 1.05-2.12]. At 6 months follow up, combination therapy had significantly higher quit rates in one clinical trial [OR=1.52; 95%CI: 1.04-2.22]. Additionally, combination bupropion and varenicline treatment were well-tolerated in these clinical trials and side effects that occurred were the common ones normally experienced with monotherapy (Vogeler, McClain & Evoy, 2016). Thus, even though varenicline was efficacious for smoking cessation, combination treatment with varenicline and bupropion may have additive effects on improving long-term cessation outcomes.

4.1.4. Adverse Effects

Overall, both bupropion and varenicline were well-tolerated and there were only a few drop-outs with no serious adverse events reported. The main side effects experienced with bupropion use were dry mouth, trouble sleeping and fatigue. Side effects of bupropion may be due its dual actions on dopamine and serotonin inhibition (Stahl et al., 2004; Warner & Shoaib, 2005; Wilkes, 2008). On the other hand, the main side effects experienced by participants using varenicline were vivid dreams, fatigue and nausea. Unlike bupropion, side effects of varenicline may be as a result of its actions on pathways not directly involved in addiction. At standard therapeutic doses, varenicline has been shown to activate α4β2, α3β4, α7 nACHR and 5-HT3 receptors. It’s believed that adverse effects of varenicline are mediated through its action on these receptors (Lummis, Thompson, Bencherif, & Lester, 2011). Of particular importance is the action of varenicline on the 5-HT3 receptor. It is believed that nausea, the most common adverse effect of varenicline use, results from varenicline’s high affinity for the 5-HT3 receptor, which regulates gut motility and the emesis reflex (Machu 2011; Thompson & Lummis 2006). Varenicline is also a full agonist of the α7ACHR receptor, which has been shown to be associated with increased risk of cardiovascular events (Koga et al., 2014).
It is important to distinguish between side effects of medication use and withdrawal symptoms experienced during a quit attempt since they can manifest themselves in similar ways (Jiménez-Ruiz et al., 2009). Nevertheless, side effects experienced by the bupropion group in our study were comparable to what has been reported in other clinical trials. Specifically, dry mouth and insomnia are consistently associated with bupropion use (Boshier et al., 2003; Johnston et al., 2001; West, 2003; Wilkes, 2008). Similarly, for the varenicline group, nausea and having vivid dreams are frequently reported in the literature (Garrison & Dugan, 2009; Lam & Patel, 2007). However, the rates of side effects experienced in our study were higher than what is reported for both bupropion and varenicline use. This could be explained by our method of data collection. Participants were asked to respond with a "yes or no" in response to experiencing any of the listed side effects. This could potentially prime their recall abilities. This could also explain the high rates of fatigue reported which is less commonly in the literature for varenicline use. Since side effects were reported only after commencement of therapy, it’s hard to determine if any of these effects were already present at baseline and thus no comparisons can be made in the treatment period. Additionally, the severity of the side effects could not be quantified on the survey. However, participants were able to email study personnel if any serious adverse events were experienced. Since no serious events occurred, it’s assumed that all the side effects experienced were tolerable.

Lastly, side effects were compared between the medication groups at each follow up time. Overall, participants randomized to varenicline experienced more adverse events than bupropion. Even though varenicline has higher efficacy than bupropion for smoking cessation, participants who cannot tolerate the side effects should reconsider taking varenicline. Previously, one study analyzed the FDA’s Adverse Event Reporting System (AERS) database found that varenicline results in higher rate of serious adverse events compared to bupropion (Moore et al., 2011). However, recent studies regarding the neuropsychiatric safety of varenicline and bupropion suggest that there were no significant difference in incidences of neuropsychiatric side effects between varenicline and bupropion use in a group of smokers with psychiatric disorders. In this study, varenicline was still being more efficacious than bupropion and NRT for smoking cessation (Anthenelli et al., 2016). Thus, overall, varenicline and bupropion use was well-tolerated and did not result in any serious side effects.

4.1.5. Medication Compliance

4.1.5.1. Self-Reported Medication Compliance and Cessation Outcome

Only 56% of participants reported finishing the medication (52% in the bupropion group and 60% in the varenicline group) at the 12 week follow up survey. However, there was also 20% of participants still using the medication (18% in the bupropion group and 22% in the varenicline group). Participants
that were still using medication may have delayed commencement of medication or paused treatment and then restarted at a later date. However, with 19% of participants discontinuing medication, medication compliance was low, despite being free of charge. The low compliance rate seen in our study is in line with previous studies using cessation pharmacotherapy (Barrueco et al., 2005; Kohlenberg et al., 2004; Liberman et al., 2013) and lower than what has been observed in clinical trials involving bupropion and varenicline (D. Gonzales et al., 2006; Jorenby et al., 2006). In a pooled analysis of the two clinical trials of varenicline versus bupropion, 70% of participants were adherent to varenicline and 65% were adherent to bupropion (Hays et al., 2010). This was comparable to compliance rates observed in our study suggesting that internet-based clinical trials have similar compliance to traditional RCTs with in-person visits. This was a promising finding considering there were no clinic visits and compliance rates were still comparable to traditional RCTs. Although clinical trials have high internal validity, it is important to conduct real-world population-based studies that give insight on use and effectiveness of these medications under more realistic conditions such as lower medication compliance.

Lastly, this reflects that even though more participants had experienced side effects whilst using varenicline, this did not affect their compliance. Since the compliance rates were not significantly different between the two medications, the superior efficacy of varenicline compared to bupropion cannot be attributed to differences in treatment adherence. Amongst participants that had discontinued medication use, the most common reported reasons for discontinuation were: achieving abstinence and having relapsed. Since complete case analysis was used for these analyses, it is unclear if this is reflective of the entire population and other smokers. Perhaps participants that had not reported a reason for discontinuation had other motives or found other aids to help them in their cessation attempts. Furthermore, discontinuation rates were compared between bupropion and varenicline and there were no significant differences between the groups.

The relationship between medication compliance and complete case analysis of treatment outcomes at end of treatment were assessed. For both medications, increased compliance was significantly associated with increased end of treatment abstinence (measured by both continuous abstinence and 7 Day Point Abstinence). The compliance classes were first classified by finished and still using. The 30 Day Continuous Abstinence rates for those who finished medication were higher for varenicline than for bupropion. Accordingly, quit rates were lower for participants who were still using medication in both medication groups. These trends were also reflected in 7 Day PPA rates but they were higher for both medication groups. Overall, there was a significant linear trend observed where compliance was associated with both continuous abstinence and 7 Day Point abstinence. Similar analyses were conducted in a study where adherence of bupropion and varenicline were compared in clinical trial
settings (Hays et al., 2010). Comparable results were found where medication compliance was correlated with treatment outcomes. In clinical trials, continuous abstinence rates reported at end of treatment were 43.1% for bupropion and 59.4% for varenicline in those who were compliant to medication regimen. Meanwhile, in those who were not compliant, the continuous abstinence rates were 29.8% for bupropion and 44.2% for varenicline (Hays et al., 2010). In another retrospective cohort study, looking at varenicline treatment and adherence in two RCTs, similar trends were observed wherein quit rates of participants fully compliant to varenicline was 50.7% compared to only about 30% in those who were non-adherent or partially adherent (Liberman et al., 2013). This compliance rate was comparable to our study and thus, real-life efficacies of bupropion and varenicline are not limited by real-world compliance.

Additionally, compliance at all follow-ups points was evaluated. There were no significant differences in quit rates at EOT between various medication discontinuation times. This indicates that discontinuing treatment at any point results in low quit success. Thus, compliance to the full 12 week treatment is an important determinant of smoking abstinence. It is also important to note that the relationship between compliance and motivation to quit could potentially be a reverse causation. In other words, instead of higher compliance resulting in higher motivation to quit due to the effectiveness of the medication, it could be that higher motivation causes higher compliance. In the first scenario, participants who discontinued medication at any point during treatment could have lost their motivation to quit, whereas those who were compliant had higher motivations to quit. The second scenario is that those who discontinued medication were unable to quit early on and thus lost motivation and stopped using medication, or they stopped using the medication because they quit smoking and felt they no longer needed to take it. Nonetheless, self-reported medication compliance was a significant predictor of quit outcome and future work should focus on ways to improve medication compliance.

4.1.5.2. Biochemically Confirmed Medication Compliance and Cessation Outcome

Biochemically confirmed compliance and treatment outcomes were evaluated for the two medications. There are limited studies on saliva biochemical confirmation of compliance since most clinical trials measured compliance during study visits either by self-report or by measuring plasma levels of each medication (Catz et al., 2011; Cooper et al., 2004; Gonzales et al., 2006; Jorenby et al., 2006; Liberman et al., 2013). Overall, participants using varenicline had dramatically lower biochemically confirmed compliance (70%) compared to bupropion (95%). This originally contradicted self-reported compliance analysis, however, this could due to the method of chemical analysis. Bupropion compliance was measured by measuring total bupropion levels, which was the sum of bupropion concentration, and its three metabolites (E-BUP, OH-BUP and TERT-BUP). Thus, even if there were
very low concentrations of each metabolite, when the sum was created, participants would be considered compliant. The half-lives of bupropion and its three metabolites (OH-BUP, E-BUP and TERT-BUP) are: 21 hours, 20 hours, 37 hours and 33 hours respectively (Jefferson, Pradko & Muir 2005). Since bupropion is extensively metabolized, presence of the metabolites is the major determinant of compliance. The half-lives of E-BUP and TERT-BUP are significantly longer than both bupropion and varenicline, thus it could contribute to the higher compliance observed for bupropion use.

The determination of compliance for varenicline was less flexible. Since varenicline is not metabolized in the body, any detectable amounts of varenicline were a good indication if participants were compliant. Varenicline also has a half-life (24 hours) that is comparable to bupropion but not compared to all the metabolites, potentially contributing to the lower compliance observed. Thus, the difference in compliance between the medications could be an inherent difference in the way their compliance was detected. Another explanation of the observed lower varenicline compliance is that participants that were non-adherent to varenicline at mid-treatment, over 70% had already self-reported abstinence at this time point. This is an indication that participants who had already achieved abstinence stopped using medication. This corresponds to the earlier quit outcomes associated with varenicline use compared to bupropion. Further analysis should focus on new standards for defining medication compliance when using saliva drug concentrations.

Lastly, biochemically confirmed compliance at mid-treatment was associated with end of treatment outcomes. Participants adherent to varenicline at mid-treatment had modestly higher continuous abstinence at end of treatment than participants adherent to bupropion. The most surprising finding was that participants non-compliant to varenicline had higher continuous abstinence than compliant participants. This can be explained by the previous finding that over 70% of non-compliant varenicline participants had already quit by mid-treatment thus the end of treatment abstinence rates are not a reflection of the predictive abilities of compliance on treatment outcomes, but rather, a reflection on early onset efficacy of varenicline. Almost all of the participants that had self-reported abstinence at mid-treatment maintained their abstinence at end of treatment thus contributing to the high quit rate observed.

This is an important finding, which could potentially affect optimal varenicline treatment duration in future regimens. Compliance to the full 12 weeks of varenicline is very low; many do not refill the rest of their prescription following the 4 week starter pack (Pfizer Canada, personal communication). From the above results, it is plausible that people do not return because they have achieved abstinence within the 4 week treatment period. This suggests that many participants are able to quit without the
entire 12 weeks of treatment. If 4 weeks of treatment could achieve similar effects as the full course, it would be a plausible solution to decrease cost of pharmacotherapy in real-world settings. This is especially relevant since most smokers do not use pharmacotherapy due to high cost. Clinical trials involving varenicline have consistently explored the effects of 12 week or longer duration of varenicline treatment (Chengappa et al., 2014; Cinciripini et al., 2013; Ebbert et al., 2015; Koegelenberg et al., 2014; Lerman et al., 2015; Rigotti et al., 2010; Stein et al., 2013) but rarely shorter treatment durations (Gray et al., 2015; Mocking et al., 2014).

4.1.6. The Role of Nicotine Metabolism on Smoking Cessation

4.1.6.1. The Correlations of NMR and Baseline Characteristics

The relationships between nicotine metabolism, as measured by the Nicotine Metabolism Ratio (NMR) and nicotine dependence, gender and cigarettes consumption per day (CPD) were explored. Nicotine metabolism was significantly positively correlated with nicotine dependence, as measured by FTND, cigarettes per day and age of first cigarette. Nicotine metabolism between each gender was evaluated. Females in our sample had significantly higher NMR than males at baseline. This finding was in line with previous literature where females have higher rates of nicotine metabolism across race (Benowitz, Swan, Jacob, Lessov-Schlaggar, & Tyndale, 2006; Kandel, Hu, Griesler, & Schaffran, 2007; Schnoll et al., 2009). The difference in nicotine metabolism indicates that females could be more dependent to nicotine compared to males. Men and women seem to smoke for different reasons. Women are believed to be more sensitive to effects of nicotine and smoke for the physical experience of cigarettes (Silverstein, Feld, & Kozlowski, 1980).

NMR was significantly correlated with nicotine dependence, as measured by the FTND. This relationship has been seen in some previous literature (Schnoll et al., 2014) where FTND and NMR seems to be related however this effect was more likely due to effects of cigarette consumption. However, it is worthy to note many other studies have failed to show this relationship (Benowitz et al., 2003; Strasser et al., 2011). The reason why these previous studies have not identified this relationship could be due to the fact that dependence is influenced by multiple genetic polymorphisms. While CYP2A6 is the main functional enzyme to metabolize nicotine, nicotine metabolism is also influenced by CYP2B6 and CYP2E1 polymorphisms (Hukkanen, Jacob & Benowitz, 2005), which were not accounted for by previous studies. Polymorphisms of the nicotine acetylcholine receptor gene (CHRN) has also been reported to affect cigarette consumption, nicotine dependence and smoking cessation outcomes (Cannon et al., 2014; Saccone et al., 2010; Wang et al., 2016). Other factors that could influence nicotine metabolism in these studies include use of oral
contraception, demographics and physiological factors (DiFranza et al, 2013; Mwenifumbo & Tyndale, 2007).

However, given the inconsistencies in the literature regarding this topic, there are still positive findings, similar to our study. The trends observed indicate that smokers with higher nicotine metabolism are more dependent on nicotine, which correspond to the basis of CYP2A6 polymorphisms and their effects on smoking behaviors (Chenoweth et al., 2014; Schnoll et al., 2014). We replicated the findings of this study within our sample suggesting that increased nicotine metabolism leads to higher dependence on nicotine, as seen by people smoking more cigarettes per day than their slow metabolizer counterparts. NMR was also significantly correlated with age. Increasing age was significantly associated with higher NMR values. As mentioned previously, average age of NM was significantly higher than average age of SM indicating that this trend is present for both medication groups.

4.1.6.2. The Role of NMR and Treatment Outcomes

4.1.6.2.1. NMR Predicting Quit Outcomes

The role of NMR in quit success was explored at end of treatment. Firstly, quit rates between the metabolizer groups were compared at end of treatment. Overall, slow metabolizers had higher quit rates (32%) compared to normal metabolizers (26%) however this was not significant. When binary regression analyses were conducted, NMR was not a significant predictor of quit outcome at EOT for both 30-Day Continuous Abstinence and 7 Day PPA. However, previous studies have found that NMR was a significant predictor of quit outcome with NRT. Specifically, normal metabolizers had lower quit rates than slow metabolizers using the same nicotine patch dose (Lerman et al., 2006). Normal metabolizers have higher dependence and low quit rates and therefore may benefit more from non-nicotinic pharmacotherapies compared to their slow metabolizer counterparts (Allenby et al., 2016; Chenoweth et al., 2016). Another study found the same trend with NMR as a significant predictor of quit outcome when using transdermal nicotine patches (Kaufmann et al., 2015). This was expected since nicotine metabolism variations were more likely to affect nicotine-based pharmacotherapy efficacy. The authors concluded that NMR might be useful in predicting early efficacy in screening approaches for compounds under development. Screening approaches could include NMR-based randomization to treatment (Chenoweth et al., 2016).

Recent studies have reported that NMR predicts early onset of withdrawal symptoms in absence of smoking. Specifically, normal metabolizers experience early and more severe nicotine withdrawal symptoms after they quit smoking (Hendricks et al., 2014). An explanation for this relationship is that
plasma nicotine is depleted faster in normal/fast metabolizers after smoking cessation. This then leads to a decrease in the nAChR activity and duration in the brain. Additionally, a functional Magnetic Resonance Imaging (fMRI) study has reported that slow metabolizers have decreased cue-reactivity to smoking-related cues. This could be explained by more fluctuations in nicotine levels in normal metabolizers and thus, they experience bursts firing of dopamine neurons that mediate the conditioning process of smoking cues in NM. This effect is not present in slow metabolizers due to their nicotine levels remains stable over time (Tang et al., 2012). In our sample, even though not significant, the odd ratio obtained indicated that normal metabolizers had lower likelihood of achieving abstinence compared to slow metabolizers.

4.1.6.2.2. Nicotine Metabolism and Treatment Efficacy

Generally, participants randomized to varenicline had higher cessation outcomes than participants randomized to bupropion. Within slow metabolizers, the varenicline group had significantly higher quit rates than bupropion at EOT. Previous studies have focused on comparing varenicline vs NRT or bupropion vs NRT between different metabolizer groups but never directly comparing bupropion vs varenicline. Studies have shown that varenicline has significantly higher quit rates (38.5%) compared to placebo or NRT (22.5%) in normal metabolizers at end of treatment (Allenby et al., 2016; Lerman et al., 2015). When medication by NMR effects were analyzed, varenicline was more beneficial for slow metabolizers whilst bupropion treatment benefited normal metabolizers. This finding was contrary to previous literature, which demonstrated superior treatment efficacy of varenicline treatment for normal metabolizers (Allenby et al., 2016; M; Lerman et al., 2015). Lerman et al showed that varenicline was more efficacious than patches for normal metabolizers with an ORR of 1.89; 95%CI: 1.01-4.22, p=0.05). A potential reason why our results did not reflect these trends is the difference in treatment duration. In Lerman et al., 2015, participants were randomized to 11 weeks of nicotine patch, varenicline or placebo whereas our study employed the full 12 weeks of pharmacotherapy. A previous clinical trial had showed that SMs achieve significant benefit from extended NRT therapy with 6 months quit rates up to 50% (Lerman et al., 2010). While a one week difference in treatment period is not long, it is possible that SM benefit more from extended pharmacotherapy, which already has higher efficacy than NRT. NMR metabolizer groups in our study also weren’t randomized for each medication. In Lerman et al., 2015, participants were randomized to medication after assignment of NMR class. However, in our study, representation was not equal especially within the SM group where there were significantly more varenicline participants. Our study used self-reported quit measures at end of treatment whereas clinical trials used biochemically confirmed quit measures and thus our results may not reflect similar trends. Lastly, it is well known that NMs smoke more per day
and conditioned smoking responses are potentially stronger in NMs. In other words, when exposed to smoking cues, there are higher responses in the brain’s dopamine reward circuitry compared to SMs (Tang et al., 2012). It is possible that varenicline and bupropion affect these systems differently due to their inherent differences in mechanism of actions.

In our study, normal metabolizers using bupropion benefited more than slow metabolizers, a finding that is consistent with previous literature comparing bupropion efficacy between metabolizer groups (Patterson et al., 2008). In this study, SM using bupropion had approximately the same quit rate at placebo (32%) while Fast metabolizers using bupropion had significantly higher quit rates than placebo (34% vs 10%). These quit rates support our finding of bupropion benefitting normal metabolizers resulting in a small increase in quit rates at EOT. Another paper found that bupropion treatment decreased relapse rates in fast metabolizers however this effect was due to CYP2B6 metabolism differences and its effect on bupropion efficacy. In other words, nicotine metabolism differences predict smoking abstinence but does not affect bupropion efficacy. Bupropion is extensively metabolized by CYP2B6 and thus, the effect of bupropion on relapse likelihood is unlikely affected by nicotine metabolism estimated from the CYP2A6 genotype (Chen et al., 2015). Thus the higher quit rates observed in fast metabolizers reflect smokers who benefit from pharmacotherapy such as bupropion and NRT. This was reflected in our own findings where bupropion’s quit rates were only slightly higher in the NM group compared to SM. Overall, faster metabolizers of nicotine benefited from pharmacotherapy and quit rates were slightly improved compared to slow metabolizers. Apart from using CYP2A6 genotype to personalize smoking cessation treatment, when prescribing bupropion, CYP2B6 variations should be considered. It has been shown previously that CYP2B6 variations in smokers directly affect bupropion’s efficacy for smoking cessation either through the parent drug or its major metabolites (Quaak et al., 2009; Zhu et al., 2012).

Bupropion has been shown to have higher quit rates than placebo or NRT at end of treatment for normal/fast metabolizers at end of treatment (Patterson et al., 2008). Pharmacotherapy, in general, is thought to benefit normal metabolizers more than slow metabolizers due to their inherent lower quit rates. Even though no studies have explored the direct comparison between bupropion and varenicline for metabolizer groups, it can be inferred from previous studies that varenicline will be superior to bupropion for both metabolizer groups. In previous studies, the superior efficacy of varenicline and bupropion was most pronounced in normal metabolizers. However, in our sample, varenicline’s superior efficacy was more pronounced in slow metabolizers contributing to the overall higher quit rates of slow metabolizers.
4.2 Strengths of Study

The MATCH study has a number of strengths, making it scientifically valuable. Firstly, although there are studies in the literature looking at real-world effectiveness of bupropion and varenicline, most of them are non-randomized longitudinal and observational studies looking at data available from clinics. The MATCH study is the first patient-driven study looking at real-world use and efficacies of bupropion and varenicline for smoking cessation. It’s also the first real-world study with head-to-head comparisons of bupropion and varenicline. This is vital because clinical findings may not reflect real-world findings. In other words, clinical findings cannot be extrapolated to the general population of smokers in the real world (Jorenby et al., 2006; Nallamothu, Hayward, & Bates, 2008). Our study also benefits from the randomization design. The successful randomization of participants to each medication group ensures that our results are not affected by bias from medication preference (either from participants themselves or prescribers). Also, randomization assures that the differences observed in baseline demographics between the medication groups were minimal and could not confound treatment outcomes (Suresh, 2011). This also ensures the medication groups were unbiased and easily comparable at various follow up times.

Another advantage of our study is the large sample size (~1000) and thus there was enough power to detect if differences were present between medication groups in various analyses. Post-hoc analyses showed that we were 99% powered to detect changes and thus if any differences were present, they were most likely not due to random error thus decreasing likelihood of Type II errors. The additional benefit of having higher power for analyses is in many regression models; other factors could be controlled for without significantly decreasing the power. Altogether, the high power of our study increases the validity and confidence of our main findings. A methodological advantage of our study is inclusion of a cost-effective internet-based approach for mass distribution of prescription pharmacotherapy. This model did not require any in-person visits, was easy to adhere to, and allowed for more smokers in remote areas of Ontario to participate in the study. The pharmacotherapy offered was appealing to most smokers and since they were free of charge, motivation to participate in the study was high. Another appealing factor of this model is the low commitment design. Participants could enroll and visit their doctors at their own pace and plan their targeted quit dates according to their lifestyle. There were no mandatory visits and compensation was provided for submission of a saliva sample at various timepoints, which only took a few minutes. In fact, it has been reported that internet-based smoking interventions are convenient, cost-effective and offer an option of anonymity since there were no in-person visits (Civljak et al., 2013).

Another important advantage of our study is incorporation of the Internet thus removing both geographic and healthcare accessibility barriers. In this age of continuous technological advances,
numerous recent studies are designed to use technology as a medium for increased treatment efficacies and development of new interventions online (Cambon et al., 2017; Hoeppner, Hoeppner, & Abroms, 2017; Iacoviello et al., 2017; McIntosh et al., 2017; Reinwand, Crutzen, Kienhuis, Talhout, & de Vries, 2017). Our model of mass pharmacotherapy distribution allows participants from both rural and urban areas of Ontario to have access to affordable pharmacotherapy. In fact, in our study, approximately 10% of participants were from Northern Ontario, which is sparsely populated with less access to cessation resources. One of the major limitations of pharmacotherapy is low accessibility to the general population. When our model is employed, it could potentially improve accessibility for small towns and remote areas. Overall, 34% of participants were from Southern Ontario, which has the highest population density and reflects the efficacy of our model for reaching smokers who are searching for medication aids. Additionally, the participation rates of surveys and medication reception were high given the real-world nature and that there were no incentives for completion of surveys. More than 70% of participants who were eligible returned a baseline saliva sample for NMR analysis. This is comparable to another study looking at feasibility of saliva sample collection by mail, which had a return rate of 80% (Etter et al., 2005). Follow up survey completion rates were satisfactory at end of treatment (60%), which was lower than clinical trials, which had approximately 70% response rate (D. Gonzales et al., 2006). Our study response rate was relatively high considering the surveys were administered online via email and were only available for 2 weeks.

Lastly, the study collects high volumes of useful information at various follow up times to gain a more comprehensive understanding of factors that could affect smoking behaviors and treatment efficacies. Addiction is a multifaceted disorder and thus there’s a greater need to understand how numerous factors could work in combination to affect smoking behaviors and cessation outcomes. By looking at larger amounts of data that include personality, socioeconomic status and etc., a more comprehensive picture of smoking can be seen and new areas of interest can be identified for future research.

4.3 Limitations of the Study

The MATCH Study has a number of limitations. The first limitation is that the study sample is not representative of all smoking populations since it was localized to Ontario residents who had a working email and a doctor, and many smokers many not meet these requirements. However, studies have demonstrated that an online study does not necessarily lead to sample representation bias (Pew, 2014). Additionally, reports suggest that Internet use across Ontario is high; approximately 75% of smokers having access in 2007 (Cunningham, 2008). Internet use has since been expected to increase. Additionally, the age range of the MATCH study was from 19 to 70 years old. This indicates
that the outreach of the MATCH study was compatible for smokers of all ages regardless of the technology aspect.

Another limitation of this study is that about 50% of eligible participants did not follow through with steps after enrollment to visit a doctor and receive medication from MATCH. Specifically, they did not visit a physician within the 5-week window to sign the prescription. The most common reason for participants not visiting a physician was that they did not have one. This was an unforeseen limitation. Smokers who do not have a family physician could visit a walk-in clinic to sign a prescription however, most of them did not. This shows that smokers may not be motivated enough to find a physician and most of them do not have a regular doctor to visit to perform medical checkups. Additionally, in 2013, Statistics Canada reported that 8.8% of Ontario residents did not have a family doctor. This rate was higher in those aged 22-44 years older (CAGov, 2014). This suggests that the shortage of doctors could be a reason why given the efficacy of pharmacotherapies, many smokers do not use them effectively.

Another limitation of the MATCH study is that while participants were randomized at baseline, participants were not randomized according to their NMR metabolizer class. There were significantly more participants randomized to varenicline in the Slow Metabolizer group. This could reflect that although randomization was successful and no baseline characteristics were significantly different, NMR classification was biased. An alternative approach would be to randomize participants to medication assignment balanced between NMR metabolizer groups similar to previous studies (Patterson et al., 2008). However, the effect of NMR on medication efficacy was not the primary aim of this study. The purpose of assessing NMR as a secondary aim was to attempt to confirm previous findings. Another major limitation to the study is the low survey response rate, especially at 6 months and 12 months follow up. Specifically, the end of treatment survey response rate was 60%. Intent to treat (mITT) analysis was used to minimize the effects of these missing data using the assumption that non-responders were non-quit (West, Hajek, Stead, & Stapleton, 2005). However, it should be noted that there are limitations when using mITT analysis. Specifically, it is an overly-conservative assumption that those who do not respond to an e-mailed link to a survey are still smoking and it is perhaps a statistically unsound assumption because there is zero variance. A more statistically sound approach may be to use multiple imputation to estimate the values of missing data points. Nonetheless, studies suggest that if the objective is to address effectiveness of treatments in the real-world, the intention to treat approach should be employed as the main analysis (Armijo-Olivo et al., 2009). Additionally, this method is employed to maintain the randomization success at baseline throughout the study.
Another limitation is the quality of the saliva samples and the low return rate. The return rate of saliva samples was approximately 50% for 6 month and 12 month samples. A number of reasons could be responsible for the low return rate. The most common would be inaccurate address input on the online portal or participants having moved but not alerting study personnel. Another possibility is that participants do not feel motivated by the incentive to complete the saliva sample. There were also 59 dry samples that could not be included in analyses at baseline and 14 dry samples at 4 weeks follow up. These dry samples could not be used for quantifiable data since their true concentrations were diluted. The main reason for this is since some participants live in remote areas, the delivery process was prolonged and samples thus dried before proper storage. Another possibility is that participants did not follow the SOPs for proper completion of the saliva sample and thus did not provide enough saliva for proper analysis.

Although biochemical medication compliance was assessed in the MATCH study, and when compared to self-reported medication compliance, they were not biased. This is because participants were mailed the 12 week supply of medication at once and medication adherence did not affect participation in the study in any way. Additionally, previous studies have demonstrated that self-reported measures of compliance in forms of questionnaires are comparable to non self-reported measures of medication compliance (Garber, Nau, Erickson, Aikens, & Lawrence, 2004). However, there are limitations with respect to biochemical confirmed adherence strategies. Specifically, a past detection point was used for compliance measures. The limit of detection of the HLPC for analysis was 1ng/ml. Any concentrations below this level were considered non-compliant. This assumption could be inaccurate since participants could be incorrectly labeled as non-compliant. In other clinical studies, medication compliance was defined in different ways. For the most part, participants were considered compliant if they’ve used more than 80% of the medication. However, since our study could not evaluate how much medication each participant used, this definition does not apply to us. By using past detection levels of medication, we potentially over-estimated the amount of non-compliant participants, affecting compliance analyses. Additionally, participant’s biochemically confirmed medication compliance measures occurred at mid-treatment and therefore this is not an indication if participants remained compliant for the duration of the 12 week treatment period. Compliance at mid-treatment was a good indicator of medication compliance however self-reported medication compliance measures occurred at EOT and therefore when comparing the two compliance measures, their trends reflect different time points.
4.4 Future Directions

Even though the MATCH study enrollment period has ended, there are still many exciting new directions from the study and follow up data to be collected. Firstly, the Genetic Samples that were collected at baseline will be analyzed to explore genetic factors that can help personalize smoking cessation regimens accounting for individual genetic differences. Genetic predispositions to nicotine dependence can be used to determine pharmacotherapy efficacy for a sub-population. The genetic factors that are identifiable can also be used to personalize pharmacotherapy. An important area for investigation is replication of this study design for other medications for other disorders. The main goal would be to test the feasibility of our model of mass-distribution using the Internet as a medium for treatment of other disorders. Ideally, if this model works effectively for other diseases and pharmacotherapies, use of this model could increase accessibility and decrease costs for treatment of a variety of diseases. This model would be especially useful for geographically isolated or rural areas where disorder prevalence is high but treatments are less readily available. Although another argument could be made that use of this model could limit participation from certain age groups. For example, throughout the study many participants emailed claiming they had no access to the Internet and did not have a working email. Most of these participants were older and had disabilities that prevented them from visiting a doctor. Taking these factors into account, our model would not be useful for populations of older participants who aren’t as tech-savvy and especially for low socioeconomic status demographics where Internet access is not attainable. Further considerations should be taken into account when designing pharmacotherapy delivery models especially for the targeted population.

The NMR data obtained from our study were heterogeneous when compared to reports in the literature. Specifically, slow metabolizers benefited more from varenicline treatment, contrary to the literature. However, it is worthy to note that the field of nicotine metabolism with use of the Nicotine Metabolite Ratio is still a relatively new field of study and thus there aren’t many studies to confirm our results with. The randomization method used for the MATCH study ensures equally distributed participants between each medication group however not within each metabolizer class. Thus, this resulted in the observed significantly more participants in the slow metabolizer group using varenicline compared to the normal metabolizers. In future study designs, eligible participants can be randomized based on their baseline NMR value into each medication group. This way, the relationship between NMR and treatment outcomes can be more clearly identified. Factors at baseline can be associated with quit outcomes for each medication group per metabolizer class. In addition, in potential future designs, participants’ demographics can be used to pre-determine which medication they would be most likely to succeed with. For example, in previous literature, females are more likely to quit when using varenicline and behavioral counseling compared to men and this effect was the most prominent.
for normal metabolizers. Thus, if a female smoker is a normal/fast metabolizer of nicotine, they would most probably benefit the most from varenicline treatment compared to bupropion. Accumulation of multiple factors can help personalize cessation pharmacotherapy, which takes into account numerous factors reflecting the multifaceted nature of nicotine addiction. Another major area to be addressed in the future is low compliance rates of pharmacotherapy. It has been well reported that compliance with pharmacotherapy is low for all pharmacotherapies in addiction studies. The compliance rates are not ideal even in controlled clinical settings and they were even lower in our study. Participants using varenicline had lower compliance than bupropion, however this was most likely due to participants not using medication since they’ve achieved abstinence due to varenicline’s earlier efficacy profile. Overall, compliance rates were lower in real-world settings and many factors could be responsible for this. Future studies should identify new intervention strategies that improve compliance rates by taking these factors into account.

One of the most important improvements to cessation designs should be consideration of long-term quit outcomes. As expected, one year abstinence rates of bupropion and varenicline were relatively low. Sustainable strategies should be employed after successfully quitting when using pharmacotherapies that could help maintain long-term abstinence. For example, behavioral emails were sent during the treatment period of our study, however, if they had been given for the entire year, cessation rates could improve. Additional resources were reported in the treatment period of our study however, it is unclear if participants continued to use these resources after treatment ended. Perhaps participants who had continued to use resources maintained long-term abstinence longer than others. Other interventions could be employed through the online platform to continuously give support to participants after the treatment period.

The major factor limiting the efficacy of this Internet-based model is that only 50% of participants visited a doctor after being deemed eligible. One contributing factor to this effect is the high demand but low supply of doctors in Ontario. The majority of participants that did not receive medication reported not having a family doctor. For some participants, even if they had a family doctor, by the time their doctor had an appointment spot available, the 5 week window had already expired. In future studies, perhaps the window for visiting a doctor can be extended or include more healthcare professionals that could prescribe medication. For example, for our study, only signed prescriptions from physicians are accepted, but selective pharmacists and nurse practitioners can also now prescribe medication independent of physicians. For future studies, instructions can be altered to include these healthcare professionals to increase the likelihood of participants obtaining a signed prescription.
4.5 Conclusion

The aim of our study was to evaluate the real-world use and effectiveness of bupropion and varenicline for smoking cessation. The main finding was that varenicline was more effective than bupropion in the real world for smoking cessation similar to clinical trials at end of treatment. However, quit rates were lower than ones reported in clinical trials illustrating the need to develop more effective and safer pharmacotherapies and combination interventions to increase cessation rates. Medication compliance was low in real-world studies and greatly affected treatment outcomes, more so than use of pharmacotherapy. Strategies should be employed to increase medication adherence to improve current and future pharmacotherapy efficacies. The importance of improving adherence should be the emphasized in future research. Although varenicline and bupropion use dramatically increases the likelihood of achieving abstinence at end of treatment, long-term quit outcomes of both medications are low comparable to clinical trials (D. Gonzales et al., 2006; Jorenby et al., 2006). Thus, due to the low quit rates mentioned even with pharmacotherapy use, there is a need to increase long-term efficacies of available interventions potentially by combination intervention or increased behavioral support after achieving abstinence. Another area of improvement is personalization of medication regimens. Therefore, role of nicotine metabolism ratio and treatment outcomes were explored. Overall, similar to the literature, normal metabolizers had lower quit rates than slow metabolizers. Based on the current findings, it’s suggested that normal metabolizers benefit from bupropion treatment whilst slow metabolizers benefit from varenicline treatment. Future work should validate these findings to implement personalized pharmacological interventions as a promising approach to increase short and long-term efficacies of smoking cessation pharmacotherapies.

Lastly, it is essential that for any pharmacotherapy to make an impact at the population level, it must be affordable and accessible to the general population. Unfortunately, a small percentage of treatment seeking smokers use bupropion or varenicline (Health Canada 2011). The results of this study show that the MATCH study’s innovative design can cross barriers and reach smokers over a broad geographic area across the province, whilst maintaining the efficacies of pharmacotherapies. Therefore, in order to reduce the prevalence of tobacco use and the costs associated with the consequences of smoking on the healthcare system, our strategy is useful for policy makers to consider as part of comprehensive smoking control designs. This is supported by studies that show smokers are more willing to make a quit attempt when treatment is free (Jiménez-Ruiz et al., 2009). In conclusion, it’s essential to improve the effectiveness and use of smoking cessation pharmacotherapies in order to reduce the burden of smoking on our society.
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APPENDICES

Appendix I: View of MATCH study Website

Welcome to the MATCH Study

Thank you for your interest in the MATCH Study.

Unfortunately, enrollment period for the study has ended. We apologize for any inconvenience this may have caused.

Good luck with your quit attempt!

Medication Aids for Tobacco Cessation and Health

If you are a current smoker and would like to quit, please continue reading to learn how the MATCH Study can help you with your journey to becoming smoke-free.

Smoking is associated with a number of serious health issues. Quitting smoking can be the single most beneficial thing smokers can do to improve their health. Well-validated research studies have consistently shown that using smoking cessation medications doubles the chances of successfully quitting.

MATCH is an internet-based research study being conducted by the scientists at the Nicotine Dependence Clinic at the Centre for Addiction and Mental Health (CAMH). The purpose of this research study is to assess the real-world effectiveness of approved prescription-only smoking cessation medications, bupropion and varenicline. This study will provide 12 weeks of medication at no cost to help participants quit smoking. MATCH is open to residents of Ontario, 19 years or older, who wish to quit smoking within 30 days of receiving the assigned study medication, and meet the study's eligibility criteria.

For more detailed information about the study click here.

REB Protocol Number # 200/2012
Appendix II: Study Information Form

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 bupropion are 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 e-mail]. 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.

Appendix III: Consent Form at Baseline

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

Please click "Begin Questionnaire" button to submit your Consent Form and proceed to the Study Questionnaire. The Study Questionnaire will determine your eligibility to participate in the study. It will take approximately 10 minutes to complete. If you are eligible to participate, you will receive an email with a copy of the Study Information and Consent Form. Please print this consent form for your records.
Appendix IV: MATCH study website enrollment link

Study Information and Enrollment

Study Enrollment:
In order to enroll, you will need to read the Study Information and Consent Form. If you agree to participate in the study, you will first complete a short questionnaire online to determine your eligibility. Then, you will be e-mailed two documents, a Letter to the Doctor and a Standard Script that you will need to take to your doctor, during 5 weeks following the enrollment date. Your doctor will need to sign the Standard Script and fax it to our research pharmacy. Once the fax is received by the pharmacy, they will call you for a brief counseling. Then, they will fill the prescription and mail the medication to you free of charge.

You will also get a saliva collection kit in mail for confirmation of your current smoking status. You will receive a $10 gift card once your saliva sample is received by us.

Additional Support:
You will receive weekly motivational emails for 12 weeks. These e-mails will include tips on quitting smoking and remaining smoke-free.

Follow-Ups:
You will be contacted by email approximately 10, 14, and 18 weeks after enrolling 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 at these times. You will be compensated with $25 gift cards for each additional saliva sample we request, once we receive them in mail.

Genetics Sub-study:
The purpose of the sub-study is to understand how genetic and personality characteristics alter an individual’s capacity to respond to smoking cessation medications. Participation in the genetics component of the MATCH Study is optional.

Appendix V: On Screen Message for eligibility

On-screen message if individual is eligible:

Congratulations! You have successfully enrolled in the MATCH Study and are eligible to participate at this time. An email will be sent to the email address you provided with further information and instructions on what to do next. If you do not receive an email in the next 24 hours, please contact us by sending an email to match.study@camh.ca.

On-screen message if individual is ineligible:

Unfortunately, you do not meet one or more of the study eligibility criteria. Therefore, it may not be appropriate and/or safe for you to use bupropion or varenicline at this time. Please visit the smoking cessation website listed below for more information on how you can quit smoking or visit a physician to discuss more appropriate medication options.

http://www.smokershelpline.ca/about

Appendix VI: Email for MATCH study promotion

Subject: New Quit Smoking Study: Opportunity to Participate

Dear @Name,
Thank you for your past participation in the Smoking Treatment for Ontario Patients (STOP) Program. When you registered for the STOP Program you indicated that you would be interested in being contacted again for related opportunities in the future.

We are pleased to announce that a new smoking cessation treatment research study is currently recruiting participants. MATCH (Medication Aids for Tobacco Cessation and Health) Study is open to all residents of Ontario (no invitation required). If you are 19 years or older, smoke 10 cigarettes or more per day, and intend to quit within 30 days of receiving the assigned study medication, you may qualify to participate.

MATCH is an internet-based research study being conducted by the scientists at the Nicotine Dependence Clinic at the Centre for Addiction and Mental Health (CAMH). The purpose of this research study is to assess the real-world effectiveness of approved prescription-only smoking cessation medications, bupropion and varenicline. This study provides 12 weeks of medication at no cost to help participants quit smoking. Interested individuals enroll online and receive medication in the mail after following the instructions that are emailed upon enrollment. To learn more about the study and to enroll, please visit the study website at: www.matchstudy.ca.

If you have any questions or desire further information, please feel free to contact the MATCH Study team at match.study@camh.ca.

If you would prefer not to be contacted for future studies, please let us know by writing an e-mail to Stop.Study@camh.ca.

If you have already enrolled in the MATCH Study, please excuse this reminder and thank you for your participation!

Kind Regards,

Dr. Laurie Zawertailo
Co-Principal Investigator, The STOP Program
Principal Investigator, MATCH Study
Clinical Scientist, Addictions Program
Centre for Addiction and Mental Health (CAMH)

*Please note that you cannot reply directly to this email address. If you have any questions or concerns, please contact us at stop.study@camh.ca.
Appendix VII: Facebook Advertisement

Link Title: Quit Smoking Research Study

Text: Take The First Step. Join the MATCH Study and receive 12 weeks of medication at no cost.

Link Text: The MATCH Study is for adult residents of Ontario. If you want to quit smoking using prescription medication (bupropion/varenicline) you may be eligible. Visit matchstudy.ca to learn more and enroll.

Images:
Appendix VIII: Facebook Blog Post

Quitting Smoking Can Be Made Easier

Do you want to quit smoking? Maybe it is for improving your health, maybe it is for saving money, maybe it is for relieving the social pressure that is put on you by the general public for smoking; these can all be reasons that you want to quit.

Quitting can be hard for anyone, but studies have shown that bupropion and varenicline are proven effective smoking cessation aids that greatly increase your chance of success in quitting. However, these medications can cost hundreds of dollars per treatment.

The Medication Aids for Tobacco Cessation and Health (MATCH) Study can now help you to quit smoking at no cost. If you are 19 years or older, a resident of Ontario, wish to quit smoking within 30 days of receiving the assigned study medication, and meet the study’s eligibility criteria, then you can receive 12 weeks of medication (bupropion or varenicline) free of charge to help you quit smoking.

MATCH Study assess the long-term cessation rates associated with bupropion and varenicline treatment in a real-world setting and explores the possibility of mass distributing these medications to a large sample of smokers to help them quit by asking participants to complete a few questionnaire periodically. We need your participation and hope to help you become smoke-free. To learn more about the study and to enroll, please visit the study website at: www.matchstudy.ca

Appendix IX: Letter to Doctors Promoting MATCH study

Dear Physician/Health Care Practitioner,

Some time ago, one of your patients reached out to you to have you sign a Script for him/her to receive 12 weeks of smoking cessation medication (bupropion/Zyban or varenicline/Champix) at no cost, provided through MATCH Study. We would like to thank you for your cooperation and assistance with your patient’s journey on becoming smoke-free.

As you may recall, MATCH (Medication Aids for Tobacco Cessation and Health) Study is an internet-based research study being conducted by the scientists at the Nicotine Dependence Service at Centre for Addiction and Mental Health (CAMH). The purpose of the MATCH study is to assess the real-world effectiveness of smoking cessation medications, bupropion and varenicline. Eligible treatment-seeking Ontario smokers receive 12 weeks supply of medication (bupropion or varenicline, randomized) at no cost. Well-validated research studies have consistently shown that using these smoking cessation medications doubles the chances of successfully quitting in clinical settings. To learn more about the study, please visit the study website at: www.matchstudy.ca.

MATCH has generated quite a bit of interest among practitioners and helped to increase enrolment. It has also been picked up by media in an article by CBC, titled “Smokers being recruited to quit in provincial study”. We would like to inform you that we are still continuing with this project and would like to request your support in sharing this opportunity with your patients, so that more of your patients can be directed to it as an option for their smoking cessation treatment. To aid with the promotion, we
have enclosed study flyers that can be distributed to interested patients or placed in the clinic’s waiting areas to promote quitting smoking. We are grateful for your continued support. Please feel free to contact the MATCH Study team at match.study@camh.ca with any questions or concerns you might have.

Kind Regards,

Dr. Laurie Zawertailo
Principal Investigator, MATCH Study
Clinical Scientist, Addictions Program
Centre for Addiction and Mental Health (CAMH)

Appendix X:

Dear Physician/Health Care Practitioner,

Smoking has long been known to be associated with increased risk of development of periodontal disease and decreased quality of oral hygiene. However, with the prevalence of smokers in Canada to be 18% and rising, there is a great need to increase the success of smoking cessation attempts made by desperate smokers.

MATCH (Medication Aids for Tobacco Cessation and Health) Study is an internet-based research study being conducted by the scientists at the Nicotine Dependence Service at Centre for Addiction and Mental Health (CAMH). The purpose of the MATCH study is to assess the real-world effectiveness of smoking cessation medications, bupropion and varenicline. Eligible treatment-seeking Ontario smokers receive 12 weeks supply of medication (bupropion or varenicline, randomized) at no cost. Well-validated research studies have consistently shown that using these smoking cessation medications doubles the chances of successfully quitting in clinical settings. To learn more about the study, please visit the study website at: www.matchstudy.ca.

MATCH has generated quite a bit of interest among practitioners and helped to increase enrolment. It has also been picked up by media in an article by CBC, titled “Smokers being recruited to quit in provincial study”. We would like to inform you that we are still continuing with this project and would like to request your support in sharing this opportunity with your patients, so that more of your patients can be directed to it as an option for their smoking cessation treatment. To aid with the promotion, we have enclosed study flyers that can be distributed to interested patients or placed in the clinic’s waiting areas to promote quitting smoking. We are grateful for your continued support. Please feel free to contact the MATCH Study team at match.study@camh.ca with any questions or concerns you might have.

Kind Regards,

Dr. Laurie Zawertailo
Principal Investigator, MATCH Study
Clinical Scientist, Addictions Program
Centre for Addiction and Mental Health (CAMH)
Appendix XI: Promotional MATCH posters

The MATCH Study
Medication Aids for Tobacco Cessation and Health

Are you thinking of quitting smoking?
MATCH Study can help!

MATCH is an internet-based research study being conducted by the scientists at the Nicotine Dependence Clinic at the Centre for Addiction and Mental Health (CAMH). The purpose of this research study is to assess the real-world effectiveness of approved prescription-only smoking cessation medications, bupropion and varenicline. This study will provide 12 weeks of medication at no cost to help participants quit smoking. MATCH is open to residents of Ontario, 19 years or older, who wish to quit smoking within 30 days of receiving the assigned study medication, and meet the study’s eligibility criteria.

To learn more about the study and to enroll, please visit:
www.MATCHstudy.ca
Appendix XII: Frequently Asked Questions (FAQ)

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

Q 1: What is the purpose of this study?
A: 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.

Q 2: What is the rationale for this study?
A: Smoking rates remain high in Ontario, although it is proven that smoking can lead to serious health conditions and cost our health care system. Prescription medications, Zyban® (bupropion) and Champix® (varenicline), can help with quitting smoking. But, their effects in general population is limited by a combination of factors. Distributing Nicotine Replacement Therapy to a large number of people in general population approaches have been successful for nicotine replacement therapy. However, bupropion and varenicline can make a greater impact since research studies have been shown them to be more effective.

Q 3: Who is conducting this study and what is the affiliated institution involved?
A: This research study is being conducted by Dr. Laurie Zawertailo, a scientist at the Centre for Addiction and Mental Health, and her group. The study is funded by the Global Research Awards for Nicotine Dependence.

Q 4: How many participants will be involved in this study?
A: About 1500 participants from Ontario will participate in this study.

Q 5: What do I need to be able to participate in the study?
A: You need to be a smoker and you will need a valid e-mail address that you check regularly in order to participate in this study. Specifics of eligibility criteria cannot be disclosed to participants. Your eligibility is determined based on the initial questionnaire answered by you. Please note that the primary mode of contact for this study is through e-mail. Any study material will be e-mailed to your email address. You will also receive the follow-up questionnaires via e-mail. You can obtain a free email address by visiting Yahoo! mail or Hotmail.

Q 6: Are there any in-person visits?
A: No, there are no required in-person visits with the study investigators for this study. The primary mode of contact for this study is through e-mail. Any study material will be e-mailed to your email address. You will also receive notification to complete the follow-up questionnaires via e-mail. All the information is collected online via the MATCH study portal.

In addition, study medication and saliva sample kits are sent to participants by mail. Saliva samples are also sent back by participants through mail and received by study investigators.

You are only required to take the Letter to the Doctor and the Standard Script to your family doctor sometime within 5 weeks of enrolling in the study. Your doctor will have to sign the Standard Script and fax the Prescription to the Pharmacy to be filled. You are also encouraged to continue seeing your doctor for additional support if needed.
Q 7: What happens after the initial questionnaire if I am determined to be eligible? Will I need to see my family doctor to decide if I can participate in this study?

A: Study eligibility will be determined once you complete the initial questionnaire online through the study portal. However, you need to see your family doctor, who will decide if it is safe to prescribe you the assigned study medication. At this time, you are encouraged to discuss your concerns regarding your medical history and any other medications you take with your family doctor.

Q 8: Can I take part in this study if I live outside Ontario?

A: No, unfortunately, this study attempts to look at quitting smoking in Ontario patients only.

Q 9: What are the study treatment groups and medications?

A: The study provides 12 weeks of bupropion or varenicline to help you quit smoking. Once you provide consent and are determined eligible, you will be randomly assigned to either bupropion or varenicline.

Q 10: Am I guaranteed to receive free medication for quitting smoking if I agree to take part in this study? Are there any placebo groups?

A: Once you provide consent and are determined eligible, you will be randomly assigned to either bupropion or varenicline. There are no placebo groups. However, you will have 5 weeks after enrollment date to take the Standard Script and Letter to Doctor and get the prescription for the assigned medication signed by your doctor and faxed to the study pharmacy. You may not receive the medication if your doctor, based on your medical history or based on his/her discretion, chooses not to prescribe you the study medication.

Q 11: What happens if I do not visit my doctor or if my doctor does not prescribe me the assigned study medication?

A: If you do not visit your doctor to have the Standard Script signed after successful enrollment in the study or if your doctor chooses not to prescribe the assigned study medication, we will still attempt to contact you with the same follow-up questions as other participants. The information we collect from you will be used to compare to the information we collect from those who have visited a doctor and are prescribed the medication. You are free to use other methods to aid your quit attempt.

Q 12: For how long do I need to take the medication provided?

A: The study provides 12 weeks of bupropion or varenicline to help you quit smoking. The instructions for the assigned medication will be provided to you by your doctor and/or the study pharmacist. This is the standard course of treatment for smoking cessation and you are encouraged to use all of the medication to increase your chances of remaining abstinent.

Q 13: How will I receive my medication? Is the medication provided free of charge?

A: Once your doctor decides it is appropriate for you to take the assigned study medication and the signed prescription’s fax is received by the study pharmacy, they will fill the prescription and mail the medication to you.

Q 14: Will a pharmacist be involved in this study and how will I have my questions regarding the study medication answered?
A: Once the study pharmacist receives the signed Prescription and verifies it, he/she will fill the medication and mail it to your mailing address. The pharmacist will call you at the time of dispensing the medication to discuss possible allergies, your current medications and to offer counseling.

Q 15: How long after the doctor faxes the signed prescription to the research pharmacy will the pharmacy call for counseling on my assigned medication? And how many times will the pharmacy call back if I am not able to take the call the first time?

A: The pharmacy will call on the same day the signed prescription is received. If they cannot get a hold of you the first time they call, they will try to contact you a few times by phone and email. The medication will not be mailed out to you unless the phone counseling has been completed.

Q 16: How long does it take for the medication to be processed by the pharmacy, mailed, and received by me?

A: It will take about 3-5 business days from the day the counseling is completed for the medication to be processed, mailed, and received by you. If you have not received your medication within a week of the phone counseling, please contact us by sending an e-mail to match.study@camh.ca.

Q 17: How long does this study run and will I be contacted again after initial enrollment?

A: This study will attempt to follow the participants for just a little over a year after enrollment. You will have 5 weeks from the enrollment date to visit your family doctor and get the Standard Script signed and faxed by your doctor. Then, the medication will be mailed to you and you will need to take the assigned study medication for 12 weeks. You will be contacted by e-mail approximately 4, 8 and 12 weeks after starting your medication to fill out the follow-up questionnaire. We will also contact you with similar questions 6 and 12 months later via e-mail. The follow-up questionnaires are 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.

Q 18: How many follow-up questionnaires will I need to answer and what will they be about?

A: You will be contacted by email 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 the follow-up questionnaires 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. This is an important way of measuring the effectiveness of providing these smoking cessation treatments free of charge.

Q 19: Are there any additional supports provided, other than the study medication?

A: You will receive weekly motivational emails for 12 weeks, starting on the 5th week after you are enrolled and are determined eligible. The e-mails will include tips on several things other than the medications that you can do to help you quit smoking.

You are also encouraged to continue seeing your doctor for additional support if needed.

Q 20: Do I need to provide any biological samples?

A: Yes, we will mail you a kit at so you can provide some of your saliva (approximately half a teaspoon) as a sample for biochemical confirmation of current smoking status. You may also be
mailed a saliva kit during the study (at about 4 weeks) and again at 6 or 12 months to confirm your smoking status.

Q 21: Am I responsible for the cost of mailing my saliva sample back to study investigators?

A: No, the saliva kits mailed out to you will contain the return envelope, with the return address label, and paid postage stamp. All you need to do is to place your saliva sample in the return envelope and send it by mail.

Q 22: What are the benefits of participating in this study?

A: 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.

Q 23: Are there any financial benefits to me if I participate in the study?

A: For compensation for your time and effort in sending in your saliva sample, you will be mailed a $10 gift card once we receive your baseline saliva sample back in mail. You will also receive additional $25 gift cards for each additional saliva sample we request, once we receive them in mail.

Q 24: Are there any risks in participating in this study?

Using Zyban (bupropion) or Champix (varenicline) for quitting smoking is approved by Health Canada. The risk is that there are some possible side effects of Zyban (bupropion) and Champix (varenicline). The most common side effects of bupropion are 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 (varenicline) 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:

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

Q 25: What happens if I have an adverse reaction to the study medication?

A: Using Zyban (bupropion) or Champix (varenicline) when quitting smoking is approved by Health Canada. You are encouraged to discuss your medical history, your current medications and any other concerns with your family doctor when you visit him/her to get the Prescription signed. This is to avoid possible adverse reactions. You can also share your concerns with the study pharmacist at the time of phone counseling. Additionally, you can contact the study investigators with your concerns in this regard. Moreover, the follow-up questionnaire will collect information about side effects you may have experienced and we will advice you to stop medication if side effects are serious. If the adverse reactions are interfering with your daily activities, you are free to withdraw from study at any point if you wish not to continue with taking the assigned medications.
Q 26: What happens if I stop taking the medication at any point during treatment? Can I be excluded from the study?

A: In case of serious adverse reaction to assigned study medication, you will be asked to stop taking the medication. However, we will continue to ask you with the same follow-up questions as other participants. The information we collect from you would be used to compare to the information we collect from those who have used all 12 weeks of medication.

Q 27: Will personal information about me be kept confidential?

A: 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. 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.

Q 28: Is my participation voluntary? What happens if I no longer wish to take part in the study?

A: 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. Even if you consent to participate, you are free to withdraw from the study at any time and for any reason and without affecting your future medical treatment. If you withdraw from this study, all biological samples will be destroyed. However, we will keep any results and clinical information collected up to that point.
Appendix XIII: Outlook of Online Data Collection Portal

Appendix XIV: Genetic Sub-study consent Form

Patient Information for Genetic Research

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

You may print out a copy of this Consent Form by clicking on the “Print” button below. 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.

The following consent element is optional. Click on the box to indicate your consent:

- I am willing to be contacted in the future regarding participation in other studies at CAMH.
Appendix XV: Baseline Demographics Questionnaire

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?
Yes
No
I don’t smoke cigarettes – I smoke a pipe, cigars or chew tobacco

[IF “I DON’T SMOKE CIGARETTES” CHOSEN, SKIP TO SECTION 4]

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?
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:
Yes ☐  No ☐

I have had seizure(s) in my lifetime:

Yes ☐  No ☐

I have had allergic reaction to bupropion or Zyban or Wellbutrin or varenicline or Champix:

Yes ☐  No ☐

I am currently taking one of more of the following drugs: Wellbutrin, Zyban, bupropion, Champix, varenicline, thioridazine, monoamine oxidase inhibitors / anti-depressants:

Yes ☐  No ☐

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 ☐
More than 5

Don’t know / prefer not to answer  [IF ANYTHING BUT “NONE”, GO TO NOTE]

(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.)

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
31. Have you ever used any of these substances?

<table>
<thead>
<tr>
<th>Substance</th>
<th>Last 30 Days</th>
<th>Past</th>
<th>Currently</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedatives</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulants</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>No</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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
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 XVI: Email Attachment: Enrollment Confirmation Email Content

Varenicline Medication Enrolment

Subject: MATCH Enrollment Confirmation - Varenicline

Dear [first name]

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

Here is the email you registered with:

Please note this information, as you will be contacted via this e-mail with instructions to fill out the follow-up surveys.

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 five weeks of enrollment. During the visit, bring 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 counselling 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
Bupropion Medication Enrolment

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

Here is the email you registered with:

Please note this information, as you will be contacted via this e-mail with instructions to fill out the follow-up surveys.

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 five weeks of enrollment. During the visit, bring 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 counselling 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 XVII: Study Information and Consent Form sent in Enrollment Confirmation Email

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 bupropion are 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 e-mail]. 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 Options]

   Are you sure that you do not want to participate?
   Clicking ‘Yes’ will return you to the home page.

   ![Yes/No Options]

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 Options]
Appendix XVIII: Letter to Doctor in Enrollment Confirmation Email

Bupropion Letter to Doctor

Date: [PATIENT-SCREENING_DATE]

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

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

Objective: 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.

Design: Open-label, Randomized Controlled Trial

Intervention: 12 weeks of bupropion or varenicline (randomly assigned) or neither (when doctor decides not to prescribe) plus weekly motivational emails

Significance: 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.

Investigators: Dr. Laurie Zawertailo (Principal Investigator), Dr. Peter Selby (Co-Investigator),

REB/IRB: 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.

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 reneges 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
Varenicline Letter to Doctor

Date: [PATIENT-SCREENING_DATE]

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

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

**Objective:** 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.

**Design:** Open-label, Randomized Controlled Trial

**Intervention:** 12 weeks of bupropion or varenicline (randomly assigned) or neither (when doctor decides not to prescribe) plus weekly motivational emails

**Significance**
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.

**Investigators**
Dr. Laurie Zawertailo (Principal Investigator), Dr. Peter Selby (Co-Investigator),

**REB/IRB:** 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.

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, varenicline 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 varenicline free of charge. The medication is delivered to the patient via mail from Pharmacy.ca. It is necessary for Pharmacy.ca to receive a signed prescription from you; please use the enclosed Study Registration Form. 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.36859/ 77

180
### Bupropion Standard Script

**STANDARD SCRIPT**

**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

<table>
<thead>
<tr>
<th><strong>Patient NAME</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENT'S MAILING ADDRESS</td>
</tr>
<tr>
<td>4650 Old Simcoe St.</td>
</tr>
<tr>
<td>City: Oshawa Province: ON Postal Code: L1H7K4</td>
</tr>
<tr>
<td>Patient's Primary Phone Number: 4165259780</td>
</tr>
<tr>
<td>Patient's Secondary Phone Number:</td>
</tr>
<tr>
<td>Patient's Tertiary Phone Number:</td>
</tr>
</tbody>
</table>

**R.**

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**

- Current medications:
- Allergies:
- Other:

**M.D.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
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<tbody>
<tr>
<td>CPSO #</td>
<td>ADDRESS</td>
</tr>
<tr>
<td>E-MAIL ADDRESS</td>
<td></td>
</tr>
</tbody>
</table>

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

**Fax:** 1 800 563 8934
**Phone:** 905 770 9795
Varenicline Standard Script

STANDARD SCRIPT

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

Date: [PATIENT-SCREENING_DATE]

Patient NAME [PATIENT-FIRSTNAME] [PATIENT-LASTNAME]

PATIENT’S MAILING ADDRESS
[ PATIENT-MAILINGADDRESSLINE1]
City: [PATIENT-MAILINGCITY] Province: [PATIENT-MAILINGPROVINCE] Postal Code: [PATIENT-MAILINGPOSTALCODE]

Patient’s Primary Phone Number: [PATIENT-HOMEPHONE]
Patient’s Secondary Phone Number: [PATIENT-WORKPHONE]
Patient’s Tertiary Phone Number: [PATIENT-MOBILEPHONE]

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 XX: Instructions for BFAs questionnaire and BFAs Questionnaire

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 - Strongly Disagree
2 - Neither Agree Nor Disagree
3 - Strongly Agree

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.
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.
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.

1. Inquire about others' well-being.
2. Find it difficult to get down to work.
3. Keep others at a distance.
4. Can handle a lot of information.
5. Get upset easily.
27. Hate to seem pushy.
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.
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.
Appendix XXI: Examples of Weekly Motivational Behavioral 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)
Appendix XXII: Screenshot of Online Pharmacy Portal
Appendix XXIII: Follow-Up Surveys

4 week 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]
When did you start to use the medication? (5.1)

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):
[IF YES, GO TO QUESTION #6.6]
- Yes
- No
- Don’t know / prefer not to answer

6.6 Please specify other:

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

- Yes
- No
[IF NO, GO TO QUESTIONS #8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, #16]
- 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):
[IF YES, GO TO #8.8]
- 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 [IF YES, GO TO QUESTION #20]
☐ 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.
8 Week Follow Up
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:
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
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.
12 Week 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
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:
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?

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

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

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

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

   Hunger / Increased Appetite:
   ☐ Yes ☐ No ☐ Don’t know / prefer not to answer

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

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

   Other symptom(s):
   ☐ Yes ☐ No ☐ Don’t know / prefer not to answer
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?

- Cravings:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

- Weight gain:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

- Depression:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

- Anxiety:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

- Stress:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

- Boredom:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

- Drinking alcohol:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

- Being around other smokers:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

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

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?

- Self-help booklets:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

- Smokers’ helpline (phone, web, or text services):
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

- Individual counseling:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer

- Single-session group counseling workshop:
  - □ Yes
  - □ No
  - □ Don’t know / prefer not to answer
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
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.
6 Months Follow Up Survey

[Administered 6 months after activation date]

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.

* Do you continue to provide consent to participate in this study and complete the following survey? Yes  No

* 1. At the present time, how often do you smoke cigarettes?
   - Daily
   - Occasionally/ non-daily
   - Not at all

* 2. Have you smoked a cigarette, even a puff, in the last 7 days?
   - Yes
   - No
   - Don't know/ prefer not to answer

* 3. Have you smoked a cigarette, even a puff, in the last 30 days?
   - Yes
   - No
   - Don't know/ prefer not to answer

Congratulations on being abstinent! Please note that you may receive a Saliva Collection kit in mail. Detailed instructions are included with the package. You will be compensated with a $25 gift card once we receive your sample back in mail.

* 4. Have you smoked a cigarette, even a puff, in the past 3 months?
* 5. How many cigarettes a day do you smoke now?

- 10 or less
- 11-20
- 21-30
- 30 or more

* 6. On the days that you smoke, how many cigarettes do you usually smoke?

- 5 or less
- 6-10
- 11 or more

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

- 10 or less
- 11-20
- 21-30

* 8. At any time in the last 3 months, have you stopped smoking, for one day or longer because you were trying to quit?

- Yes
- No
- Don't know/ prefer not to answer

* 9. What is the longest number of days in a row that you went without smoking in the last 3 months?


* 10. If you have quit, which statement best describes your smoking behaviour 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

* 11. 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?

* 12. 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?

* 13. 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?

* 14. 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?

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

☐ Yes
☐ No

* 15b. Did you finish taking all 12 weeks supply of the study medication?

☐ Yes
☐ No

16. After you finished the study's treatment period, did you purchase any additional bupropion/Zyban, varenicline/Champix, nicotine replacement therapy (NRT) patch, gum, inhaler or lozenges, or electronic cigarettes to help you with your quit attempt?

* Bupropion/ Zyban:

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

* Varenicline/ Champix:

☐ Yes ☐ No ☐ Don't know/ prefer not to answer
* NRT (patch, gum, inhaler or lozenges):
  - Yes  
  - No  
  - Don't know/ prefer not to answer

* Electronic Cigarettes (also known as e-cigarettes):
  - Yes  
  - No  
  - Don't know/ prefer not to answer

17. Over the last 3 months, have you experienced any of the following symptoms that you think are related to quitting or reducing your smoking?

* Irritable/cranky:
  - Yes  
  - No  
  - Don't know/ prefer not to answer

* Inability to concentrate:
  - Yes  
  - No  
  - Don't know/ prefer not to answer

* Depression:
  - Yes  
  - No  
  - Don't know/ prefer not to answer

* Restlessness:
  - Yes  
  - No  
  - Don't know/ prefer not to answer

* Hunger/ increased appetite:
  - Yes  
  - No  
  - Don't know/ prefer not to answer

* Trouble sleeping:
  - Yes  
  - No  
  - Don't know/ prefer not to answer

* Anxiety:
  - Yes  
  - No  
  - Don't know/ prefer not to answer

* Other symptom(s):
  - Yes  
  - No

18. Over the last 3 months, did any of the following make it harder for you to quit or reduce your smoking?
19. Over the last 3 months, did you seek any of the following additional resources to help you quit or reduce smoking?

* Self-help booklets:
  
  - Yes
  - No
  - Don't know/ prefer not to answer
* Smokers' Helpline (phone, web, or text services):
  - Yes
  - No
  - Don't know/ prefer not to answer

* Individual counseling:
  - Yes
  - No
  - Don't know/ prefer not to answer

* Single-session group counselling workshop:
  - Yes
  - No
  - Don't know/ prefer not to answer

* Multi-session group counselling workshops:
  - Yes
  - No
  - Don't know/ prefer not to answer

* Other:
  - Yes
  - No

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

* 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
* 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
- More than half the days

* 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

* More than half the days

* 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

12 Months Follow Up Survey
[Administered 12 months after activation date]

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.

* Do you continue to provide consent to participate in this study and complete the following survey?
Yes No

* 1. At the present time, how often do you smoke cigarettes?

* Daily
* Occasionally/ non-daily
* Not at all

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

* Yes
* No
* Don't know/ prefer not to answer

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

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Congratulations on being abstinent! Please note that you may receive a Saliva Collection kit in mail. Detailed instructions are included with the package. You will be compensated with a $25 gift card once we receive your sample back in mail.

* 4. Have you smoked a cigarette, even a puff, in the past 3 months?
   - Yes
   - No
   - Don't know/ prefer not to answer

* 5. Have you smoked, even a puff, in the past 6 months?
   - Yes
   - No
   - Don't know/ prefer not to answer

* 6. How many cigarettes a day do you smoke now?
   - 10 or less
   - 11-20
   - 21-30
   - 30 or more

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

* 8. In the past 30 days, on how many days did you smoke 1 or more cigarettes?
   - 10 or less
   - 11-20
   - 21-30
* 9. At any time in the last 6 months, have you stopped smoking, for one day or longer because you were trying to quit?

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

* 10. What is the longest number of days in a row that you went without smoking in the last 6 months?

☐

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

☐ I have not smoked since my quit date
☐ I have smoked rarely since my quit date (less than 5 cigarettes in total)
☐ 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 be quitting smoking altogether?

☐

* 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 quit smoking altogether?

* 14. 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?

☐

* 15. 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?

☐

* 16a. Did you receive 12 weeks supply of the study medication you were assigned to?
* 16b. Did you finish taking all 12 weeks supply of the study medication?

- Yes
- No

17. After you finished the study's treatment period, did you purchase any additional bupropion/Zyban, varenicline/Champix, nicotine replacement therapy (NRT) patch, gum, inhaler or lozenges, or electronic cigarettes to help you with your quit attempt?

* Bupropion/ Zyban:

- Yes
- No
- Don't know/ prefer not to answer

* Varenicline/ Champix:

- Yes
- No
- Don't know/ prefer not to answer

* NRT (patch, gum, inhaler or lozenges):

- Yes
- No
- Don't know/ prefer not to answer

* Electronic Cigarettes (also known as e-cigarettes):

- Yes
- No
- Don't know/ prefer not to answer

18. Over the last 6 months, have you experienced any of the following symptoms that you think are related to quitting or reducing your smoking?

* Irritable/cranky:

- Yes
- No
- Don't know/ prefer not to answer

* Inability to concentrate:

- Yes
- No
- Don't know/ prefer not to answer

* Depression:

- Yes
- No
- Don't know/ prefer not to answer
* Restlessness:
  ○ Yes ○ No ○ Don't know/ prefer not to answer

* Hunger/ increased appetite:
  ○ Yes ○ No ○ Don't know/ prefer not to answer

* Trouble sleeping:
  ○ Yes ○ No ○ Don't know/ prefer not to answer

* Anxiety:
  ○ Yes ○ No ○ Don't know/ prefer not to answer

* Other symptom(s):
  ○ Yes ○ No

19. Over the last 6 months, did any of the following make it harder for you to quit or reduce your smoking?

* Cravings:
  ○ Yes ○ No ○ Don't know/ prefer not to answer

* Weight gain:
  ○ Yes ○ No ○ Don't know/ prefer not to answer

* Depression:
  ○ Yes ○ No ○ Don't know/ prefer not to answer

* Anxiety:
  ○ Yes ○ No ○ Don't know/ prefer not to answer

* Stress:
  ○ Yes ○ No ○ Don't know/ prefer not to answer

* Boredom:
  ○ Yes ○ No ○ Don't know/ prefer not to answer
20. Over the last 6 months, did you seek any of the following additional resources to help you quit or reduce smoking?

* Self-help booklets:

  | Yes | No | Don't know/ prefer not to answer

* Smokers’ Helpline (phone, web, or text services):

  | Yes | No | Don't know/ prefer not to answer

* Individual counseling:

  | Yes | No | Don't know/ prefer not to answer

* Single-session group counselling workshop:

  | Yes | No | Don't know/ prefer not to answer

* Multi-session group counselling workshops:

  | Yes | No | Don't know/ prefer not to answer

* Other:

  | Yes | No

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

* a. Little interest or pleasure in doing things
* b. Feeling down, depressed, or hopeless

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

* d. Feeling tired or having little energy

* e. Poor appetite or overeating

* f. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down
<table>
<thead>
<tr>
<th></th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>g.</td>
<td>Trouble concentrating on things, such as reading the newspaper or watching TV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>Several days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More than half the days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nearly every day</td>
</tr>
<tr>
<td>h.</td>
<td>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</td>
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<tr>
<td></td>
<td>Not at all</td>
<td>Several days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More than half the days</td>
</tr>
<tr>
<td></td>
<td>More than half the days</td>
<td></td>
</tr>
<tr>
<td>i.</td>
<td>Thoughts that you would be better off dead, or of hurting yourself in some way</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>Several days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More than half the days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nearly every day</td>
</tr>
</tbody>
</table>
Appendix XXIV: Saliva Sample Collection Instruction

PAGE 1: General Instructions for Saliva Sample: The MATCH Study

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 back 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)595-8501 ext: 77297
PAGE 2: Saliva Sample Collection Instructions:

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

Please make sure the Cotton Swab is wet!

6. Replace Cap on Inner Container- Snap on Tightly
7. Place Inner Container Into Outer Container- Snap Together Tightly

Completed Saliva Sample Collection Container

On the container label, please write the DATE and TIME you gave your sample.
Appendix XXV: Participant Information Sheet for Genetic Sample

Participant Information Sheet: The MATCH Study

Dr. Laurie Zawertailo  Dr. Peter Selby  Dr. Bernard Le Foll  Dr. James Kennedy

This section to be completed by Neurogenetics lab:

Neurogenetics Lab #: MATCH  Family #: 

Date Received (dd/mm/yyyy): 

- Collaborator ID: 
- Date sample collected (dd/mm/yyyy): 
- Relationship to Proband: Proband 
- Date of Birth (dd/mm/yyyy): 
- Sex: ☐ Female ☐ Male ☐ Other 

Ethnicity: (What ethnic group do each of your following blood relatives belong to?) Please fill in the table.

Adopted? ☐  Don’t know ☐
If adopted or do not know, Which ethnic group from the list below do you most closely identify with? 

<table>
<thead>
<tr>
<th>Maternal Grandmother</th>
<th>Maternal Grandfather</th>
<th>Paternal Grandmother</th>
<th>Paternal Grandfather</th>
</tr>
</thead>
<tbody>
<tr>
<td>European/Caucasian</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>African Descent/</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>African American</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>East Indian Caucasian</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>(e.g. Pakistani, Indian)</td>
<td></td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Asian</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>(e.g. Chinese, Japanese)</td>
<td></td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Native N. American</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other:_______________</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Religion

Primary Language: 

Yours: 

Mother: 

Father: 

Don’t know/ prefer not to answer ☐ 

Primary Language: 

Don’t know/ prefer not to answer ☐ 

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Appendix XXVI: Genetic Sample Collection Instructions

MATCH Genetics Sub-Study Saliva Sample Instructions

1. Please complete the enclosed form, called Participant Information Sheet: The MATCH Study and place it in the bubble-padded envelope to send with the sample.

2. Please see the inside of the kit for directions on how to give your saliva sample.

3. After giving your saliva sample, please write the DATE you gave your sample on the tube label.

4. Place closed collection tube (containing sample) in the plastic bag, found in the bubble-padded envelope. Do NOT remove the absorbent material from within the bag. Please ensure that only the tube itself is placed in the plastic bag. The rigid plastic packaging (labeled Oragene DNA self-collection kit) that contained the tube can be discarded.

5. Remove as much air as possible and seal the bag.

6. Place the sealed plastic bag (containing sample) into the bubble envelope.

7. Ensure that the Participant Info Sheet is included. Then, seal the bubble envelope properly and mail it immediately. Postage has already been prepaid.
Appendix XXVII: Protocol for NMR analysis (Dr. Rachel Tyndale)

**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</td>
</tr>
<tr>
<td></td>
<td>Cotinine 1000</td>
</tr>
<tr>
<td></td>
<td>3-Hydroxycotinine 1000</td>
</tr>
<tr>
<td>500</td>
<td>Nicotine 500</td>
</tr>
<tr>
<td></td>
<td>Cotinine 500</td>
</tr>
<tr>
<td></td>
<td>3-Hydroxycotinine 500</td>
</tr>
<tr>
<td>100</td>
<td>Nicotine 100</td>
</tr>
<tr>
<td></td>
<td>Cotinine 100</td>
</tr>
<tr>
<td></td>
<td>3-Hydroxycotinine 100</td>
</tr>
<tr>
<td>10</td>
<td>Nicotine 100</td>
</tr>
<tr>
<td></td>
<td>Cotinine 10</td>
</tr>
<tr>
<td></td>
<td>3-Hydroxycotinine 10</td>
</tr>
<tr>
<td>1</td>
<td>Nicotine 1</td>
</tr>
<tr>
<td></td>
<td>Cotinine 1</td>
</tr>
<tr>
<td></td>
<td>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 Infinity 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 → 84</td>
</tr>
<tr>
<td>Nicotine-d₄</td>
<td>167 → 84</td>
</tr>
<tr>
<td>Cotinine</td>
<td>177 → 80</td>
</tr>
<tr>
<td>Cotinine-d₃</td>
<td>180 → 80</td>
</tr>
<tr>
<td>3-Hydroxycotinine</td>
<td>193 → 80</td>
</tr>
<tr>
<td>3-Hydroxycotinine-d₃</td>
<td>196 → 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.

*Appendix XXVIII: Protocol for Varenicline and Bupropion Concentration Analysis (Dr. Rachel Tyndale)*

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NMR and Varenicline method

Chemicals

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

Specimen

Whole blood, plasma 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</td>
</tr>
<tr>
<td></td>
<td>Cotinine 1000</td>
</tr>
<tr>
<td></td>
<td>3-Hydroxycotinine 1000</td>
</tr>
<tr>
<td></td>
<td>Varenicline 1000</td>
</tr>
<tr>
<td>500</td>
<td>Nicotine 500</td>
</tr>
<tr>
<td></td>
<td>Cotinine 500</td>
</tr>
<tr>
<td></td>
<td>3-Hydroxycotinine 500</td>
</tr>
<tr>
<td></td>
<td>Varenicline 500</td>
</tr>
<tr>
<td>100</td>
<td>Nicotine 100</td>
</tr>
<tr>
<td></td>
<td>Cotinine 100</td>
</tr>
<tr>
<td></td>
<td>3-Hydroxycotinine 100</td>
</tr>
<tr>
<td></td>
<td>Varenicline 500</td>
</tr>
<tr>
<td>10</td>
<td>Nicotine 100</td>
</tr>
<tr>
<td></td>
<td>Cotinine 10</td>
</tr>
<tr>
<td></td>
<td>3-Hydroxycotinine 10</td>
</tr>
<tr>
<td></td>
<td>Varenicline 10</td>
</tr>
<tr>
<td>1</td>
<td>Nicotine 1</td>
</tr>
<tr>
<td></td>
<td>Cotinine 1</td>
</tr>
<tr>
<td></td>
<td>3-Hydroxycotinine 1</td>
</tr>
<tr>
<td></td>
<td>Varenicline 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, trans-3’-hydroxycotinine-d₃ and varenicline-d₄ prepared in 0.01 M HCl (6).

Instrumentation

HPLC system:

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

Column (6):
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 (6).

HPLC gradient (6):

<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, 21 eV for varenicline and varenicline-d4.

SRM transitions monitored:

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Transition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>163 → 84</td>
</tr>
<tr>
<td>Nicotine-d4</td>
<td>167 → 84</td>
</tr>
<tr>
<td>Cotinine</td>
<td>177 → 80</td>
</tr>
<tr>
<td>Cotinine-d3</td>
<td>180 → 80</td>
</tr>
<tr>
<td>3-Hydroxycotinine</td>
<td>193 → 80</td>
</tr>
<tr>
<td>3-Hydroxycotinine-d3</td>
<td>196 → 80</td>
</tr>
<tr>
<td>Varenicline</td>
<td>212 → 169</td>
</tr>
<tr>
<td>Varenicline-d4</td>
<td>216 → 169</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, nicotine-d₄ and varenicline-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 “NMR and VAR apci” on LCMS 1 (old) to analyze human blood, plasma, saliva or urine samples for nicotine, cotinine and 3-hydroxycotinine
Appendix XXIX: Electronic Amazon gift cards for compensation

Message:

Dear [first name],

We have successfully received your [baseline, genetic, mid-treatment, 6 month] sample back in mail. Thank You! Here is a gift card as promised to show that we appreciate your time and effort. Enjoy!

Sincerely,
MATCH Study Team

Appendix XXX: List of Criteria for DSM-V

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