Factors Influencing the Effectiveness of Mass Distribution of Free Nicotine Replacement Therapy

by

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Abstract

Despite over 50 years of tobacco control efforts, tobacco use remains the leading preventable cause of disease and premature death in Canada. The mailed distribution of free nicotine replacement therapy (NRT) has been shown to be a promising population-level approach for promoting smoking cessation, increasing accessibility to efficacious treatment, and helping smokers quit. The present body of research aimed to gain a comprehensive understanding of factors that may mediate the effectiveness of the mailed free distribution of NRT approach via a large, single blinded, randomized controlled trial of mailed free nicotine patches to adult smokers across Canada, in absence of behavioural support. The mailed provision of 5-weeks of free nicotine patches was found to increase the odds of smoking cessation irrespective of lifetime history of depression or anxiety, both highly prevalent comorbidities that are well established moderators of cessation success. Evaluating demographic and smoking history predictors of nicotine patch use and cessation, only those who were unemployed, previously used NRT, and expressed greater intent for change at baseline were more likely to take advantage of and use at least some of the freely provided nicotine patches to make a quit attempt. Past NRT use and use

of all provided nicotine patches were the only predictors of smoking cessation at a 6-month follow-up. In general, the conscientiousness personality trait and attitudes towards smoking cessation aids were found to be predictive of whether smokers quit using formal assistance or unassisted. Further, compared to a control cohort, receipt and use of nicotine patches corresponded to higher prevalence of primary care support, suggesting that the provision of free NRT particularly to those who are likely to use it may facilitate opportunities for benefits beyond the direct pharmacological effects of the medication. In summary, the research outlined the benefit of the mass distribution approach even among those with presumed difficulty in quitting smoking, delineated predictors of treatment utilization and cessation, as well as developed insights on the impact of the approach in harnessing additional smoking cessation support, thus strengthening support for the inclusion of free NRT provision as part of a comprehensive tobacco control strategy.

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List of Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ANOVA	Analysis of Variance
CATI	Computer Assisted Telephone Interview
CI	Confidence Interval
EPV	Events per Predictor Variable
FCTC	Framework Convention for Tobacco Control
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
ITC	International Tobacco Control
MTurk	Mechanical Turk
nAChRs	nicotinic acetylcholine receptors
NPs	Nicotine Patches
NRT	Nicotine Replacement Therapy
OR	Odds Ratio
OTC	Over the Counter
RCT	Randomized Controlled Trial
RR	Risk Ratio
SD	Standard Deviation
SES	Socioeconomic Status
SR	Sustained Release
STOP	Smoking Treatment for Ontario Patients
TSRQ	Treatment Self-Regulation Questionnaire
U.S.	United States
WHO	World Health Organization

Chapter 1: Introduction

1.1   Statement of the Problem

Tobacco use is the leading known cause of preventable death and disability worldwide. Responsible for claiming an estimated 100 million lives during the 20th century and at present, 6 million deaths per year globally, the tobacco epidemic places significant health, societal and economic burdens worldwide (World Health Organization, 2015). The accumulated evidence on the health effects of tobacco and second-hand smoke are overwhelming, being linked to diseases in nearly every organ in the body. Regular active cigarette smoking is associated with at least 14 types of cancer (twelve of which causally), cardiovascular diseases such as stroke, as well as many respiratory diseases, reproductive problems, and many others (U.S. Department of Health and Human Services, 2014). Carcinogens in cigarette smoke have been also demonstrated to cause DNA damage and mutations, dose-dependently increase the risk of type-2 diabetes and obesity, impair fetal development and autoimmune function, and be associated with rheumatoid arthritis and macular degeneration (U.S. Department of Health and Human Services, 2014). Such direct and indirect health effects of smoking, in part, contribute to enormous fiscal consequences. It has been recently estimated that the global economic cost of smoking-attributable diseases (i.e., those caused by direct exposure to smoking) totalled US$422 billion in 2012, or 5.7% of global health expenditure, whereas the total economic costs from smoking-attributed health expenditures and productivity losses together totalled $US1.4 trillion, equivalent to 1.8% of the world's gross domestic product (Goodchild, Nargis & Tursan d'Espaignet, 2017). In Canada, the

annual economic burden attributed to tobacco smoking (direct and indirect) accounted for $18.7 billion in 2013 (Krueger, Krueger & Koot, 2015).   In an effort to tackle the global tobacco use epidemic, the World Health Organisation (WHO) introduced the first international public health treaty in 2005, the Framework Convention for Tobacco Control (FCTC). Becoming the most widely and rapidly embraced treaty in United Nations history, the WHO FCTC reaffirmed the rights of all people to the highest standard of health, while addressing the causes of the epidemic, regulation (i.e., illicit trade, foreign investment, smoke free environments), factors effective in reducing demand (i.e., cessation, price and tax measures, bans on advertising, promotion and sponsorship), as well as efforts for increased research, surveillance, and information exchange (World Health Organization, 2003). In 2008, the WHO further promoted six proven measures to help countries improve specific provisions of the WHO FCTC: Monitor tobacco use and prevention policies; Protect people from tobacco smoke; Offer help to quit tobacco use; Warn about the dangers of tobacco; Enforce bans on tobacco advertising, promotion and sponsorship; and Raise taxes on tobacco (collectively referred to as MPOWER)(World Health Organization, 2013). To date, an estimated 2.3 billion people are covered by at least one MPOWER measure, with at least 30 countries mandating health warning labels measures, 37 enforcing smoke-free laws, and 27 have raised taxes to 75% of retail prices. Since its ratification, Canada has fully implemented the provisions of the FCTC through the Federal Tobacco Control Strategy and has been a leader in exceeding minimum FCTC standards, for example sustaining a strong tobacco use monitoring system, banning the use of flavours and other additives (except menthol) in cigarettes and little cigars, restricting retail display of tobacco products, and requiring pictorial health warnings on tobacco packages, just to name a few (Health Canada, 2014; World Health Organization, 2014). In part due to these initiatives, in 2013, Canada has seen record low

smoking prevalence rates of 14.6% among those age 15 years or older (Health Canada, 2015). While this rate represents a marked reduction from 25% in 1999, an estimated 4.2 million Canadians continue to smoke and in recent years the reduction in smoking rates have been minimal. Therefore, for the purposes of ending suffering and saving future lives, there continues to be an urgent need for enhanced tobacco control efforts to reduce the smoking prevalence rates even further.

In light of the relatively plateaued smoking prevalence rates, over the past several years there has been recognition and increased discourse for the development of a "Tobacco Endgame" strategy. It rests on the perspective that "control" of tobacco will not be enough to deal with the tobacco epidemic and that a shift in focus and authentic public policy commitment is necessary to develop strategies that will produce a tobacco-free future. The notion of the "Tobacco Endgame" defines a desired target of smoking prevalence of 0% or less than 5%, and has been presently adopted only by Ireland, Scotland, Finland, and New Zealand. Canada's Tobacco Endgame initiative is in development, with a steering committee meeting on July 8, 2015 agreeing on a set target of less than 5% smoking prevalence by the year 2035 (Armes, 2016). It was further recognized that while prevention strategies will be central to achieving this goal, they alone will be insufficient and new approaches will need to be introduced to increase the proportion of smokers who are successful in quitting. Central to this theme is improved access and availability of interventions best known to help smokers quit (i.e., counselling, medication, behavioural interventions), which may not only motivate smokers to quit but also improve their chances of success.

Over the past several decades, a number of population-level interventions for increasing smoking cessation have been implemented. Zhu and colleagues (2012) reviewed such

interventions, delineating those with assumed specificity of their mechanism (Primary; i.e.,

pharmacotherapy, smokers' helplines, technology-based interventions, cessation focused media

campaigns) from interventions that claim to have population effects but were not originally

designed for cessation purposes (Secondary; i.e., second hand smoking policies, tobacco price

increases, general anti-smoking media messages). While the most effective interventions in the

United States (U.S.) were noted to be increased cigarette prices (usually due to tax increases),

smoke-free policies, and healthcare provider assistance, variations in annual cessation rates,

defined as the percentage of smokers who quit smoking for at least 3 months in the past year,

could not be effectively attributed to any particular intervention. In fact, the mean annual quit

rate after the establishment of many large-scale tobacco control programmes (2001 to 2010;

4.2%) did not significantly differ from 1991 to 2000, whose mean was 4.7% (Zhu, Lee, Zhuang

et al., 2012). Moreover, since the approval and availability of over-the-counter (OTC) purchase

of the clinically effective gum and patch forms of nicotine replacement therapy (NRT) in the

U.S. in 1996, substantial improvements in smoking cessation have unfortunately not been seen

(Amodei & Lamb, 2008; Pierce & Gilpin, 2002). Increasing the reach of such interventions

therefore, while necessary, may not be sufficient in improving cessation rates. Explanations of

their limited effectiveness have rested on possible unintended consequences. It is plausible that

an overemphasis of the power of medications was responsible for lowering self-efficacy and

reducing base quit rates. Alternatively, interventions with proven efficacy in randomized clinical

trials with specific inclusion criteria and regulated medication adherence protocols have not been

able to translate well into the "real-world" setting. With quit attempt rates being a good indicator

of population cessation, Zhu and colleagues (2012) further point out that to improve smokers'

odds of cessation, future interventions should evaluate how to get more smokers to try to quit

and to quit more frequently. Certainly, population-level interventions that promote cessation, assist with cessation efforts, and remove or reduce barriers in accessing treatment, could aid in the goal of reducing smoking prevalence rates.

The availability and distribution of free smoking cessation aids is one such possible measure. Since their initial implementation in North America in 2003 (Cummings, Hyland, Fix et al., 2006; Frieden, Mostashari, Kerker et al., 2005; Miller, Frieden, Liu et al., 2005), regional free NRT giveaway or distribution programs have been developed to encourage and motivate smokers to quit. While eliminating cost as a barrier to using NRT among those wanting to quit (Land, Warner, Paskowsky et al., 2010), these programs also provide another element of support as they are most commonly implemented through existing smokers' helplines. Eligible adult smokers as part of these programs are typically mailed 2 – 8-week supply of NRT and receive either counselling or periodic telephone calls to assess their progress in quitting smoking. One program in New York State provided over 40,000 smokers who called in to a smokers' quitline with one to six weeks of free nicotine patches or vouchers for two weeks of NRT. Evaluation of the giveaway program revealed that quit rates four months later varied from 21% (among smokers receiving one week of NRT for free) to 35% (among smokers receiving 6 weeks of NRT for free). This compared with a quit rate of 12% among an earlier comparison group of callers to the quitline (not randomly assigned) who received counseling support and some self-help materials but no NRT (Cummings, Fix, Celestino et al., 2006). Similar results have been demonstrated in a large-scale distribution of free NRT initiative in Ontario, Canada, the STOP (Smoking Treatment for Ontario Patients) Study, responsible for delivery of 5 weeks of free NRT to over 13,000 smokers. At a 6-month follow-up of the call-based mass distribution initiative, 17.8% of participants reported 30-day smoking abstinence, while 9.8% reported

abstinence in a concurrent no-intervention cohort of Ontario smokers matched for eligibility (Zawertailo, Dragonetti, Bondy et al., 2013).

To date, nearly a dozen studies have been conducted evaluating the effectiveness free NRT distribution. Research has demonstrated that smokers are interested in easier access to such smoking cessation therapies (Jardin, Cropsey, Wahlquist et al., 2014; Tinkelman, Wilson, Willett et al., 2007), they are particularly satisfied with its receipt (Bush, McAfee, Deprey et al., 2008), and this form of cessation intervention is very cost effective per each individual quit as well as compared to other widely accepted and effective medical interventions (i.e., mammography screening) (Ahern & Shen, 2009; Zawertailo, Dragonetti, Bondy et al., 2013). There has also been accumulating evidence that the implementation of free NRT giveaway programs is associated with increased rates of quitting smoking. However, because the vast majority of such mass distribution initiatives have been evaluated via assessment of quit rates pre-post the availability of free NRT, without a randomly assigned control group, there has previously been no reliable information on the efficacy of the approach. Moreover, most research has been limited in scope, focusing on quit rates as the primary outcome, and neglecting to consider factors that are crucial for guiding policy on the widespread implementation of the mass distribution of free NRT on a national scale. Much remains unknown about the effectiveness of this relatively novel population-level cessation approach, including but not limited to, predictors of NRT utilization and smoking cessation success, effectiveness of free NRT distribution among patient populations with increased smoking prevalence, reduced quit rates, and those who face the bulk of smoking-attributed health burden (i.e., those in lower socioeconomic groups and suffer from mental health comorbidities) (Prochaska, Das & Young-Wolff, 2017; World Health

Organization, 2015), as well as the impact of free NRT distribution on further cessation help-seeking.

While several jurisdictions around the world now offer cost-free or low-cost NRT as part of a national public health program, in Canada, only the British Columbia and Ontario health ministries currently have programs in place offering free NRT to smokers who want to quit. More research is therefore needed to validate the benefit of free NRT distribution in guiding public policy for its inclusion as part of a national Tobacco Endgame strategy.

1.2   Overall Research Purpose

There is currently limited knowledge on the determinants of smoking cessation success as part of the mailed distribution of free NRT paradigm. While there is suggestive evidence that the provision of free NRT as part of smokers' helplines aids in driving increased cessation rates, the effectiveness of the mailed distribution approach has not been well established, and the underlying factors that predict or mediate its effectiveness have not been explored. The aim of the present research line was thus to gain a more comprehensive understanding of individual and treatment-level factors that may mediate the effectiveness of this population-level approach in helping smokers quit. Specifically, the research attempted to elucidate the influence of mental illness on free NRT distribution effectiveness, uncover which demographic and smoking history factors influence NRT utilization and cessation following the provision of free NRT, and further, explore whether the mailed free NRT smoking cessation paradigm promotes further help-seeking from primary care providers.

1.3 Specific Research Objectives

1.3.1 Impact of Self-Reported Lifetime Depression or Anxiety on Effectiveness of Mass Distribution of Nicotine Patches (Manuscript 1)

The objective of the study was to examine the influence of lifetime history of depression and/or anxiety on smoking cessation success following the free distribution of nicotine patches. The research attempted to answer the question: Are smokers with lifetime depression or anxiety as likely to quit as smokers without such diagnoses when provided free NRT, compared to those not offered NRT?

1.3.2 Mailed Distribution of Free Nicotine Patches Without Behavioral Support: Predictors of Use and Cessation (Manuscript 2)

The objective of the study was to evaluate which *a-priori*-defined demographic and smoking history factors previously shown to be associated with purchase and use of over-the-counter NRT predict use of a 5-week course of mailed free nicotine patches (without any additional counselling or support), among smokers expressing interest in using free NRT to quit smoking. Further, the study aimed to explore reasons for not using freely provided nicotine patches and investigate the association between use of free nicotine patches and cessation at a 6-month follow-up.

1.3.3 Unassisted Smoking Cessation: The Role of Motivation and Personality Factors (Manuscript 3)

The objective of the study was to retrospectively evaluate what role motivational reasons for quitting smoking and personality factors play in determining the quit methods used by smokers to achieve cessation.

1.3.4 Impact of Large-Scale Distribution and Subsequent Use of Free Nicotine Patches on Primary Care Physician Interaction (Manuscript 4)

The objective of the study was to examine whether and to what extent the provision of free NRT impacts smokers' interaction with primary care physicians. In particular, the research attempted to answer the question: Does the provision and subsequent use of free nicotine patches to smokers interested in quitting promote interaction with their primary care physicians, and whether that interaction has a role in quitting smoking?

1.4   Rationale for the Projects

1.4.1   Neuropharmacology of Nicotine Addiction

Quitting smoking conveys numerous immediate, intermediate and long-term health benefits. While some benefits, such as substantial decrease in carbon monoxide levels in the blood, can be seen within 24 hours of quitting (U.S. Department of Health and Human Services, 1990), the most prominent benefit is reduced risk of developing many types of cancer, cardiovascular disease and premature death. For example, coronary heart disease risk is reduced by 50% after 12 months without smoking, and after 15 years the risk is as low as that of a non-smoker. Ten years after quitting the mortality rate from lung cancer is about half that of a continuing smoker (U.S. Department of Health and Human Services, 1990).

Although most smokers know that cigarette smoking is harmful and recognize that they should quit (Babb, Malarcher, Schauer et al., 2017; Reid, Hammond, Rynard et al., 2014), many are unable to do so. The psychoactive component of tobacco in cigarettes, nicotine, perpetuates continued use of cigarettes and is largely responsible for the ensuing addition with repeated exposure. Initially, upon inhalation, nicotine from tobacco is carried by smoke particles into the lungs, where it rapidly enters arterial circulation. Within as little $10 - 20$ seconds, nicotine crosses the blood brain barrier, moving into the brain and binding to different subtypes of neuronal nicotinic acetylcholine receptors (nAChRs), the most abundant of which being the $\alpha4\beta2$ receptors (Benowitz, 1996; Le Houezec, 2003). Due to their high affinity for nicotine, $\alpha4\beta2$ receptors have been identified as the main receptors mediating nicotine addiction (Dani & De Biasi, 2001; Picciotto, Zoli, Rimondini et al., 1998). Stimulation of nAChRs results in the release

of various neurotransmitters, including dopamine, whose release in the ventral tegmental area of the midbrain and the shell of the nucleus accumbens is recognized as the principal pathway of the rewarding, pleasurable, and reinforcing effects of nicotine, as well as other drugs of abuse (Dani & De Biasi, 2001; Nestler, 2005; Nisell, Nomikos & Svensson, 1994; Sherwood, 1993). With repeated exposure, the brain develops neuroadaptations to some of the effects of nicotine. Specifically, long-term exposure to nicotine results in a continuous process of activation and desensitization of nAChRs, which over the long term triggers a homeostatic upregulation of nAChRs (Fenster, Whitworth, Sheffield et al., 1999; Ulrich, Hargreaves & Flores, 1997). It is believed that such upregulation of nAChRs creates the basis of tolerance – the need for increased amounts of nicotine (or greater number of cigarette smoking) to achieve its mild stimulant, euphoric and anxiolytic effects – and physical dependence (Henderson & Lester, 2015). It has been suggested that when previously desensitized α4β2 nAChRs become unoccupied and recover to a responsive state, such as in periods of abstinence or nighttime sleep, symptoms of craving and withdrawal may follow (Dani & Harris, 2005; Dani & Heinemann, 1996; Jackson, Muldoon, De Biasi et al., 2015). These symptoms are often expressed through irritability, restlessness, anxiety, insomnia, fatigue, lack of ability to concentrate and strong urges to smoke (cravings) (Brands, Sproule & Marshman, 1998). Upon smoking once again, and thus re-administration of nicotine, the symptoms are alleviated. To avoid withdrawal or provide relief from withdrawal symptoms, some smokers attempt to self-regulate sufficient levels of plasma nicotine, and near complete saturation of α4β2 nAChRs, by way of smoking in regular intervals throughout the day. In its relief of withdrawal symptoms and ability to attenuate negative affective states, namely transient sadness, anxiety, as well as boredom and environmental stressors, the smoking process thus becomes highly reinforcing.

In addition to the direct pharmacological mechanisms underlying nicotine addiction, continued smoking is further mediated by way of conditioned behaviour. As people engage in smoking in the context of certain situations, such as after a meal, with coffee, when stressed or consuming alcohol, the pleasurable or relief-inducing effects of smoking repeated many times become highly associated with these moods and environmental stimuli (Benowitz, 2009). Habitually paired with smoking, these stimuli on their own can thus serve as powerful cues that trigger the urge to smoke. Aspects of the drug taking process, such as the smell, taste, and manipulation of the smoked product, also become positively reinforcing, driving continued smoking and trigger relapse during periods of abstinence. This pairing between the pharmacological mechanism of action of nicotine and smoking behaviour develops and maintains the psychological addiction to smoking, which can most effectively be treated through counselling and cognitive-behavioural approaches.

1.4.2 First-Line Pharmacotherapies for Nicotine Addiction

Three medications are currently recommended by clinical practice guidelines as first-line pharmacotherapies for smoking cessation: nicotine replacement therapy, bupropion hydrochloride (sustained release), and varenicline titrate (CAN-ADAPPT, 2011; Fiore, Jaen, Baker et al., 2008). All three have been shown to be efficacious when compared to placebo in clinical settings, with a recent meta-analysis documenting that NRT increases the odds of cessation by 1.84 times, bupropion SR by 1.82 times, and varenicline by 2.88 times (Cahill, Stevens, Perera et al., 2013). With low risk of adverse events, these first-line agents are highly

promoted by healthcare and public health communities in combatting nicotine addiction. Other therapies, such as cytisine, the tricyclic antidepressant nortriptyline, and the anxiolytic clonidine, are also available. However, due to issues concerning either licensing requirements (Samet, 2014) or greater side-effect profiles (Aveyard, Johnson, Fillingham et al., 2008; Hughes, Gust, Skoog et al., 1991), these medications are typically reserved as second-line smoking cessation aids and are not the foci of the present thesis.

1.4.2.1 Nicotine Replacement Therapy

Since the approval of NRT for purchase without a prescription, NRT has become the preferred and most commonly used smoking cessation aid. Available in a number of different formulations, such as the transdermal patch, gum, lozenge, oral spray, and oral inhaler, NRT's mechanism of action mimics that of nicotine obtained from tobacco smoke. Delivering a non-toxic form of nicotine in absence of the harmful constituents of tobacco smoke, NRTs stimulate nAChRs to reduce craving and nicotine/tobacco withdrawal symptoms that often precipitate in the days and weeks following smoking cessation (West, Jarvis, Russell et al., 1984). Fast acting buccally absorbed oral forms of NRT, such as the nicotine spray, gum, oral spray and lozenge, provide immediate relief of cravings, allowing patients to self-titrate the dosage and time-adjust administration based on individual needs (Aubin, Luquiens & Berlin, 2014; Russell, Jarvis, Feyerabend et al., 1983). The transdermal nicotine patch on the other hand, is readily absorbed through the skin and delivers slow sustained release of nicotine (Fant, Henningfield, Shiffman et al., 2000). It produces sustained plasma nicotine levels throughout the day and hence amelioration of withdrawal symptoms and nicotine's positively reinforcing effects. Overall,

because nicotine delivery through the various formulations is considerably slower, occurs in lower doses compared to that from cigarettes, and results in lower plasma concentrations, NRTs are less likely to be associated with physical dependence (Hukkanen, Jacob & Benowitz, 2005). A brief review of the administration, side effects and efficacy of the most commonly used NRT formulations in Canada is provided below.

The *nicotine gum,* available in 2mg and 4mg dosage forms, is a complex of nicotine bound to a polyacrylic matrix in a sugar-free chewing gum (Shiffman, Fant, Buchhalter et al., 2005). The nicotine is released upon chewing; however, it should not be chewed like ordinary confectionary gum. The gum is advised to be chewed over about 30 minutes slowly and intermittently (i.e., repeatedly chewed slowly until it tingles and parked between cheek and gum until the tingle is gone), 10-12 times a day and in anticipation or presence of cravings (Shiffman, Fant, Buchhalter et al., 2005). Non-adherence to the recommended chewing technique can result in increased gastrointestinal adverse events and decreased nicotine absorption (Barboza, Patel, Patel et al., 2016). Because nicotine gum, lozenge, and inhaler absorption occurs via buccal membranes and thus pH dependent, acidic foods are further advised to not be consumed for at least 15 minutes before or after using these NRTs (Henningfield, Radzius, Cooper et al., 1990; Shiffman, Fant, Buchhalter et al., 2005). A systematic review of 56 studies evaluating the efficacy of the nicotine gum compared to placebo or a no intervention control condition, conducted primarily in primary care settings and involving more than 22,000 participants, had discerned that the nicotine gum resulted in approximately 50% higher odds of quitting smoking (Hartmann-Boyce, Chepkin, Ye et al., 2018). While the gum is an effective cessation aid, it is also approved to be used to decrease cravings and withdrawal symptoms during periods of enforced temporary abstinence and not necessarily just for smoking cessation (Foulds, 2010).

The *nicotine inhaler* consists of a reusable mouthpiece and a plastic cylinder that can be fitted with nicotine-containing cartridges (10mg/cartridge). Upon inhalation or "puffing", nicotine volatizes when warm air is passed over the cartridge. Users are advised to take approximately 10 short puffs to withdraw the volatize nicotine and subsequently hold the vapour in their mouth to allow for buccal mucosa absorption, in contrast to the alveolar absorption facilitated via inhaled cigarette smoke. The puffing action involves a 'hand-to-mouth ritual' familiar to individuals who smoke and satisfies the behavioural aspect of smoking. Evidence from a limited number of studies suggests that the inhaler increases the chances of cessation by 90%, compared to placebo or no intervention (Hartmann-Boyce, Chepkin, Ye et al., 2018).

The *nicotine lozenge* is a small white lozenge containing a resin complex of nicotine. Like the nicotine gum in composition, dosage formulations, and instructions for use, the lozenge is not meant to be chewed or constantly sucked on, however, rather simply placed in the mouth and switched from side to side as needed. It provides an alternative to the nicotine gum for those that do not find gum chewing acceptable, albeit delivering approximately 25% more nicotine than equivalent strength of gum (Choi, Dresler, Norton et al., 2003). Pooled estimate of the lozenge effectiveness report 52% increased odds of smoking cessation compared to placebo or no intervention control (Hartmann-Boyce, Chepkin, Ye et al., 2018).

The *oral spray* is a nicotine aerosol that is sprayed to relieve cravings to smoke and upon smoking cessation initially used as 1 or 2 sprays to replace each cigarette. The oral spray possesses faster onset of action than the either the gum, inhaler, or lozenge, and has increased odds of cessation by 2.48 times compared to placebo (Tonnesen, Lauri, Perfekt et al., 2012). Most common side effects have been noted to be throat irritation, coughing and oral burning, occurring in greater frequency than placebo (Schneider, Olmstead, Nilsson et al., 1996).

Nicotine patches are adhesive patches that, when applied to the skin, deliver nicotine through the skin at a relatively steady state. Available in 16hr or 24hr delivery formats with strengths of 15mg, 10mg, or 5mg, and 21mg, 14mg, or 7mg, respectively, the patches are typically administered in the morning and worn for the directed period of time. The range of doses allows users to gradually reduce their nicotine intake over time with the ultimate goal of achieving a nicotine-free state. The main advantage of nicotine patches over other more acute formulations of NRT is the ease of administration, with which the user engages by typically putting one patch once a day, rather than repeatedly using a product throughout the day. Some evidence is available that the 24hr delivery patches provide superior relief of withdrawal and cravings, as well as reduced sleep disturbances (Aubin, Luthringer, Demazieres et al., 2006; Shiffman, Elash, Paton et al., 2000). Skin irritations from the patch are common, however, affecting up to 54% of users (Fiore, Jorenby, Baker et al., 1992), albeit these incidences are typically mild and can be minimized by switching the application site daily. Compared to placebo or a no NRT control, a systematic review of 51 studies involving more than 25,000 participants concluded that nicotine patches have a risk ratio (RR) of 1.64 (95% CI 1.53 to 1.75) on smoking cessation at 6 months or longer follow-up (Hartmann-Boyce, Chepkin, Ye et al., 2018) . Off-label prescribing of high doses of nicotine patches (e.g., ≥42mg daily) is common among heavy, more addicted smokers, who typically smoke more than 30 cigarettes per day (Winnipeg Regional Health Authority, 2013), however this practice has been reported to provide only marginal benefit compared to standard dose (RR 1.14 (95% CI 1.01 to 1.29) (Stead, Perera, Bullen et al., 2012). Serious adverse events are highly uncommon with such higher doses, although nonetheless, a dose-response relationship with adverse events is evident (Brokowski, Chen & Tanner, 2014).

Several additional considerations regarding the use and effectiveness of various forms of NRT should be noted. Of particular importance, when compared head to head, the various formulations of NRT are equally effective in achieving cessation (Stead, Perera, Bullen et al., 2012). More smokers however, prefer nicotine patch over the other NRTs, primarily due to their ease of use and once a day administration schedule (Etter & Schneider, 2013). The combination of the short acting nasal spray, lozenge, or gum along with the long-lasting nicotine patch, on the other hand, has been repeatedly shown to be superior to either one single form of NRT promoting higher abstinence rates in the short term (Fiore, Jaen, Baker et al., 2008; Shah, Wilkens, Winkler et al., 2008; Stead, Perera, Bullen et al., 2012). For example, one study comparing the effectiveness of patch + gum to patch alone, found that the combined NRT resulted in higher quit rates at six-month follow-up (28% vs. 15%) but not at one year (18% vs. 13%) (Kornitzer, Boutsen, Dramaix et al., 1995). Further, while product monograph instructions for NRT use recommend initiating use on the day of the quit attempt, starting NRTs several days or weeks prior to the quit date (referred to as "pre-cessation NRT" or 'pre-loading'), has been researched and implemented in clinical practice. The rationale behind this practice rests on the possibility that a lead-in period prior to the quit date would allow individuals to reduce the reinforcing properties of smoking, gain confidence in their quit efforts, familiarize themselves with the product and its administration, as well as adjust the dosage as needed (Carpenter, Jardin, Burris et al., 2013). Reviews of randomized controlled trials using pre-cessation NRT for two to four weeks prior to quitting smoking suggest the effect of pre-cessation treatment on quitting is modest, with approximately half of the reviewed studies reporting non-significant treatment effects (Carpenter, Jardin, Burris et al., 2013; Stead, Perera, Bullen et al., 2012). Pooled

estimates of specifically pre-cessation nicotine patch trials however, have detected treatment effects (RR 1.18, 95% CI 0.98 to 1.41) (Stead, Perera, Bullen et al., 2012), albeit this was primarily driven by one study. The trial reported a near doubling of continuous abstinence rates at 10 weeks post quit date among pre-cessation nicotine patch recipients, an effect that was even more pronounced within less dependent smokers (Rose, Herskovic, Behm et al., 2009). Overall, there is some evidence to suggest that preloading with the patch is more effective for short-term smoking abstinence than more fast onset NRT forms and that the outcomes do not vary as a function of pre-treatment duration (Lindson & Aveyard, 2011).

1.4.2.2 Sustained-Release Bupropion (Bupropion SR)

Bupropion is a weak re-uptake inhibitor of dopamine and norepinephrine in the mesolimbic and nucleus accumbens areas of the brain, as well as an antagonist of nAChRs (Wilkes, 2008). Originally marketed as an atypical antidepressant, the discovery that it reduced cravings, symptoms of withdrawal, and helped people stop smoking (Durcan, Deener, White et al., 2002; Jorenby, Leischow, Nides et al., 1999), led to bupropion's approval for smoking cessation as a sustained-release formulation under the brand names Zyban^{TM} and Wellbutrin^{TM}. Dosing recommendations for this indication advise use of 150mg per day bupropion SR for the first three days and if no significant side-effects are observed, increase the dosing schedule to 150mg twice daily for 7 – 12 weeks (Selby & Samakhvalov, 2012). Because it takes 7-8 days to reach steady state concentration (due to its long half-life of 21hr), smokers are typically advised to set a quit date within one to two weeks after initiating treatment (GlaxoSmithKline, 2011). Bupropion SR is currently available only as prescribed medication either through a physician,

nurse practitioner, dentist or pharmacist. A 2016 review of pharmacists' scope of practice in Canada has reported the prescription and dispensing of bupropion SR and varenicline for smoking cessation as part of pharmacists' prescriptive authority is available in 8 provinces (Canadian Pharmacists Association, 2016).

Several meta-analyses have confirmed the efficacy of bupropion SR (Fiore, Jaen, Baker et al., 2008; Hughes, Stead, Hartmann-Boyce et al., 2014; Hughes, Stead & Lancaster, 2007), with the most recent Cochrane review identifying significantly improved quit rates compared to placebo or no intervention control (Hughes, Stead, Hartmann-Boyce et al., 2014). Outcomes of 17 studies evaluating cessation rates at a 6 month follow-up revealed superior quit rates among the bupropion SR intervention groups, pooled risk ratio of 1.69, 95% CI 1.45 to 1.97, and similar outcomes were noted among 27 studies evaluating a longer efficacy duration of 12 months, risk ratio of 1.59, 95% CI 1.44 to 1.76 (Hughes, Stead, Hartmann-Boyce et al., 2014). The weighted average quit rates for bupropion SR was 18% (range: 4 – 43%), whereas that of placebo was 9% (range: 0 – 33%). While bupropion is also used to treat depression, few studies have evaluated the effectiveness of bupropion SR for smoking cessation among patients with current or past depression. Among patients with current depressive symptoms, a review of five trials involving 410 participants had failed to identify significant benefit of the medication among this particular cohort (RR of 1.37, 95% CI 0.83 to 2.27) (van der Meer, Willemsen, Smit et al., 2013). Conversely, among a similar sample size of smokers with past history of depression, it was concluded that bupropion does appear to increase the odds of cessation compared to placebo (RR of 2.04, 95% CI 1.31 to 3.18), although the small number of studies and post-hoc use of subgroups weakened the evidence. Overall, as strong evidence is lacking for an interaction between bupropion SR's effect on smoking cessation and current or past depression, its

preferential use over other cessation aids in the treatment of these smoker populations is not clearly merited. Further, among non-psychiatric samples, direct comparisons between bupropion SR and NRT also demonstrated similar efficacy in helping people quit smoking (OR of 0.99, 95% CI 0.86 to 1.17) (Cahill, Stevens, Perera et al., 2013).

1.4.2.3 Varenicline

Varenicline is a partial agonist of the α4β2 nAChRs, binding selectively and with greater affinity than nicotine. It is hypothesized to have a dual mechanism of action of: a) inducing mesolimbic dopamine release via α4β2 receptor-mediated activity, but to a lesser extent than nicotine, which ultimately leads to relief of cravings and withdrawal of symptoms from smoking cessation, and b) antagonising the activity of nicotine through high affinity for α4β2 receptors, blocking nicotine-induced dopamine activation (Rollema, Chambers, Coe et al., 2007; Tonstad & Rollema, 2010). Prescribing recommendations advise the implementation of a 12-week treatment regimen involving an initial, 1-week titration period of 0.5mg daily on days 1-3, followed by 0.5mg twice daily for days 4 -7. Upon smoking cessation and for the subsequent 11 weeks, the recommended dosage is 1mg twice daily. Some evidence is available however, that flexible, self-regulated dosing regimens can have superior effectiveness compared to placebo and longer (4-week) pre-treatment periods result in higher abstinence rates compared to standard dosing (Hajek, McRobbie, Myers et al., 2011; Niaura, Hays, Jorenby et al., 2008). Because varenicline does not undergo significant hepatic metabolism and its renal clearance is dose-proportional, dose adjustment is necessary particularly for patients with severe renal impairment. Similar to

bupropion SR, varenicline is a medication which can only be prescribed by physicians, nurse practitioners, dentists and pharmacists.

The therapeutic efficacy of varenicline has been established through a number of well-designed placebo randomized controlled trials (RCT)s. For instance, a Cochrane network meta-analysis of 14 placebo-RCTs, involving over 6,000 participants, concluded that varenicline use resulted in increased rates of biochemically validated continuous abstinence for 6 months (RR of 2.27, 95% CI 2.02 to 2.55) (Cahill, Stevens, Perera et al., 2013). The analysis further compared varenicline to both NRT and bupropion SR, revealing that it is over 50% more effective than either of the other two first-line pharmacotherapies, with odds ratios (OR)s of 1.57, 95% CI 1.29 to 1.91 and 1.59, 95% CI 1.29 to 1.96, respectively. Additional benefits of varenicline have been noted upon re-initiation in patients who had previously failed with varenicline and had not made a quit attempt in the past 3 months as well as via a maintenance therapy of an additional 12-week treatment period (Gonzales, Hajek, Pliamm et al., 2014; Tonstad, Tonnesen, Hajek et al., 2006).

It is important to recognize that since the initial approval of varenicline and bupropion for smoking cessation treatment, data from post-marketing surveillance reports have suggested an increased incidence of suicidal ideation, aggression, and suicidal, self-injurious behaviour with these medications (Harrison-Woolrych & Ashton, 2011; Kuehn, 2012; Moore, Glenmullen & Furberg, 2010). In response, in 2009 the U.S. Food and Drug Administration (FDA), required for labels of both medications to carry black box warnings (the strongest safety warnings administered by the agency), alerting physicians and patients of increased risk of neuropsychiatric events. It is these indications that likely contributed to cessation medication fears among both physicians and patients, as evidenced by a 25% decrease in the number of

varenicline units dispensed in England from their peak in 2011 (Primary Care Team Health and Social Care Information Centre, 2014), and helped establish NRT as the dominant pharmacotherapeutic quitting method (Morphett, Partridge, Gartner et al., 2015; Thomas, Abramson, Bonevski et al., 2015). Over the course of the past 5 - 7 years however, results from RCTs and several meta-analyses evaluating the safety and efficacy of these medications, have challenged FDA's assertion of greater harm (Thomas, Martin, Knipe et al., 2015; Wightman, Foster, Krishen et al., 2010). For example, a systematic review and meta-analysis of 39 RCTs involving over 10,000 participants had found no evidence of increased risk of suicide or attempted suicide (OR of 1.67, 95%CI 0.33 to 8.57), suicidal ideation (OR of 0.58, 95% CI 0.28 to 1.20), depression (OR of 0.96, 95% CI of 0.75 to 1.22), irritability (OR of 0.98, 95% CI 0.81 to 1.17), aggression (OR of 0.91, 95% CI of 0.52 to 1.59), or death (OR of 1.05, 95% CI 0.47 to 2.39) with varenicline compared to placebo (Thomas, Martin, Knipe et al., 2015). Similarly, a meta-analysis of suicidal behaviour and ideation among the depressive disorder population, who are at an increased risk of these behaviours, found there was no statistically significant difference between those taking bupropion and placebo (OR of 1.28, 95% CI 0.59 to 2.86), and the incidence of these behaviour was very low (0.48% to 0.53%) (Wightman, Foster, Krishen et al., 2010). Results from one of the largest multi-centre placebo controlled RCTs, involving more than 8,000 participants across 16 countries, further indicated no elevated risk of neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo (Anthenelli, Benowitz, West et al., 2016). These latter outcomes, combined with evidence from prospective studies and meta-analyses, were instrumental in guiding the recent FDA decision on December 16, 2016 to remove the black box warnings for both varenicline and bupropion. Their labels however, nonetheless indicate that neuropsychiatric adverse events can occur. Prescribers

are advised to observe patients attempting to quit smoking for the occurrence of such symptoms and patients are recommended to discontinue the drug if they experience such adverse events.

1.4.3   Effectiveness of Over-The-Counter Nicotine Replacement Therapy

The efficacy of NRT has now been well established through meta-analyses of over 100 RCTs concluding that NRTs nearly double the odds of cessation (Cahill, Stevens, Perera et al., 2013; Fiore, Jaen, Baker et al., 2008). Almost all trials included in the meta-analyses, however, were conducted in clinical settings and provided some degree of behavioural support to help smokers with their quit efforts, unlike when NRT is purchased over-the-counter (OTC). As most OTC NRT users do not receive any behavioural counselling (Cummings & Hyland, 2005), suspicion arose that the efficacy of NRT in clinical settings may not be translatable to its "real-world" effectiveness. Indeed, through large population surveys in California between 1992 and 1999, Pierce and Gilpin (2002) had demonstrated that while NRT use and cessation attempts had increased in several years following the approval of OTC sale of NRT, a long-term cessation advantage could not be seen. Other research further questioned the population-level effectiveness of NRT altogether (Alpert, Connolly & Biener, 2013; Kotz, Brown & West, 2014a, 2014b). For example, Alberg et al. (2005) had found that in a prospective study of a cohort of 1,954 adult smokers surveyed in 1989 and res-surveyed in 1998, those who had ever used NRT were significantly less likely to quit smoking compared to those who had never used NRT. Another prospective survey of 1560 adult smokers who participated in an English national household survey found that while use of prescribed NRT in combination with specialist behavioural

support was associated with over 2.5 times increased odds of cessation at a 6-month follow-up, those who had bought NRT over the counter were less likely to quit than smokers who had not used any cessation aids (Kotz, Brown & West, 2014a). In contrast, research from the International Tobacco Control (ITC) survey of a cohort of recently quit smokers from United Kingdom, Canada, Australia and United States presented contradictory evidence, demonstrating that nicotine patch users, but not other forms of NRT, were more likely to maintain 6-month continuous abstinence compared to those who attempted to quit without medication (adjusted OR of 4.09, 95% CI 1.72 to 9.74) (Kasza, Hyland, Borland et al., 2013). Taken together, such contradictory evidence certainly questions the effectiveness of NRT outside of specialized treatment settings. Being limited to prospective and cross-sectional designs however, these studies were vulnerable to confounding factors that may have influenced the likelihood of quitting in 'unsupervised' settings. Randomized controlled trials on the other hand, where efforts are taken to contain confounding variables and bias is presumed to be equally spread across conditions, would thus be necessary to ascertain NRT effectiveness in real-world settings causal certainty.

To determine whether OTC NRT is pharmacologically efficacious outside of clinical settings, Hughes et al. (2003) conducted two meta-analyses of RCTs, one, comparing the efficacy between freely provided OTC NRT and free OTC placebo, and another, comparing purchased OTC NRT with prescribed NRT. A meta-analysis of four trials comparing free OTC transdermal patch versus OTC placebo concluded that the patch was significantly more efficacious (OR of 2.5, 95% CI 1.8 to 3.6) at 6-month follow-up. The other meta-analysis of two RCTs and two non-randomized trials revealed that both OTC NRT and prescribed NRT produced equivalent quit rates and similar odds of cessation (OR of 1.4, 95% CI 0.6 to 3.3)

(Hughes, Shiffman, Callas et al., 2003). Although the authors of the meta-analyses concluded that OTC NRT was more efficacious than placebo and produced modest (7%), long-term quit rates similar to those seen when NRT is prescribed by a physician in "real-world" practice, the reviewed studies cannot be described as testing the efficacy of NRT completely in absence of behavioral support. All trials entailed between 3 and 10 face-to-face visits with researchers or pharmacists and thus likely received either brief advice or instructions on NRT use, possibly improving their chances of quitting. This is highly divergent from how NRT is typically purchased and used OTC, where only a small proportion of NRT users report being advised on cessation by pharmacists (Paul, Walsh & Girgis, 2003). Additionally, smokers purchasing NRT from supermarkets or via the Internet receive no advice or audio-visual support for cessation. Therefore, the superiority of OCT NRT over placebo or unaided cessation has not been convincingly demonstrated.

In reviewing the Hughes et al. meta-analyses and methodological differences of RCTs evaluating the effectiveness of OTC NRT, Walsh (2008) proposed several recommendations for improving the quality, generalizability, and reporting of such trials. It was acknowledged that while it is difficult to simulate typical OTC conditions in a randomized controlled trial, employing the below recommendations (Table 1) could help resolve whether a net benefit of OTC NRT is present.

Table 2. Recommendations for improving the quality, generalizability and reporting of NRT trials in OTC or minimal intervention environments (Walsh, 2008).

Feature	Number	Recommendation
Study/ author sponsorship and relationship	1	Provide full details of pharmaceutical industry finding and links
Randomization	2	Document method of randomization
Recruitment	3	Consider proactive telephone recruitment strategies
	4	Estimate population reach in large-scale effectiveness trials
Eligibility	5	Minimize eligibility criteria
	6	Document proportion of screened subjects judge eligible
	7	Document proportion of eligible subjects consenting
NRT cost	8	Do not provide NRT free, where feasible, unless this is being considered as a permanent population strategy.
Personal contact	9	Document approximate duration of screening, assessment & intervention contacts
	10	Minimise number of visits and phone calls
Assessment	11	Eliminate/minimise medical aspects of screening/assessment
	12	Eliminate/minimize self-monitoring tasks
	13	Collect limited data to allow comparisons with smokers in the general population
	14	Evaluate NRT compliance at end of treatment
	15	Assess integrity of subject blindness at end of treatment
Follow-up	16	Follow-up all subjects, not just returnees or past visit abstainers
	17	Blind follow-up assessors
	18	Incorporate 12-month measurement or longer
	18	Report drop-out rates
Outcomes	19	Report both point prevalence and sustained/continuous cessation proportions

1.4.4 Mailed Distribution of Free NRT

Following the switch from NRT availability by prescription to OTC, NRT use rates increased by over 50% (Hyland, Rezaishiraz, Giovino et al., 2005; Pierce & Gilpin, 2002). This increase in NRT accessibility and subsequent utilization however, did not result in greater effectiveness, with some evidence even showing that quit rates with nicotine patch being lower in the post-OTC period (Hyland, Rezaishiraz, Giovino et al., 2005). One plausible explanation to these observations was that use of NRT in the OTC setting was led by individuals with less desire to stop smoking, thus while increased NRT accessibility encouraged smokers to make a quit attempt, actualized cessation was compromised in absence of physician advice or support. Another explanation rested on findings that quit attempts were less likely to be accompanied by attendance to a stop smoking program and that the duration of NRT use was reported to decrease following the OTC switch (Hyland, Rezaishiraz, Giovino et al., 2005). With less oversight on how the medications are taken and presumably minimal counselling throughout a cessation attempt, the net public health benefit of OTC NRT could not be readily seen. Further, because insurers typically only reimburse the cost of prescription only medications, OTC NRT availability meant that smokers began to bear the bulk of NRT-related costs. Indeed, Hyland et al. (2005) reported that insurance coverage decreased by approximately 50% since NRT became available OTC. With cost of NRT remaining a significant barrier to using NRT for many years after OTC NRT availability (Bansal, Cummings, Hyland et al., 2004; Land, Warner, Paskowsky et al., 2010; Leatherdale & Shields, 2009; Vogt, Hall & Marteau, 2008), efforts were undertaken to reduce this barrier and increase smokers' chances of quitting by offering cost-free (to smokers) or discounted NRT via smokers' helplines. Given that the best absolute quit rates are

achieved through a combination of counselling and pharmacotherapeutic support (Fiore, Jaen, Baker et al., 2008), the availability of free NRT was thought to broaden the accessibility to and reach of efficacious smoking cessation treatment, encourage more smokers to quit, as well as strengthen the individual effectiveness of smokers' helplines and NRT outside of the clinical setting.

Since their inception in early 2000's, nearly a dozen initiatives offering free NRT through smokers' helplines or specialized programs have now been evaluated. Typically, these select smokes' helplines advertise the availability of free NRT through various media outlets, including TV, radio, and direct mail, inviting smokers interested in quitting to call a toll-free telephone number. To receive the free NRT (most commonly in the form of the patch), smokers must meet some initial criteria, consisting of a) 18 years or older, b) speak English, c) smoke a minimum of 5 to 10 cigarettes per day, d) have a working telephone number, e) be willing to receive pro-active counselling and follow-up phone calls, f) willing to set a quit date between 7 to 30 days from initial call, and g) have no contraindications for NRT use. The number of phone calls and the extent of the phone-based intervention has varied across programs, however, most counselling calls were provided by experienced tobacco treatment specialists who initially helped individuals prepare for a quit attempt, understand their tobacco use patterns and triggers, and develop coping skills to deal with cravings. Additional educational information was also provided on the benefits and proper use of NRT, as well as management of their side-effects (Bush, McAfee, Deprey et al., 2008; McAfee, Bush, Deprey et al., 2008; Miller, Frieden, Liu et al., 2005; Swartz, Cowan, Klayman et al., 2005; Tinkelman, Wilson, Willett et al., 2007). While individuals eligible for participation in such programs most commonly received 2 to 8 weeks of NRT directly mailed to their homes, some programs sent smokers vouchers for free NRT to be

claimed at participating pharmacies (Bauer, Carlin-Menter, Celestino et al., 2006; Cummings, Hyland, Fix et al., 2006; Swartz, Cowan, Klayman et al., 2005). A 2004-5 survey of smokers' helplines in North America (52 helplines in the US and 10 in Canada participating) had reported that approximately 35% of all US helplines and none in Canada had provided free cessation medications (Cummins, Bailey, Campbell et al., 2007).

The vast majority of studies examining the impact of offering and mailing free NRT through smokers' helplines or specialized distribution programs have been conducted in the U.S. Success of such programs was primarily determined via comparison of smoking abstinence rates at 6 or 12 months follow-up before and after program implementation, however helpline utilization and cost-effectiveness (i.e., program cost associated with one individual achieving cessation) have also been commonly evaluated. For instance, Tinkelman et al. (2007) had documented considerable interest in the availability of free NRT from the Ohio State quitline, as evidenced by more than 140% increase in average daily call volume compared to a 9-month period immediately preceding its availability. Using intent to treat analyses, such that those who could not be contacted at follow-up were considered active smokers, the 7-day point prevalence abstinence at 6-month follow-up increased from 10.3% before NRT availability to 14.9% after a 4-week supply of nicotine patches was made available (Tinkelman, Wilson, Willett et al., 2007). Similarly, Bush et al. (2008) reported that through the Oregon State quitline, the 6 month follow-up, 7-day point prevalence quit rate was 17.0% following the availability of 2 weeks of mailed free nicotine patches, compared to 9.3% among pre-initiative controls. Overall, recipients of the free NRT were 2 times more likely to quit than pre-initiative controls, were 1.6 times more likely to be very or somewhat satisfied with the Oregon quitline, and the majority of follow-up survey respondents stated that they would not have obtained the patches if they were not offered for free

(Bush, McAfee, Deprey et al., 2008). Analyses of the program's cost effectiveness revealed that while total annual costs of the programme were 30% more than the cost of the pre-initiative programme, the total cost per quit was $2688 lower for the free NRT recipients ($1050). Similar intervention costs per quit were observed in Maine ($1344) (Swartz, Cowan, Klayman et al., 2005) and slightly larger in Minnesota ($1934) (An, Schillo, Kavanaugh et al., 2006). Altogether, the Oregon free NRT distribution initiative cost $86 more per additional life-year-saved (Fellows, Bush, McAfee et al., 2007). These costs compare very favorably with the cost-effectiveness of other commonly provided preventative and healthcare services, where for instance, the cost of biennial mammography screening in Canada is $87,420 per each life-year-saved (Mittmann, Stout, Lee et al., 2015).

Several prospective cohort studies, where a cohort of mailed NRT recipients were compared to a similar, non-randomly allocated cohort of no intervention controls, have also found greater quit rates among those who received the free NRT. In 2003, the New York State Department of Health and the Roswell Park Cancer Institute undertook a large-scale distribution effort of free NRT, sending a 6-week course of nicotine patches to over 34,000 interested and eligible smokers (Miller, Frieden, Liu et al., 2005). At a 6-month follow-up, the 7-day point prevalence quit rates were compared between a randomly selected sample of 1305 responders and a non-randomly selected group of 159 eligible smokers who, because of mailing errors, did not receive the patches. Quit rates were found to be 33% among nicotine patch recipients and 6% among the non-NRT cohort. Among the nicotine patch recipients, receipt of counselling calls and use of all the patches received were associated with greater likelihood of quitting smoking (Miller, Frieden, Liu et al., 2005). The sole Canadian exploration of mailed NRT program effectiveness, that compared recipients of mailed 5 weeks of NRT (66.7% opted and received

patch; 33.3% opted and received gum) to a random cohort of smokers from the Ontario Tobacco

Survey, found that NRT recipients were 1.81 times more likely to achieve 30-day smoking

abstinence at 6 months (Zawertailo, Dragonetti, Bondy et al., 2013). Further, Canadian cost-

effectiveness data was provided, demonstrating that the cost per quitter amounted to

approximately $1720 CAD, assuming that non-responders at follow-up were active smokers.

　　　Taken together, such accrual of evidence is certainly suggestive that the mailed

distribution of NRT is cost-effective and helps smokers quit. However, in absence of studies

with randomly allocated control groups, causality could not be inferred from these findings that

it is indeed the provision of NRT that is responsible for the observed treatment effect. As

systematic differences between NRT recipients and comparative cohorts of non-NRT users may

have contributed to the likelihood of achieving cessation, a well conducted randomized

controlled trial would be necessary to conclude with confidence that mailed free NRT provision

is efficacious in promoting smoking abstinence. One randomized controlled trial has showed no

additional benefit of providing free NRT or proactive counseling as part of a British national

quitline, compared to standard care (Ferguson, Docherty, Bauld et al., 2012). In fact, the trial

demonstrated that eligible callers randomized to receive 3 weeks of nicotine patches exhibited

lower carbon-monoxide validated prolonged quit rates (6.6%) at 6 months compared to those not

offered NRT (9.4%) (Adjusted OR of 0.65, 95% CI 0.48 to 0.88). Similar odds of self-reported

cessation, albeit with greater quit rates, were reported among the two groups. While the trial was

limited by low (58%) follow-up rates and confirmation of smoking status was attempted only

among those self-reporting abstinence (thus contributing to reluctance among NRT recipients to

verify smoking status), more importantly, the findings could not be directly generalized to the

North American setting. Given that support for smoking cessation (including NRT) in Britain is

available to all smokers either for free or at a relatively low cost, the offer of free NRT is not as pronounced of an incentive to quit when its cost is not a barrier to accessing treatment. Therefore, to definitively answer whether the offer and mailed provision of free NRT would be beneficial in helping smokers quit in the Canadian setting, a randomized controlled trial with random assignment to receive or not receive NRT would be necessary.

1.4.5   Randomized Controlled Trial of Mailed Free NRT to Canadian Smokers

In an effort to determine the effectiveness of the mass distribution of free NRT and the effectiveness of NRT in naturalistic settings, a research team consisting of scientists and clinicians at the Centre for Addiction and Mental Health and the University of Waterloo, conceived a randomized controlled trial (RCT) to evaluate whether the mass distribution of free nicotine patches without behavioural support significantly increases quit rates above those who do not receive patches. As the project manager on the team, I oversaw all implementation and operational aspects of the trial, while also developing all surveys, trial protocol, standard operating procedures, as well as overseeing all data collection and analysis efforts. The study protocol was published in the BMC Public Health journal in 2011 (Cunningham, Leatherdale, Selby et al., 2011).

Briefly, this trial was designed to employ a single blinded, panel survey design, with random assignment to an experimental and a control group. A two-stage recruitment process was employed, in the context of a general population survey with two follow-ups (8 weeks and 6 months). Using random digit dialing of Canadian home and cellular telephone numbers,

households were identified with adult (18 years of age or older) smokers who smoked 10 or more cigarettes per day and were willing to take part in a smoking study that involved three interviews (baseline, 8-week and 6-month follow-ups), with saliva collection for 3-HC/cotinine ratio measurement at baseline and saliva cotinine verification of smoking status at 8-week and 6-month follow-ups. The sampling procedure was based on population distribution estimates across the Canadian provinces and territories from the 2011 census data (Statistics Canada, 2016). The trial aimed to contact 3,290 individuals in order recruit 1,000 smokers for the randomized controlled trial. As part of the baseline survey, eligible subjects were identified for the second recruitment stage - randomization of smokers into experimental and control groups to receive versus not receive 5 weeks of free nicotine patches. The 5-week course of nicotine patches (to be mailed via expedited postal mail and consisting of a tapered regimen of 3 weeks of 21mg patches, 1 week of 14mg patches, and 1 week of 7mg patches) was chosen because it mimicked the quantity of nicotine patches sent in the Ontario-based mass distribution initiative (STOP Study) and was in line with the amount of nicotine patches mailed in other mass distribution initiatives (Cummings, Fix, Celestino et al., 2006; Zawertailo, Dragonetti, Bondy et al., 2013).

Eligibility for the RCT component of the study was determined by a series of questions regarding hypothetical interest in nicotine patches to quit smoking (including willingness to have nicotine patches sent to their home and use them within one week of receipt), having no contraindications for using nicotine patches, and having a home address that was not a post-office box (for timely delivery of nicotine patches and saliva sample kits). Specifically, participants were asked: "The Ministry of Health is considering different ways to help people stop smoking. One option would be to provide interested smokers with free nicotine patches. If

nicotine patches were offered for free, would you be interested in receiving them?" Those who expressed hypothetical interest in receiving nicotine patches were further asked if they would use them within 1 week to quit smoking and whether they were willing to have the patches sent to their home. All completers of the baseline survey were also asked whether they had contraindications for nicotine patch use as stipulated in the product monograph, namely being pregnant, intending to become pregnant, breastfeeding, having a serious heart or circulation problem (not including high blood pressure), and hypersensitivity of the skin to nicotine patch or tape. Participants who did not meet eligibility for the randomized controlled trial were thanked for their participation in the survey and were not recontacted for the follow-up surveys.

Of subjects meeting eligibility criteria, a randomized half were informed that "As part of a pilot trial, the Centre for Addiction and Mental Health has a supply of nicotine patches to distribute to interested smokers. You told us that you would be interested in receiving a free supply of nicotine patches. Do we have your permission to mail them directly to your home?" Individuals having a valid home address and answering 'yes' to this question were subsequently sent a nicotine patch kit containing the 5-week regimen of nicotine patches, a cover letter instructing them on the recommended use of nicotine patches, a list of commonly asked questions (with answers) on NRT and specifically patch use, and advice to consult their physician or pharmacist if they had any further questions. No other assistance of any kind was provided. The nicotine patches used as part of this trial were purchased at below retail value through an open tender contract; the vendor had no role in the design or conduct of the study, nor the collection, management, analysis or interpretation of the data.

Subjects randomized to the no-intervention control group were not offered free nicotine patches to be sent to their home and were not informed of this offer to others. In fact, participants

in the trial were not informed that they were taking part in a randomized controlled trial and of the existence of separate trial groups. Thus, control group participants had no expectation that they would receive anything and were blinded to the nicotine patch offer. At the completion of the baseline survey, participants in the control group were simply informed that they would be recontacted at the next follow-up survey "to ask some more questions related to smoking". All participants in the RCT were followed-up by telephone at 8 weeks and 6 months, with interviewers being masked to participants' group at each follow-up (ensured through the use of the computer-assisted telephone interviewing program used to complete all surveys).

Upon completion of the baseline survey, all subjects were mailed a $20 honorarium cheque. Those eligible for the RCT were also sent a Salivette saliva sample collection kit (Sarstedt AG & Co.) for confirmation of smoking status and measurement of the nicotine metabolic (3-HC/cotinine) ratio. One week prior to the scheduled 8-week and 6-month follow-up interviews, subjects were again sent $20 cheques and saliva sample kits. As an added incentive for the return of saliva samples, all subjects were further informed that upon submission of saliva samples they would receive $10 for each sample. The primary and secondary outcomes of this trial, respectively, were 30-day point prevalence smoking abstinence at 6 months, defined as not smoking even a puff in the past 30 days, and 7-day point prevalence at 8 weeks, defined as not smoking even a puff in the past 7 days.

Primary outcomes of the core trial were recently published in the JAMA Internal Medicine journal (Cunningham, Kushnir, Selby et al., 2016). In brief, the findings revealed that the provision of free nicotine patches via mail, in absence of behavioural support, resulted in more than a doubling of self-reported 30-day abstinence quit rates at the 6-month follow-up compared

to the no-intervention control group (Intent to treat: 7.6% versus 3.0%; odds ratio of 2.65, $p =$ .002; Complete case: 9.8% versus 3.6%; odds ratio 2.89, $p = .001$). Unfortunately, despite following postal mail saliva collection protocols used in other research (Binnie, McHugh, Macpherson et al., 2004; Etter, Neidhart, Bertrand et al., 2005), a large proportion of participants did not return usable saliva samples. Biochemical validation of smoking abstinence could thus be conducted of 50.9% participants who self-reported abstinence at 6 months, reducing confidence in the validity of biochemically validated abstinence. Large population-based studies however are considered to be largely exempt of the same biases observed in clinical settings and do not require biochemical validation of tobacco cessation (Patrick, 1994; SRNT Subcommittee on Biochemical Verification, 2002; West, Zatonski, Przewozniak et al., 2007; Wong, Shields, Leatherdale et al., 2012). Nonetheless, nicotine patch recipients were significantly more likely to have biochemically verified smoking abstinence at 6-months, compared to the no-intervention control group (2.8% versus 1.0%; odds ratio 2.85, $p = .046$).

The trial design has a number of strengths that made it ideal not just for determining with strong evidence whether mailed free NRT is an effective approach in promoting cessation, but also for studying important factors that enable and hinder the effectiveness of the approach. First, the random allocation of participants to experimental and control groups is considered the gold-standard approach in clinical trial experimentation as it minimizes possible sources of bias and confounding variables. Second, by providing nicotine patches in absence of any other forms of smoking cessation assistance the trial effectively mimicked how NRT is commonly used in "real-world" world settings, thus increasing the generalizability of the study findings. Third, masking of interviewers to participants' condition at the point of outcome assessment, as well as

participants not being informed that they were taking part in a randomized trial, increased the

likelihood of accurate reporting by eliminating observer and subject bias. This was further

heightened by asking all subjects to submit a saliva sample at follow-up, irrespective of self-

reported abstinence. Overall, the trial design could positively address 16 of 19 recommendations

made by Walsh (2008) for establishing the real-world/ OTC benefit of NRT. As such, given the

strong design of the RCT and the trial's large scope, from its inception I recognized that it was

opportune for also exploring important issues surrounding the mechanisms and implications of

the mailed, mass distribution of free NRT model for promoting smoking cessation. With an

interest in exploring the effectiveness of free NRT distribution among smokers with mental

health comorbidities, examining predictors of NRT utilization and cessation, as well as

uncovering the broader implications of this cessation approach in promoting additional help-

seeking, I proposed and incorporated independent research questions into its design and survey

development process. The trial thus formed the basis for the present doctoral work.

1.4.6 Factors Associated with Smoking Cessation Success

Numerous factors have been demonstrated to directly influence the likelihood of smoking

cessation, and specifically smoking cessation using NRT. While some are inter-related and can

be compounded to increase or decrease the chances of smokers successfully quitting, these

factors can be grouped into 6 broad categories of socioeconomic/demographic, individual-level,

smoking history, environment, support-level and community/social-level indicators of cessation success.

There is considerable evidence that the prevalence of smoking is disproportionately higher among adults who have lower levels of education, unemployed, or who are within lowest income levels, collectively considered as low socioeconomic status (SES). For example, in 2014, individuals in the U.S. below the poverty level were nearly twice as likely to smoke as those at or above the poverty level (Jamal, Homa, O'Connor et al., 2015). In the developing countries, this disparity in smoking prevalence by SES is even greater (Bobak, Jha, Nguyen et al., 2000; Hosseinpoor, Parker, Tursan d'Espaignet et al., 2011). Accordingly, the burden of tobacco use and related diseases among those in lower SES groups is also proportionally greater, such that the most economically deprived groups and those with less than high school education have higher incidences of lung cancer (Clegg, Reichman, Miller et al., 2009; Singh, Williams, Siahpush et al., 2011). When it comes to cessation, there is also evidence to suggest that SES and demographic factors play an important role in the likelihood of attempted and successful cessation. For instance, findings from the ITC survey involving more than 16,000 responders have revealed that smokers with university or higher education were more likely to intend to quit, attempt to quit, as well as successfully quit for at least 1 to 6 months, compared to those with high school education or less (Reid, Hammond, Boudreau et al., 2010). While the study also noted that higher income levels were associated with increased odds of cessation only in the short term, a systematic review of demographic predictors of smoking cessation success found that such associations were not consistent throughout various samples (Vangeli, Stapleton, Smit et al., 2011). Interestingly, higher social grade and occupational status are associated with greater likelihood of quitting (Fidler & West, 2011; Ham, Przybeck, Strickland et al., 2011; West,

McEwen, Bolling et al., 2001), and some evidence is available that older smokers are also more likely to be successful in their quit efforts (Li, Borland, Yong et al., 2010). Pooled analyses however failed to find an association between quit success and either gender or marital status (Vangeli, Stapleton, Smit et al., 2011).

In addition to the influence of social determinants of health on the likelihood of cessation, considerable individual variability is also present. For example, several independent clinical trials have provided strong evidence that smokers who are fast metabolizers of nicotine, as indicated by the 3-HC/cotinine (nicotine metabolic ratio or 'NMR'), are significantly less likely to quit smoking using nicotine patches, compared to smokers who are slow nicotine metabolizers (Kaufmann, Hitsman, Goelz et al., 2015; Lerman, Tyndale, Patterson et al., 2006; Schnoll, Patterson, Wileyto et al., 2009). Mental health status among smokers has also been shown to negatively affect the odds of cessation. Population-level research on the well-documented comorbidity between smoking and mental illness has consistently shown that adult smokers with lifetime, past year, and current diagnoses of mental illness had considerably lower cross sectional and longitudinal quit rates, compared to those with no mental illness (Donald, Chartrand & Bolton, 2013; Lasser, Boyd, Woolhandler et al., 2000; Smith, Mazure & McKee, 2014). Other individual-level factors such as motivation to quit, confidence in quitting, and perception of smoking cessation aids must also be recognized as stable determinants of making a serious quit attempt, although evidence on their proximal impact on cessation is mixed (Borland, Owen, Hill et al., 1991; Borland, Yong, Balmford et al., 2010; Dijkstra, de Vries & Bakker, 1996; Vangeli, Stapleton, Smit et al., 2011).

Among the predictors of cessation related to smoking history, it is well known that smokers with greater levels of nicotine dependence and smoking more cigarettes per day have

greater difficulty in adhering to treatment and quitting smoking than less dependent smokers, thus being proportionally less likely to do so (Balmford, Borland, Hammond et al., 2011; Breslau & Johnson, 2000; Fiore, Jaen, Baker et al., 2008; Killen, Fortmann, Kraemer et al., 1992). Conversely, those with lower levels of nicotine dependence or smoke fewer cigarettes per day have greater odds of successfully quitting smoking. Individuals who have made previous quit attempts, have used smoking cessation aids in the past, and quit for longer periods of time are further more likely to succeed in quitting (Hyland, Borland, Li et al., 2006; West, McEwen, Bolling et al., 2001; Zhu, Sun, Billings et al., 1999).

The environment within which a smoker resides or is exposed to also greatly affect whether a smoker is successful in their quit efforts. Specifically, having a smoke-free home and smoking restrictions in public and workplaces is believed to create barrier for continuous cigarette consumption and reinforces smoking behaviour change among those motivated to quit. Indeed, data from large population surveys have shown that NRT, bupropion, or both were significantly more effective if individuals resided in a smoke-free home and had no other smokers in the household (Gilpin, Messer & Pierce, 2006). Relatedly, smoking-associated environmental stimuli, such as seeing someone smoke or tobacco advertising, have been demonstrated to elicit conditioned craving responses that may undermine quit attempts (Hutchison, Niaura & Swift, 1999; Niaura, Rohsenow, Binkoff et al., 1988). Neuroimaging studies have repeatedly demonstrated that the presentation of smoking-related cues to smokers is associated with activation of the mesocorticolimbic dopamine reward pathway in the brain, similar to the effects of nicotine administration (Brody, Mandelkern, London et al., 2002; McBride, Barrett, Kelly et al., 2006; McClernon, Hiott, Huettel et al., 2005; Rose, Behm,

Westman et al., 2003). Exposure to such highly salient stimuli has thus been suggested to reinforce continued smoking as well as contribute to relapse during periods of abstinence.

Many support level factors also influence the likelihood of smoking cessation, including access to treatment (Jardin, Cropsey, Wahlquist et al., 2014), the treatment type alone or in combination (e.g., pharmacotherapy , cognitive behavioural therapy, motivational interviewing, group therapy or individual therapy) (Fiore, Jaen, Baker et al., 2008), as well as treatment duration and adherence (Raupach, Brown, Herbec et al., 2014; Siahpush, Shaikh, McCarthy et al., 2015; Zhang, Cohen, Bondy et al., 2015). Lastly, community efforts related to anti-tobacco media campaigns as well as social attitudes/norms towards smoking and smokers are believed to motivate smokers to quit (Cowling, Modayil & Stevens, 2010; National Cancer Institute, 2008). Directly quantifying their impact on cessation however has been challenging, and may reflect more of a contributory role among other factors.

1.5   Restatement of Research Objectives

1.5.1   Overall Purpose

There is currently limited knowledge on the determinants of smoking cessation success as part of the mailed distribution of free NRT paradigm. While there is suggestive evidence that the provision of free NRT as part of smokers' helplines aids in driving increased cessation rates, the effectiveness of the mailed distribution approach has not been well established, and the

underlying factors that predict or mediate its effectiveness have not been explored. The aim of the present research line was thus to gain a more comprehensive understanding of individual and treatment-level factors that may mediate the effectiveness of this population-level approach in helping smokers quit. Specifically, the research attempted to elucidate the influence of mental illness on free NRT distribution effectiveness, uncover which demographic and smoking history factors influence NRT utilization and cessation following the provision of free NRT, and further, explore whether the mailed free NRT smoking cessation paradigm promotes further help-seeking from primary care providers.

1.5.2   Specific Research Objectives

1.5.2.1 Impact of Self-Reported Lifetime Depression or Anxiety on Effectiveness of Mass Distribution of Nicotine Patches (Manuscript 1)

The objective of the study was to examine the influence of lifetime history of depression and/or anxiety on smoking cessation success following the free distribution of nicotine patches. The research attempted to answer the question: Are smokers with lifetime depression or anxiety as likely to quit as smokers without such diagnoses when provided free NRT, compared to those not offered NRT?

1.5.2.2 Mailed Distribution of Free Nicotine Patches Without Behavioral Support: Predictors of Use and Cessation (Manuscript 2)

The objective of the study was to evaluate which *a-priori*-defined demographic and smoking history factors previously shown to be associated with purchase and use of over-the-counter NRT predict use of a 5-week course of mailed free nicotine patches (without any additional counselling or support), among smokers expressing interest in using free NRT to quit smoking. Further, the study aimed to explore reasons for not using freely provided nicotine patches and investigate the association between use of nicotine patches and cessation at a 6-month follow-up.

1.5.2.3 Unassisted Smoking Cessation: The Role of Motivation and Personality Factors (Manuscript 3)

The objective of the study was to retrospectively evaluate what role motivational reasons for quitting smoking and personality factors play in determining the quit methods used by smokers to achieve cessation.

1.5.2.4 Impact of Large-Scale Distribution and Subsequent Use of Free Nicotine Patches on Primary Care Physician Interaction (Manuscript 4)

The objective of the study was to examine whether and to what extent the provision of free NRT impacts smokers' interaction with primary care physicians. In particular, the research attempted to answer the question: Does the provision and subsequent use of free nicotine patches to smokers interested in quitting promote interaction with their primary care physicians, and whether that interaction has a role in quitting smoking?

Chapter 2: Impact of Self-Reported Lifetime Depression or Anxiety on Effectiveness of Mass Distribution of Nicotine Patches (Manuscript 1)

Manuscript citation:

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Impact of self-reported lifetime depression or anxiety on effectiveness of mass distribution of nicotine patches

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Abstract

Background: Large-scale public health initiatives providing free nicotine replacement therapy have been shown to increase smoking cessation rates, however their effectiveness among the highly prevalent population of smokers with depression and anxiety disorders has not been explored. The aim of this study was to investigate the influence of lifetime history of depression or anxiety on smoking cessation success following the free distribution of nicotine patches.

Method: In the context of a randomized controlled trial, a secondary analysis was conducted on 1000 adult regular smokers randomized to be mailed a 5-week supply of nicotine patches or to a no intervention control group. Participants were divided into subgroups based on presence of self-reported lifetime diagnosis of depression and anxiety.

Results: Irrespective of self-reported lifetime history of depression or anxiety, odds of self-reported cessation at 6 months were significantly greater among groups receiving nicotine patches compared to no intervention control (no history of depression or anxiety: OR of 2.20; 95% CI 1.05 to 4.63; history of depression or anxiety present: OR of 3.90; 95% CI 1.28 to 11.88). Among nicotine patch recipients only, quit outcomes did not differ between those with and without self-reported lifetime depression or anxiety in models unadjusted and adjusted for differences in demographic and smoking characteristics.

Conclusions: The mass distribution of free nicotine patches (without behavioral support) is effective among smokers with or without lifetime history of depression or anxiety alike, providing further support for the adoption of similar initiatives as a means of promoting tobacco cessation on a population level.

Trial registration: clinicaltrials.gov, NCT01429129

What this paper adds

- The mailed distribution of nicotine patches without behavioral support is effective in increasing the odds of quitting irrespective of lifetime history of depression or anxiety.

- The finding that NRT is effective in real world settings despite known moderators of cessation success provides further evidence for the implementation of widespread mailed distribution initiatives as a means of promoting tobacco cessation on a population level.

INTRODUCTION

Tobacco use and mental illness are highly comorbid; a recognition even more evident with overall reductions in smoking prevalence (Talati et al., 2016). Population-level survey research has consistently shown that those with a current or past history of a psychiatric diagnosis have considerably greater odds of smoking than individuals without a psychiatric diagnosis (Breslau & Johnson, 2000; Lasser et al., 2000; Smith et al., 2014), and conversely, smokers are more likely to be diagnosed with a mental illness compared to non-smokers (John et al., 2004). Mood and anxiety disorders in particular, are two of the most prevalent psychiatric diagnoses among smokers, affecting as many as 46% of smokers in the United States (US) at some point in their life (Grant et al., 2004). Smokers with a history of depression or anxiety are reported to exhibit higher levels of tobacco dependence (John et al., 2004), earlier onset of daily smoking (Breslau et al., 2004), as well as reduced likelihood of quitting (Donald et al., 2013; Lawrence et al., 2011; Smith et al., 2014), all of which are thought to contribute to a greater incidence of morbidity and mortality (Prochaska, 2010), Despite overall lower cessation rates (Donald et al., 2013; Smith et al., 2014), a considerable proportion of smokers with depression or anxiety express a strong desire and motivation to quit smoking (Morris et al., 2014; Solty et al., 2009). These smokers have been found to report more quit attempts as well as greater use of cessation aids such as nicotine replacement therapy (NRT) (Morris et al., 2014; Rae et al., 2015).

While the latest clinical practice guidelines on treating tobacco use and dependence have recommended for clinicians to use the same smoking cessation strategies in patients with mental illness as with the general population (Fiore et al., 2008), treatment modalities shown to be particularly effective at achieving cessation have constituted of tailored, high intensity, high frequency motivational and behavioral counseling, combined with cessation medication

(MacPherson et al., 2010; Ziedonis et al., 2008). Such cessation assistance integrated with routine mental health treatment has been demonstrated to improve quit rates even further (McFall et al., 2006; McFall et al., 2010), garnering considerable support for this treatment approach in the research community (Gierisch et al., 2012; Hall & Prochaska, 2009; Richards et al., 2013). Unfortunately however, due to the often cited limited availability of services, lack of provider education, and the commonly held misconception that cigarette abstinence will result in the recurrence or worsening of psychiatric symptoms (Hall & Prochaska, 2009), these personalized and multifaceted interventions are seldom implemented.

Population-level efforts aimed at reducing the smoking prevalence, by way of policy changes, education, or increased accessibility to cessation interventions, are another resource with potential benefit for this patient population. Although a wide range of populated-based cessation efforts have been implemented since the 1960's (US Department of Health and Human Services, 2000), surprisingly little research has been conducted to evaluate their effectiveness within the highly prevalent subpopulation of smokers with comorbid mental illness. Smokers' quitlines and programs giving away free NRT, in particular, are interventions that have led to increased utilization of services, treatment satisfaction, cost-effectiveness, and greater cessation rates (Bush et al., 2008; Cummings et al., 2006; Cummings et al., 2011; Miller et al., 2005; Tinkelman et al., 2007). While primarily limited to pre-post assessment, studies have documented that smokers receiving free NRT as part of smokers' quitlines were generally more than twice as likely to quit compared to when it was not offered (Bush et al., 2008; Cummings et al., 2006; Miller et al., 2005; Swartz et al., 2005). However, with as many as 20% to 50% of smokers with comorbid mental illness accessing these cessation interventions (Morris et al., 2011; Zawertailo et al., 2013) and nearly a dozen studies to date on the effectiveness of the free

NRT distribution approach, we are aware of only one that has detailed its impact on the highly prevalent population of smokers with mental illness (Zawertailo et al., 2015). Although that study provided preliminary evidence of reduced NRT effectiveness in recurrent depression, similar to other mass distribution efforts, it did not include a randomly allocated control group to test for the causal effects of NRT. Our recently published trial (Cunningham et al., 2016) is the only study to employ randomly allocated groups to identify the effectiveness of mailed NRT distribution in the general population. It is therefore presently unknown whether the distribution of free NRT is effective in predicting cessation specifically among smokers with mental illness. Further, with rising concern as to the effectiveness of NRT in real-world settings (obtained over the counter) (Alberg et al., 2005; Alpert et al., 2013; Kotz et al., 2014a, 2014b) identifying the impact of NRT without behavioral support among smokers with mental illness is ever important.

In the context of a large randomized controlled trial (RCT) examining the efficacy of mailed distribution of NRT to Canadian smokers (Cunningham et al., 2011), the objective of the current study was to examine the influence of lifetime history of depression and/or anxiety on smoking cessation success following the free distribution of nicotine patches. The randomized trial recruited participants who were interested in receiving free nicotine patches and compared quit rates between participants who were sent a 5-week course of nicotine patches (without behavioral assistance) and those who were not offered the patches. The present secondary analysis of data attempted to answer the question: Are smokers with lifetime depression or anxiety as likely to quit as smokers without such diagnoses when provided free NRT, compared to those not offered NRT?

METHODS

Study design

A detailed research protocol has been published elsewhere (Cunningham et al., 2011). Briefly, this RCT employed a single blinded, survey design with random assignment to an experimental and a control condition. Recruitment for the trial commenced on June 4, 2012, and concluded on June 26, 2014. The study was approved by the Research Ethics Board of the Centre for Addiction and Mental Health.

Eligibility and recruitment

Using random digit dialing of Canadian telephone numbers, adult (age 18 and over) smokers who smoked 10 or more cigarettes per day were identified to participate in a longitudinal smoking survey. Participants agreeing to complete a baseline, 8-week, and 6-month interviews and submit a saliva sample by mail at each time point provided verbal consent prior to the start of the baseline interview. Recruitment and interviews were conducted by trained interviewers at the Survey Research Centre, University of Waterloo, using the computer assisted telephone interview (CATI) technology. Participants were paid $20 for the completion of each telephone survey. As part of the baseline survey, subjects were asked: "The Ministry of Health is considering different ways to help people stop smoking. One option would be to provide interested smokers with free Nicotine Patches. If Nicotine Patches were offered for free, would you be interested in receiving them?" Those who stated interest in the free nicotine patches were further asked if they would use them to quit smoking, use them within one week of receipt, and

whether they would be willing to have the patches sent to their home. Individuals who said 'yes' to all those questions, had no contraindications for using nicotine patches (being pregnant, intending to become pregnant, or breastfeeding; having a serious heart or circulation problem, not including high blood pressure), and a valid home address that was not a post office box (for timely expedited postal delivery of nicotine patches) were randomized into experimental and control conditions to receive versus not receive free nicotine patches.

Randomization and interventions

Participants meeting eligibility criteria were randomly allocated to condition using a random number generator housed in the CATI program. Participants in the experimental condition were told that, "as part of a pilot trial, the Centre for Addiction and Mental Health has a supply of Nicotine Patches to distribute to interested smokers", and were offered to have the nicotine patches sent to their home. All who were offered the nicotine patches consented to have them sent. These individuals were sent a 5-week course of nicotine patches (3 weeks of Step 1 [21 mg of nicotine]; 1 week of Step 2 [14 mg of nicotine]; 1 week of Step 3 [7 mg of nicotine]) by expedited postal mail along with a cover letter instructing them on the proper use of nicotine patches, answers to some frequently asked questions on patch use, as well as advice to speak to a doctor or pharmacist if they had any further questions (no other support was provided). Participants randomized to the control condition were not informed of or offered the nicotine patches or any other intervention. All participants were followed-up by telephone at 8 weeks and 6 months. At each follow-up, interviewers were blinded to subjects' condition until the primary outcome measures were assessed.

Baseline measures

In addition to assessing eligibility for the RCT, the baseline survey collected information on participants' detailed demographic, clinical and smoking characteristics. Amongst baseline measures, separate questions were used to assess participants' lifetime and current diagnosis of depression and/or anxiety. Participants were specifically asked "Have you ever been diagnosed with any of the following: depression, anxiety, schizophrenia, bipolar disorder, personality disorder, or attention deficit hyperactivity disorder (ADHD)", with the response to each option recorded before proceeding to the next. If a participant had endorsed ever diagnosis of a particular disorder, they were subsequently asked if they had a current diagnosis of that disorder. Those who endorsed ever diagnosis of depression or anxiety were identified as the cohort of interest, with participants reporting a current diagnosis considered as part of the lifetime diagnosis cohort. Responses to these questions were used to categorize participants into distinct groups based on the presence or absence of self-reported lifetime diagnosis of depression or anxiety.

Outcome assessment

All outcomes were based on self-report data, with the primary outcome being self-reported abstinence at 6 months, with a 30-day point prevalence (reporting not smoking a cigarette, even a puff in the past 30 days). Quitting smoking at the 8-week follow-up was considered as the secondary outcome measure and defined as not smoking a cigarette, even a puff, in the past 7 days (7-day point prevalence). Self-reported smoking abstinence has been previously

documented in a Canadian population survey to be highly accurate, with 91.6% sensitivity (Wong et al., 2012), and is generally regarded as an appropriate outcome measure for population-based studies with limited face-to-face interaction between participants and investigators (SRNT Subcommittee on Biochemical Verification, 2002).

Statistical Analysis

Of 2093 participants that were interviewed as part of the baseline survey, 1000 were eligible for the trial and randomized to experimental or control condition. One individual had reported at follow-up that their responses had been falsified and another had refused to disclose their mental illness status, therefore following their exclusion, the present analyses were conducted on a total of 998 subjects. Based on self-reported lifetime diagnosis of depression or anxiety, all participants were divided into subgroups of diagnosis presence and further into experimental and control conditions within each diagnostic category (see Figure 1 for CONSORT flowchart). Baseline demographic and smoking characteristics were compared between smokers with and without lifetime history of depression or anxiety and between experimental and control participants of each diagnosis-based group. Separate logistic regression models were subsequently conducted to test the impact of depression or anxiety diagnosis on quit outcomes at both 6-month and 8-week follow-ups. Models comparing outcomes between diagnosis-based groups controlled for observed differences in demographic and smoking characteristics found between those with lifetime depression or anxiety and those without. Models comparing outcomes between experimental and control conditions within each diagnosis-based group did not control for differences in demographic characteristics as none were found. Analyses were

conducted by way of an intent-to-treat approach, such that subjects lost to follow-up were considered active smokers. All statistical analyses were conducted using IBM SPSS Statistics, version 22.0.

Figure 1. Trial CONSORT flowchart
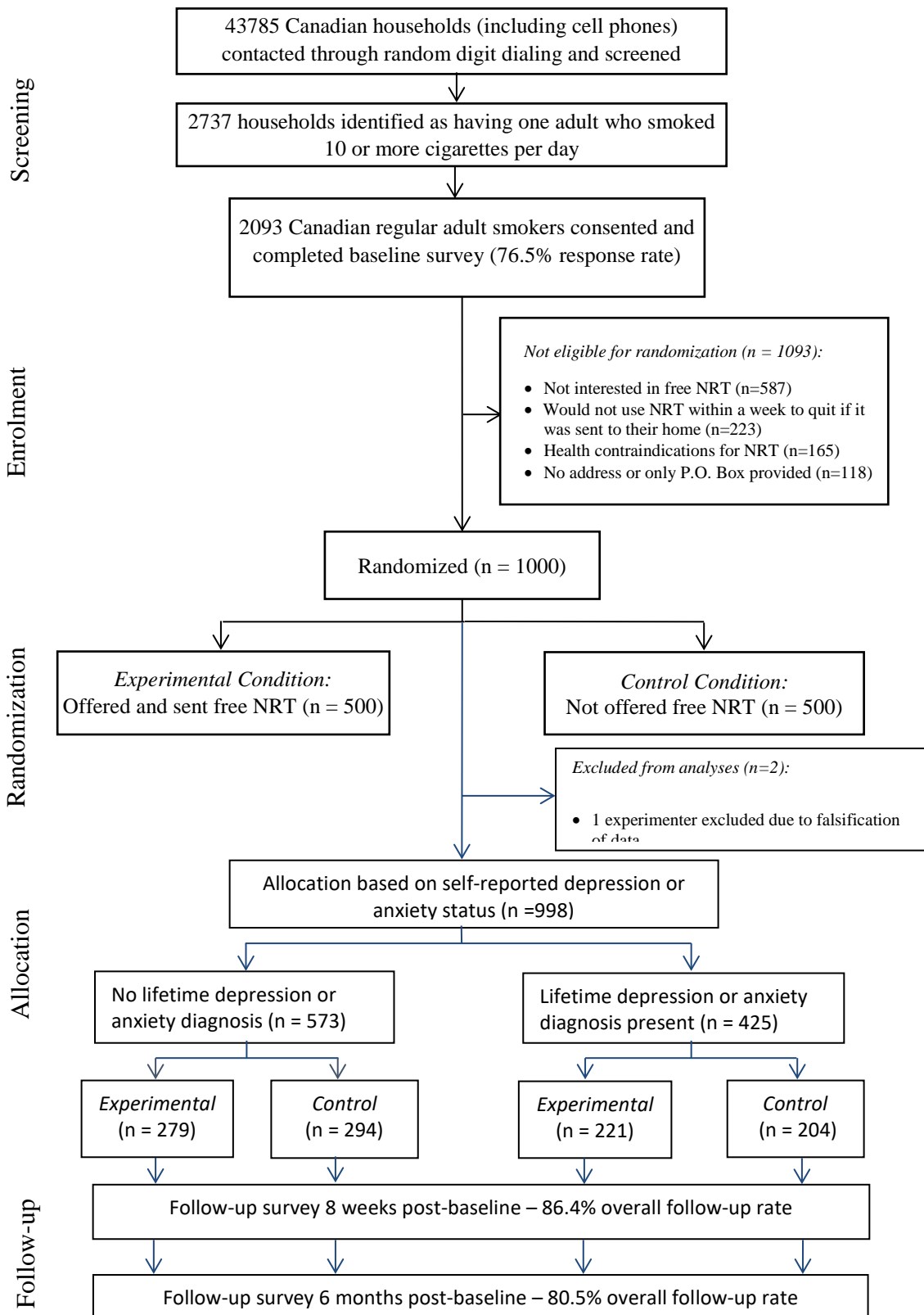
RESULTS

Sample Characteristics

Table 1 presents participant demographic and smoking characteristics based on presence of self-reported lifetime diagnosis of depression or anxiety: no lifetime history of depression or anxiety (n=573) and lifetime history of depression or anxiety present (n=425). Significant differences between diagnosis-based groups were noted in numerous domains, such that those with a lifetime history of depression or anxiety were more likely to be female, not married or employed, have reduced household income, greater levels of nicotine dependence, initiated smoking at an earlier age, more likely to have used NRT, bupropion, counseling, and alternative therapies, and lower confidence in the ability to quit. Further, those with a history of depression or anxiety were more likely to have other psychiatric diagnoses, both currently and throughout their lives, and endorse current use of psychotropic substances. Irrespective of the diagnosis group, no differences in demographic or smoking characteristics were observed between those randomized to nicotine patch vs. no intervention conditions ($p > .05$).

Of participants within the lifetime depression or anxiety group, 29.6% reported a lifetime diagnosis of depression, but not anxiety, 19.5% reported a lifetime diagnosis of anxiety but not depression, and 50.8% reported ever being diagnosed with both depression and anxiety. From the same sample, 16.2% reported having a current diagnosis of depression, but not anxiety, 14.1% reported a current diagnosis of anxiety, but not depression, and 23.3% endorsed a current diagnosis of both depression and anxiety. In total, 53.6% of the lifetime diagnosis positive group reported a current diagnosis of either depression or anxiety.

Table 1. Demographic and smoking characteristics

	No History of Depression or Anxiety (n = 573)[a]	Lifetime Depression or Anxiety (n = 425)[a]	p-value
Demographic Characteristics			
Age, mean (SD)	49.5 (12.9)	48.0 (12.5)	0.072
Female, % (n)	41.0 (235)	64.7 (275)	**<0.001**
Married/Common-law, % (n)	59.7 (342)	48.7 (207)	**0.001**
Employed full- or part- time, % (n)	70.0 (401)	50.1 (213)	**<0.001**
Education Level, % (n)			0.950
Less than high school diploma	21.7 (124)	21.0 (89)	
High school diploma	42.8 (245)	42.7 (181)	
Post-secondary	35.5 (203)	36.3 (154)	
Household Income, % (n)			**0.003**
<$60,000	60.3 (320)	69.7 (288)	
≥$60,000	39.7 (211)	30.3 (125)	
Smoking Characteristics			
Cigarettes/day, mean (SD)	18.1 (8.0)	18.8 (7.5)	0.172
FTND score, mean (SD)	4.7 (2.0)	5.2 (2.0)	**<0.001**
Level of Nicotine Dependence, % (n)[b]			**<0.001**
Low	13.8 (76)	9.2 (38)	
Low to Moderate	31.2 (172)	25.8 (107)	
Moderate	48.3 (266)	51.5 (214)	
High	6.7 (37)	13.5 (56)	
Age at first smoking, mean (SD)	15.0 (4.1)	14.4 (4.1)	**0.041**
Number of previous quit attempts, % (n)			0.653
0	7.2 (41)	6.8 (29)	
1-5	68.6 (393)	66.4 (282)	
6 +	24.3 (139)	26.8 (114)	
Past quit methods or aids used, % (n)			
Nicotine replacement therapy (patch/gum/inhaler)	57.5 (306)	65.9 (261)	**0.010**
Bupropion	25.2 (134)	31.6 (125)	**0.032**
Varenicline	26.1 (139)	26.8 (106)	0.827
Counselling (individual or group)	5.5 (29)	9.8 (39)	**0.011**
Acupuncture/hypnosis/herbal remedies	13.3 (71)	18.7 (74)	**0.027**
Self-help materials	13.2 (70)	16.9 (67)	0.110
Years as smoker, mean (SD)	25.0 (14.1)	25.2 (13.8)	0.814
Confidence in ability to quit, mean (SD)	5.6 (2.52)	5.2 (2.56)	**0.013**
Psychiatric History and Substance Use			
Other psychiatric disorders, % (n)[c]			
Lifetime history	4.5 (26)	17.9 (76)	**<0.001**

Current	2.3 (13)	12.9 (55)	**<0.001**
Current substance use, % (n)[d]	17.5 (100)	27.1 (115)	**<0.001**

Note: SD = standard deviation; FTND = Fagerström Test for Nicotine Dependence

[a] Sample sizes vary due to missing data on some variables.

[b] Level of nicotine dependence is based on Fagerström Test for Nicotine Dependence scores. Scores range from 1 to 10, with higher scores indicating a more intense physical dependence on nicotine. Low dependence corresponds to a score of 1 or 2, low-to-moderate dependence a score of 3 or 4, moderate dependence a score of 5 to 7, and high dependence a score of 8 to 10.

[c] Other psychiatric conditions included schizophrenia, bipolar disorder, personality disorder, and attention deficit hyperactivity disorder.

[d] Marijuana, cocaine, sedatives, opiates, stimulants and other drugs.

For the entire sample, follow-up rates at 8 weeks and 6 months were 86.4% and 80.5%, respectively. Participants lost at the 6-month follow-up differed on a number of baseline characteristics from those that completed the interview, namely being of younger age (mean: 44.9 years vs. 49.8 years; $p < .001$), being a smoker for shorter duration (mean: 22.0 years vs. 25.8 years; $p = .001$), and less likely to have used non-traditional cessation methods (10.4% vs. 16.8%; $p = .036$) and self-help techniques (9.8% vs. 15.9%; $p = .042$). No differential loss to follow-up at 6 months was observed between the diagnosis-based groups, such that 81.2% (n=465) of participants with no self-reported depression or anxiety were followed-up at 6 months, compared to 79.8% (n=339) with lifetime diagnosis of depression or anxiety present ($p = .584$).

Effectiveness of mass distribution of nicotine patches based on self-reported lifetime depression or anxiety diagnosis

Figure 2 displays abstinence rates at 6-month and 8-week follow-ups for the four diagnosis and condition-based groups, as per intent-to-treat analyses. Separate logistic regression analyses were conducted to examine odds of quitting between nicotine patch and no intervention participants

with and without self-reported lifetime diagnosis of depression or anxiety. Among smokers with

no history of depression or anxiety, participants receiving nicotine patches were more likely to

quit at 6 months (30-day point prevalence: 7.9% (22 of 279) vs. 3.7% (11 of 294); odds ratio

(OR) of 2.20; 95% CI 1.05 to 4.63) and 8 weeks (7-day point prevalence: 8.6% (24 of 279) vs.

2.0% (6 of 294); OR of 4.52; 95% CI 1.82 to 11.23), compared to the no intervention condition.

Similarly, among smokers with self-reported lifetime history of depression or anxiety present,

those that received nicotine patches were also more likely to quit at 6 months but not 8 weeks,

compared to their counterparts in the no intervention condition. In this group, those receiving

free nicotine patches were nearly 4 times more likely to quit by 6 months (7.2% (16 of 221) vs.

2.0% (4 of 204); OR of 3.90; 95% CI 1.28 to 11.88), however, at the 8-week follow-up, those in

the experimental condition were no more likely to quit than control participants (5.9% (13 of

221) vs. 2.5% (5 of 204); OR of 2.49; 95% CI 0.87 to 7.11).
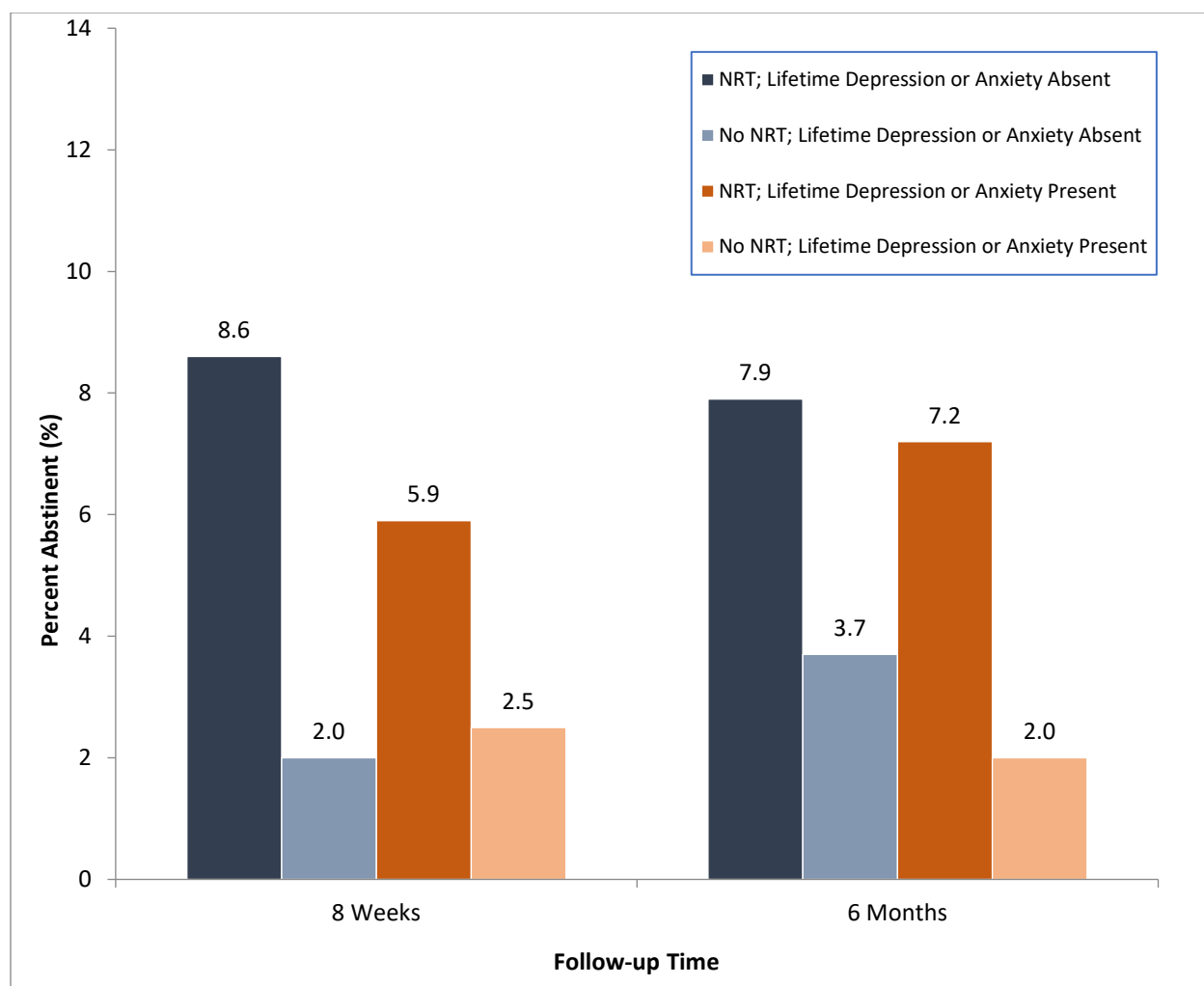
Figure 2. Smoking cessation outcomes at 8-week and 6-month follow-ups based on self-reported lifetime presence of depression or anxiety and condition allocation.

Comparing quit outcomes between nicotine patch recipients with and without lifetime depression or anxiety, quit rates between the two diagnosis-based groups did not differ at either 6-months (7.2% (16 of 221) vs. 7.9% (22 of 279); OR of 0.91; 95% CI 0.47 to 1.78) or 8 weeks (5.9% (13 of 221) vs. 8.6% (24 of 279); OR of 0.66; 95% CI 0.33 to 1.34). Fittingly, logistic regression analyses, even adjusted for observed differences in demographic and smoking characteristics

between the two diagnosis-based groups, revealed similar odds of cessation at both follow-up points (6 months: adjusted OR of 0.86; 95% CI 0.40 to1.87; 8 weeks: adjusted OR of 0.74; 95% CI 0.34 to 1.59). Use of nicotine patches, assessed by asking if participants had used any, and if so, all nicotine patches provided by the 8-week follow-up, also did not differ between the two diagnosis-based groups. Of participants with no lifetime depression or anxiety, 44.6% had used some and 11.2% had used all of the sent nicotine patches by 8 weeks, compared to those with the lifetime diagnoses present, of which 51.1% used some patches and 10.6% had used all nicotine patches provided ($p = .406$). Further, purchase of additional smoking cessation aids (including nicotine patches) beyond the 8-week follow-up did not differ between the two groups ($p > .05$).

Effectiveness of mass distribution of nicotine patches based on self-reported current depression or anxiety diagnosis

Exploratory sub-analyses evaluated the impact of mailed NRT specifically in smokers with a current diagnosis of the two psychiatric disorders (n=228), of which (n = 100) received nicotine patches and (n = 118) did not. The findings revealed no differences in quit rates between nicotine patch recipients and control participants at both 6-month (7.3% (8 of 110) nicotine patch vs. 2.5% (3 of 118) no intervention; OR of 3.01, 95% CI .78 to 11.64) and 8-week follow-up periods (4.5% (5 of 110) nicotine patch vs. 1.7% (2 of 118) no intervention; OR of 2.76, 95% CI .53 to 14.54). Due to the much smaller sample size of this subgroup and small observed effect sizes, however, these analyses resulted in insufficient statistical power to detect differences between experimental and control subgroups.

Evaluating quit outcomes between nicotine patch recipients with self-reported current depression or anxiety and those with no lifetime history of the disorders revealed no group differences in quit rates at either 6-month (7.9% (22 of 279) no lifetime depression or anxiety vs. 7.3% (8 of 110) current depression or anxiety present; OR of 0.92, 95% CI .40 to 2.13) or 8 week (8.6% (24 of 279) no lifetime depression or anxiety vs. 4.5% (5 of 110) current depression or anxiety present; OR of 0.51, 95% CI .19 to 1.36) follow-ups.

DISCUSSION

This study demonstrated that irrespective of lifetime diagnosis of depression or anxiety, mailing a 5-week course of nicotine patches to smokers is effective in achieving short-term cessation. While smokers with a history of depression or anxiety may generally require more personalized cessation interventions, the present findings suggest that the lifetime diagnostic status does not affect quit outcomes when NRT is provided through the mass distribution approach. The findings lend further support to the effectiveness of NRT in real world settings, providing comparable benefit in absence of behavioral support to smokers with or without lifetime depression or anxiety alike. In recent years, a number of cohort studies (Alberg et al., 2005; Alpert et al., 2013) have questioned the effectiveness of NRT purchased over the counter or used in the absence of behavioral support, suggesting that findings of NRT efficacy from RCTs conducted in clinical settings are not optimally generalizable to populations in the 'real world'. The present RCT of real world effectiveness of nicotine patches however, has demonstrated that not only are nicotine patches effective in helping smokers quit, but even in a population of smokers with presumed reduced likelihood of quitting.

Significant differences in demographic and smoking characteristics were present between smokers with and without lifetime depression or anxiety. The observed differences in gender, household income, level of nicotine dependence, previous use of NRT, and history of other psychiatric diagnoses between the two groups have all been previously reported in other trials and shown to predict poor cessation outcomes (Blalock et al., 2011; Breslau & Johnson, 2000; Hyland et al., 2006; Hymowitz et al., 1997; Morris et al., 2014; Shiffman et al., 2005; Zawertailo et al., 2015). Despite these differences however, unadjusted logistic regression models revealed that the odds of cessation were similar between the two diagnosis-based groups receiving nicotine patches, suggesting that the inherent effectiveness of nicotine patches is stable and independent of depression or anxiety history or known moderators of cessation success. Both use of sent nicotine patches and purchase of additional smoking cessation aids were also similar between the two groups, hence no one group had ancillary benefit in their cessation efforts. An observational study by Zawertailo et al. (2015) similarly found no difference in unadjusted odds of abstinence between smokers with past history of depression and those with no history of depression, at 6 months following a mailed 5-week supply of NRT and self-help material. After adjusting for differences in demographic and smoking characteristics akin to those observed in the present study, only recurrent depression, defined as having past and current/recent depression, was a predictor of reduced odds of quitting. Both the present findings and those of Zawertailo et al. are supported by a meta-analysis of traditional treatment clinical trials demonstrating that a history of depression is not a predictor of treatment success (Hitsman et al., 2003), suggesting that perhaps recurrence of symptoms, episode duration, or even specific symptoms may be better predictors (Niaura & Abrams, 2001).

Notably, given that over 50% of the lifetime diagnosis positive group in the present study had reported a current diagnosis of either depression or anxiety, it is further encouraging that abstinence could not be differentially predicted in this entire group. While this group of smokers may have been receiving concurrent antidepressant treatment or counselling, in absence of such data it is difficult to know what impact additional treatment for depression or anxiety may have had on this group's cessation outcomes. It is possible to speculate that if used, antidepressants would have likely provided no additional benefit to smokers using nicotine patches (Hughes et al., 2014). Psychosocial mood management on the other hand, has been found to exhibit a positive effect on smoking cessation by two meta-analyses (Gierisch et al., 2012; van der Meer et al., 2013) and thus it is reasonable to expect that it would have elevated quit rates. Delineating the possible impact of concurrent treatment for mood or anxiety disorders is further complicated given the paucity of research on the effectiveness of smoking cessation treatment for those with anxiety disorders other than post-traumatic stress and the absence of studies examining smoking cessation outcomes between effectively controlled and untreated anxiety (Richards et al., 2013).

Several limitations should be considered. First, although evaluating the effectiveness of the mass distribution of nicotine patches specifically among those with current depression or anxiety was of particular interest, these sub-analyses were not sufficiently powered to detect differences and were thus deemed inconclusive. Second, despite taking considerable efforts to biochemically validate smoking status (Cunningham et al., 2016), this aspect of the trial could not be effectively executed, leading all outcomes to be based on self-report data. As participants were recruited from across all of Canada, with no physical contact similar to other mass distribution efforts, perhaps the difficulty in confirming smoking abstinence via biochemical means is an inherent limitation of pragmatic trials of this nature. Nevertheless, self-reported

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abstinence in population surveys are considered to be largely exempt of the same biases observed in clinical settings (Patrick, 1994; West et al., 2007; Wong et al., 2012), therefore there can be sufficient confidence in the reliability of the present results. Third, we note that the receipt of follow-up telephone survey interviews may have contributed to the effectiveness of the mailed NRT intervention, however this aspect of the trial could not have been controlled for. Fourth, the self-reported diagnosis of depression or anxiety was also not confirmed by validated tools or structured interview, however, as questions on depression and anxiety referred specifically to a diagnosis of the disorder as opposed to only symptomatology, this method of assessment is regarded as robust as the CIDI Short Form (Kessler et al., 1998) commonly used in population-based surveys (Zawertailo et al., 2015). Confidence in the validity of the self-reported diagnoses is gained particularly when the prevalence of self-reported current diagnosis of depression (16.2%) and anxiety (14.1%) among smokers in the current study is compared to that found in the U.S. National Epidemiological Survey on Alcohol and Related Conditions (Grant et al., 2004), providing population-based estimates of 12-month prevalence of major depression and specific phobia of 16.6% and 14.3%, respectively among respondents with nicotine dependence. Given such close proximity to national rates of depression and anxiety found among nicotine dependent smokers, endorsement of mental illness diagnosis in the current trial was likely accurate. Lastly, the temporal duration of current diagnosis of mental illness was not explicitly specified to participants but was implied to refer to the presence of diagnosis at time of survey completion.

Overall, this study provides further support for the adoption of similar mass distribution initiatives as a means of promoting tobacco cessation on a population level. Future research is warranted to examine the effectiveness of this approach among smokers from other vulnerable

populations and with other psychiatric diagnoses, as well as examine the impact of

socioeconomic factors as predictors of cessation success within the mass distribution model.

Competing interests: All authors declare that no support from any organization was received for the submitted work; RFT has consulted with Apotex on topics unrelated to smoking cessation. PS received consultancy fees in the past year from manufacturers of smoking cessation products. No other authors have financial relationships with any organizations that might have an interest in the submitted work in the previous three years; all authors have no other relationships or activities that could appear to have influenced the submitted work.

Note: A similar version of the Abstract of this work has been published before in The College on Problems of Drug Dependence (CPDD) 78th Annual Scientific Meeting Program book and part of the research findings were presented at the CPDD conference in June, 2016.

Ethical approval: This research was approved by the institutional review board at the Centre for Addiction and Mental Health (No 192/2012).

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Chapter 3: Mailed Distribution of Free Nicotine Patches Without Behavioral Support: Predictors of Use and Cessation (Manuscript 2)

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Mailed Distribution of Free Nicotine Patches Without Behavioral Support: Predictors of Use and Cessation

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Abstract

Introduction: There is growing evidence that the mailed distribution of free nicotine replacement therapy (NRT), usually as part of smokers' helplines, can been effective in increasing the odds of cessation on a population level. However, limited information is available on the utilization of NRT when it is provided for free, and factors associated with regimen adherence have remained largely unexplored.

Methods: In the context of a randomized controlled trial, 500 adult smokers across Canada hypothetically interested in free NRT were mailed a 5-week supply of nicotine patches, but no other support was offered. Analyses evaluated which a priori-defined demographic and smoking characteristics predicted nicotine patch use at 8-week follow-up of 421 patch recipients, as well as examined the association between patch use and smoking cessation at 6 months.

Results: At 8 weeks, 10.9% had used all, 47.5% had used some but not all, and 41.6% had not used any of the provided nicotine patches. Lower age, unemployment, past NRT use and intent to quit in the next 30 days at baseline (preparation stage of change) were all identified as independent predictors of some nicotine patch use. Only use of all patches was associated with greater odds of smoking cessation, compared to non-users (Adj. OR = 2.96; 95%CI = 1.06 – 8.27).

Conclusions: The mailed distribution of free nicotine patches to smokers at large can be effective at promoting cessation, particularly among financially disadvantaged groups, those with previous NRT experience and among individuals with already advanced intent to quit.

Keywords: Smoking, Tobacco, Nicotine Replacement Therapy, Smoking Cessation, Adherence, Free Distribution

Highlights

- Age, unemployment, past NRT use and intent to quit associated with free patch use.
- Past NRT use was predictive of abstinence at 6 months.
- Odds of quitting were higher only among users of all 5 weeks of nicotine patches.

1. Introduction

It is well established that smokers who use smoking cessation aids are more likely to be successful in quitting smoking than those who do not use quit aids. Nicotine replacement therapy (NRT) in particular, significantly increases a smoker's chances of quitting by as much as 50% - 70%, irrespective of the clinical setting in which he/she is treated (Stead et al., 2012), and has thus been recommended as a first-line pharmacotherapy for smokers wanting to quit. As a means of promoting smoking cessation in the general population, a number of public health initiatives have explored the advantages of offering free NRT as part of smokers' quitlines or specialized giveaway programs, providing smokers with both pharmacological and phone-based counselling during a quit attempt. These efforts have demonstrated that the availability of free NRT increased both quitline utilization and treatment satisfaction (Bush et al., 2008; Cummings et al., 2006a; Tinkelman et al., 2007). Their distribution has also been documented to increase the odds of cessation at follow-up (Bush et al., 2008; McAfee et al., 2008; Miller et al., 2005; Swartz et al., 2005; Tinkelman et al., 2007) and was identified as a highly cost-effective intervention in promoting smoking cessation (Cummings et al., 2006a; Zawertailo et al., 2013).

Although there is growing evidence that the distribution of free NRT can be effective in increasing the odds of cessation on a population level, surprisingly little is known about the acceptance and actual use of NRT when it is provided for free via postal mail. With nearly a dozen retrospective cohort treatment studies on the large-scale distribution of mailed free NRT, only four had reported use rates, citing that between 63% and 89% of their sample had used at least some NRT when it was provided in combination with counselling (Bush et al., 2008; Cummings et al., 2006a; Cummings et al., 2010; Ferguson et al., 2012). These studies have

documented that while use of 1 to 8 weeks of freely distributed NRT is proportionally related to

the amount of NRT provided (Cummings et al., 2006a; McAfee et al., 2008), recipients of larger

amounts of NRT are actually less likely to use all of it and do not necessarily exhibit higher quit

rates (Cummings et al., 2006a; Cummings et al., 2010; Cummings et al., 2011). Regardless, the

amount and duration of NRT used is predictive of quit outcomes, with those using more or for a

longer duration exhibiting higher quit rates (Cummings et al., 2010; Cummings et al., 2006b), a

distinction that highlights the need to identify the most optimal and cost-effective amount of

NRT to provide, while encouraging adherence.

Recently, our group uncovered, through a randomized controlled trial (RCT), that the

mailed distribution of free NRT to smokers across Canada in the absence of behavioral

assistance is also an effective intervention in promoting cessation (Cunningham et al., 2016).

Among recipients of the free nicotine patches, use of any of the 5 weeks of patches provided as

part of the trial was reported by 58% of the sample, in contrast to predominant use rates of

greater than 80% when nicotine patches are distributed through smokers' helpline efforts

(Cummings et al., 2006a; Cummings et al., 2010). These lower utilization rates also conflicted

with an earlier Canada-wide population survey identifying that over 90% of regular adult

smokers expressing interest in free NRT stated that they would use it to quit for good

(Cunningham & Selby, 2008). Although the RCT had identified that the large-scale distribution

of NRT is effective in 'real-world' settings, that is, in absence of behavioral support as when

used by most smokers attempting to quit (Kotz et al., 2014), the disparity between intended and

actual use of freely provided smoking cessation aids to smokers motivated to quit underscored a

need to uncover characteristics that predict the actual use and compliance with free NRT offers

so that treatment and support can be optimized effectively.

The current study evaluates which *a-priori*-defined demographic and smoking history factors previously shown to be associated with purchase and use of over-the-counter NRT predict use of a 5-week course of mailed free nicotine patches (without any additional counselling or support), among smokers expressing interest in using free NRT to quit smoking. Further, the study explores reasons for not using the freely provided nicotine patches, and investigates the association between use of nicotine patches and cessation at a 6-month follow-up. In this study we also take special consideration in differentiating the terminology used to describe the utilization of NRT. With 'adherence' being defined as "the extent to which patients are able to follow the recommendations for prescribed treatments," (Hugtenburg et al., 2013) this wording is appropriate when treatment regimens of free NRT are prescribed or provided by a healthcare professional in concert with additional support and agreed upon treatment plans. Mailed free NRT on the other hand, is often distributed through promotional offers and in absence of face-to-face interaction with a healthcare professional, therefore the non-clinical nature of this intervention method facilitates 'use' as the more relevant term when referring to NRT acceptance and utilization.

2. Methods

2.1   *Design*

In the context of a randomized controlled trial (Cunningham et al., 2016; Cunningham et al., 2011), this study employed random digit dialing of Canadian household telephone numbers to

identify adult (aged 18+) current daily smokers who had smoked at least 10 cigarettes per day. Of 43,785 households contacted, 2,737 contained at least one adult daily smoker. The Survey Research Centre, University of Waterloo, interviewed 2,093 consenting individuals (response rate of 76.5%) in English or French using Computer Assisted Telephone Interviewing technology. As part of a baseline survey, a randomized half of participants (n=500) who endorsed hypothetical interest in receiving free nicotine patches, who indicated they would use them within one week, who had no contraindications for using nicotine patches (being pregnant, intending to become pregnant, or breastfeeding; having a serious heart or circulation problem, not including high blood pressure), and who had a valid home address that was not a post office box (for timely expedited postal delivery of nicotine patches) were told that "as part of a pilot trial, the Centre for Addiction and Mental Health has a supply of Nicotine Patches to distribute to interested smokers". These participants were subsequently sent 5 weeks of nicotine patches (3 weeks of Step 1 [21 mg of nicotine]; 1 week of Step 2 [14 mg of nicotine]; 1 week of Step 3 [7 mg of nicotine]) to their home, by expedited postal mail. The 5-week supply of nicotine patches was accompanied by a cover letter instructing participants on the proper use of nicotine patches, answers to some frequently asked questions, as well as advice to speak to a doctor or pharmacist if they had further questions. No behavioral or other support was provided and no mention was made to participants at any time that they were taking part in a randomized controlled trial. All participants were followed-up by telephone at 8 weeks and 6 months post baseline. The study was approved by the standing research ethics board of the Centre for Addiction and Mental Health.

2.2   *Measures*

The baseline survey collected data on demographics, smoking history and characteristics, motivation to quit smoking and psychiatric history. At follow-up, participants were asked about their current smoking status, with smoking abstinence using 30-day point prevalence at 6 months defined as the primary outcome measure. The amount of nicotine patches used was assessed at an 8 week follow-up (end-of-treatment) survey by asking respondents "how much of the nicotine patches did you use?", with the response options of "none", "some", "all". Participants who reported not using any or all of the nicotine patches were asked about their reasons for not using all the patches in an open-ended response option. These responses were subsequently coded and categorized into one category for each participant using inductive content analysis (Elo & Kyngas, 2008).

2.3   Statistical analyses

Of the 500 participants that were sent free nicotine patches, 427 were contacted at the 8-week follow-up (85.4% follow-up rate), of which 421 claimed to have received the nicotine patch supply (98.6%). All analyses were conducted on the 421 nicotine patch recipients. Participants were divided into three subgroups based on the amount of nicotine patches reported to be used (none, some, all) at the 8-week follow-up. Baseline demographic and smoking characteristics were compared between these three subgroups using one-way analyses of variance for continuous variables and chi-square tests for categorical variables.

Multinomial logistic regression analyses were used to determine independent predictors of nicotine patch use, with the group not using any of the nicotine patches by 8 weeks serving as

the reference. Regression models used a number of *a-priori*-defined factors previously

demonstrated to be associated with the purchase and use of over-the-counter NRT. These factors

include gender (Zhang & Chaiton, 2015; Zhang et al., 2015), marital status (Zhang & Chaiton,

2015), Fagerström Test for Nicotine Dependence score (FTND), which assessed severity of

tobacco dependence (Heatherton et al., 1991), residence in an urban or rural region (Zhang &

Chaiton, 2015), health status (Bondy et al., 2012; Zhang et al., 2015), age (Balmford et al., 2011;

Zhang & Chaiton, 2015; Zhang et al., 2015), education (Alberg et al., 2005; Balmford et al.,

2011), number of cigarettes smoked at baseline (Alberg et al., 2005; Balmford et al., 2011;

Swartz et al., 2005; Zhang et al., 2015), intent to quit (stages of change according to the

Transtheoretical Model of behavioral change; precontemplation, contemplation, and preparation)

(Bondy et al., 2012; Prochaska & Velicer, 1997), previous use of NRT (Bondy et al., 2012),

number of times intentionally trying to quit in the past (Bondy et al., 2012; Zhang et al., 2015),

and importance and confidence to quit (Bondy et al., 2012). Health status was assessed by way

of the World Health Organization Quality of Life Instrument (WHOQOL-BREF) question on

health satisfaction over the past 2 weeks (Skevington et al., 2004), where participants were asked

to rate how satisfied they are with their health on a 5-point Likert scale of 1 (very dissatisfied) to

5 (very satisfied). Responses were recoded into binary values, where scores of 1 to 3 were

categorized as 'dissatisfied', and scores of 4 to 5 as 'satisfied'. Additional variables such as

employment status, and presence of current mental illness (assessed by asking whether

participants have a current diagnosis of any of the following: depression, anxiety, schizophrenia,

bipolar disorder, personality disorder, or attention deficit hyperactivity disorder (ADHD)) were

also entered into the model. A purposeful selection of variables approach was used to establish a

final model, where non-significant factors were excluded in a stepwise fashion (Hosmer et al., 2008).

To evaluate how use of different nicotine patch quantities affects cessation at the 6-month follow-up, separate binomial logistic regressions were conducted. First, we examined which demographic and smoking characteristics predicted cessation, and subsequently, examined the association between patch use quantity and cessation while controlling for factors identified to be associated with cessation and factors demonstrated to be predictive of nicotine patch use in the preceding multinomial logistic models. These analyses employed an intent-to-treat approach, such that subjects lost to follow-up were considered active smokers. All statistical analyses were conducted using IBM SPSS Statistics, version 21.0.

3. Results

3.1 Sample characteristics

Of the 421 participants followed-up at 8 weeks, 41.6% (n = 175) surveyed had not used any of the nicotine patches supplied, 47.5% (200 of 421) had used some but not all of the nicotine patches supplied, and 10.9% (n = 46) had used all the nicotine patches. At the 6-month follow-up the response rate was 88.1% (371 of 421). Participants lost at the 6-month follow-up were of younger age (mean: 45.0 ± 12.4 years) compared to completers of the interview (mean: 49.5 ± 12.4 years) ($p = 0.02$), however no other demographic or smoking characteristic differences were observed. Demographic and smoking characteristics of participants based on levels of nicotine patch use are presented in Table 1, depicting differences in employment, number of past quit

attempts, previous NRT use, and stages (readiness) of change. Participants using any of the nicotine patches provided had lower rates of employment, greater incidence of previous NRT use, greater proportion of more than 6 quit attempts, and more prevalent intent for change, compared to those not using any of the nicotine patches.

Table 1. Demographic and smoking characteristics by amount of nicotine patches used at 8-week follow-up.

| | Overall (N = 421) | Amount of nicotine patches used[a] | | | |
		All (n = 46)	Some (n = 200)	None (n = 175)	*p*-value
Demographic Characteristics					
Age, mean (SD)	49.0 (12.4)	51.8 (12.6)	47.8 (12.4)	49.6 (12.3)	0.098
Female, % (n)	52.0 (219)	43.5 (20)	49.5 (99)	57.1 (100)	0.158
Married/Common-law, % (n)	54.6 (230)	52.2 (24)	53.5 (107)	56.6 (99)	0.786
Employed full- or part- time, % (n)	62.5 (263)	54.3 (25)	57.0 (114)	70.9 (124)	**0.011**
Education Level, % (n)					0.146
Less than high school diploma	23.3 (98)	34.8 (16)	19.1 (38)	25.1 (44)	
High school diploma	39.3 (165)	39.1 (18)	39.7 (79)	38.9 (68)	
Post-secondary	37.4 (157)	26.1 (12)	41.2 (82)	36.0 (63)	
Household Income, % (n)					0.301
<$60,000	62.9 (249)	64.4 (29)	66.3 (126)	58.4 (94)	
≥$60,000	37.1 (147)	35.6 (16)	33.7 (64)	41.6 (67)	
Smoking Characteristics					
Cigarettes/day, mean (SD)	18.5 (7.9)	19.9 (9.3)	17.8 (7.1)	19.1 (8.4)	0.120
FTND score, mean (SD)	5.0 (2.0)	5.0 (2.0)	4.9 (1.9)	5.1 (2.0)	0.763
Level of Nicotine Dependence, % (n)[b]					0.895
Low	10.4 (42)	13.6 (6)	9.9 (19)	10.0 (17)	
Low to Moderate	26.7 (108)	22.7 (10)	28.8 (55)	25.3 (43)	
Moderate	52.6 (213)	50.0 (22)	52.4 (100)	53.5 (91)	
High	10.4 (42)	13.6 (6)	8.9 (17)	11.2 (9)	
Age at first smoking, mean (SD)	14.6 (4.2)	13.8 (3.9)	14.5 (4.1)	14.9 (4.4)	0.217
Number of previous quit attempts, % (n)					**0.018**
0	7.1 (30)	4.3 (2)	6.0 (12)	9.1 (6)	
1-5	67.5 (284)	60.9 (28)	63.5 (127)	73.7 (129)	
6 +	25.4 (107)	34.8 (16)	30.5 (61)	17.1 (30)	

Past quit methods or aids used, % (n)					
Nicotine replacement therapy (patch/gum/inhaler)	61.4 (240	63.6 (28)	68.6 (129)	52.2 (83)	**0.007**
Bupropion	29.2 (114)	27.3 (12)	33.0 (62)	25.2 (40)	0.268
Varenicline	28.3 (112)	27.3 (12)	29.8 (56)	27.7 (44)	0.890
Counselling (individual or group)	7.2 (28)	6.8 (3)	8.0 (15)	6.3 (10)	0.828
Acupuncture/hypnosis/herbal remedies	14.8 (58)	11.4 (5)	16.0 (30)	14.5 (23)	0.732
Self-help materials	15.6 (61)	18.2 (8)	16.5 (31)	13.8 (22)	0.701
Years as smoker, mean (SD)	25.3 (13.6)	29.1 (13.3)	24.4 (13.1)	25.3 (14.1)	0.111
Confidence in ability to quit, mean (SD)	5.6 (2.6)	5.9 (2.4)	5.7 (2.6)	5.4 (2.5)	0.309
Importance in quitting, mean (SD)	7.3 (2.3)	7.5 (2.1)	7.5 (2.3)	7.1 (2.4)	0.143
Stage of Change, % (n)					**0.001**
Precontemplation	29.5 (124)	15.2 (7)	24.0 (48)	39.4 (69)	
Contemplation	35.4 (149)	39.1 (18)	36.0 (72)	33.7 (59)	
Preparation	35.2 (148)	45.7 (21)	40.0 (80)	26.9 (47)	
Psychiatric History and Substance Use					
Self-reported history of psychiatric diagnosis, % (n)[c]					0.632
No history	52.5 (221)	54.3 (25)	48.5 (97)	56.6 (99)	
Past history only	21.4 (21.4)	21.7 (10)	23.0 (46)	19.4 (34)	
Current	26.1 (110)	23.9 (11)	28.5 (57)	24.0 (42)	
Current substance use, % (n)[d]	21.1 (89)	21.7 (10)	24.0 (48)	17.7 (31)	0.329

Note: SD = standard deviation; FTND = Fagerström Test for Nicotine Dependence

[a] Sample sizes vary due to missing data on some variables.

[b] Level of nicotine dependence is based on Fagerström Test for Nicotine Dependence scores. Scores range from 1 to 10, with higher scores indicating a more intense physical dependence on nicotine. Low dependence corresponds to a score of 1 or 2, low-to-moderate dependence a score of 3 or 4, moderate dependence a score of 5 to 7, and high dependence a score of 8 to 10.

[c] Psychiatric conditions included depression, anxiety, schizophrenia, bipolar disorder, personality disorder, and attention deficit hyperactivity disorder.

[d] Current substance use was assessed by asking participants whether they currently used any of the following substances: marijuana, cocaine, sedatives, opiates, stimulants and other drugs.

3.2 Use of nicotine patches

Reasons for not using any or all provided nicotine patches are presented in Table 2. The most common reasons for using only some of the 5 weeks of nicotine patches were relapse back to smoking, delayed initiation - still using patches, side effects, and discontinuation of use due to stress. Among individuals who have not used any of the nicotine patches, the most common reasons were not being ready to quit, stress, and hesitance to use because of misperception of nicotine patch effects or side-effects. Of those who stated 'not ready to quit', not using any of the nicotine patches could not be explained by baseline intent for change as no differences were found in the proportion of stages of change distribution among these individuals ($p = 0.909$).

Table 2. Reasons for non-adherence to provided 5 weeks of nicotine patches by 8-week follow-up.

	Amount of nicotine patches used	
	Some (n = 200)	None (n = 175)
Relapsed back to smoking (e.g. experienced cravings; patches ineffective)	28.0 (56)	-
Still using patches (delayed initiation)	15.5 (31)	-
Experienced side effects	14.0 (28)	-
Stress	13.5 (27)	18.9 (33)
Forgot to use them	7.0 (14)	4.6 (8)
Patches did not adhere	6.0 (12)	-
Not knowledgeable about nicotine patch effects/side-effects	3.0 (6)	6.9 (12)
Patches no longer needed	3.0 (6)	-
Not ready to quit/ not right time	2.5 (5)	41.7 (73)
Advised to discontinue use by doctor/ waiting to seek medical advice	1.5 (3)	9.1 (16)
Not interested in quitting	-	6.3 (11)
Did not want to use nicotine patches	-	5.1 (9)
Preferred other cessation aid or to quit unassisted	-	2.9 (5)
Other	5.5 (11)	4.6 (8)
No reason provided	0.5 (1)	-

Note: Data are presented as percentage (number). Reponses were coded into one category for each participant.

Evaluating which *a-priori* defined demographic and smoking characteristics predicted nicotine patch use, multinomial logistic regression models revealed that lower age, unemployment, past NRT use and being in the preparation stage of change (intent to quit in the next 30 days at baseline) were all independent predictors of some nicotine patch use (Table 3). Being in the contemplation (intent to quit smoking in the next 6 months) and preparation stages

of change at baseline however, were the only independent predictors of using all 5 weeks of

freely provided nicotine patches.

Table 3. Final model of predictors of nicotine patches use among recipients of mailed free
nicotine patches, without behavioral support (n = 421).

	All NPs used	**Some NPs used**
	OR (95% CI)	**OR (95% CI)**
Age	1.00 (0.96-1.00)	**0.98 (0.96-0.99)***
Employment		
Unemployed	1.00	1.00
Full / Part-time Employed	0.54 (0.26-1.09)	**0.49 (0.31-0.77)****
Past NRT Use		
Did not use	1.00	1.00
Used	1.47 (0.75-2.90)	**1.92 (1.25-2.96)****
Stage of Change at Baseline		
Precontemplation	1.00	1.00
Contemplation	**2.87 (1.12-7.40)***	1.62 (0.97-2.73)
Preparation	**4.15 (1.62-10.65)****	**2.27 (1.33-3.88)****

$*<0.05, **<0.005$
Note: Reference category is having not used any of the nicotine patches received.
NPs, nicotine patches
NRT, nicotine replacement therapy (nicotine patch, gum, or inhaler)

3.3 *Impact of nicotine patch use on cessation*

Cessation rates at 6-month follow-up corresponding to the amount of nicotine patches used were

15.2% among users of all nicotine patches, 9.0% among users of some, and 5.7% among those

that did not use any nicotine patches. Of all variables used to examine predictors of nicotine

patch use, only past NRT use was predictive of abstinence at 6 months, such that those who used

NRT in the past were more likely to quit smoking (OR of 5.69; 95%CI = 1.86 - 17.38, p =

0.002). After adjusting for variables that predicted nicotine patch use, including past NRT use,

only use of all nicotine patches was associated with greater odds of smoking cessation, compared

to non-users (Adj. OR of 2.96; 95%CI = 1.06 – 8.27, p = 0.038). Odds of quitting among users

of some nicotine patches did not differ from those who used all provided patches (Adj. OR of

0.52; 95%CI = 0.20-1.39, p = 0.192). Significantly greater proportion of individuals using

varying amounts of nicotine patches by 8 weeks purchased additional nicotine patches by the 6-

month follow-up, compared to those who have not used any nicotine patches (proportion of

nicotine patch users: all (9.8%), some (9.4%), none (2.0%), p = 0.017). However, the nicotine

patch use subgroups did not differ in purchase rates of nicotine gum (average rate: 9.2%),

nicotine inhaler (6.7%), bupropion (1.6%), or varenicline (3.0%) (p > 0.05).

4. Discussion

The present study evaluated predictors of nicotine patch use as part of a mass distribution model

of mailed free nicotine patches, as well as examined the association between nicotine patch use

and smoking cessation. We note that the overall utilization of free nicotine patches when

provided in absence of behavioral support is indeed less prevalent than when they are provided

in concert with phone-based support through smokers' helplines. This may certainly be a

reflection of the proactive recruitment of a non-help-seeking sample used in the current study,

where it is possible that some participants accepted the offer of nicotine patches simply because

they were offered for free and had no true plans or intent to use them. The offer of free nicotine patches may have acted on decisional heuristics linked with zero-risk bias, where a 'nothing to lose' mentality may have enticed some smokers to accept the nicotine patches despite having no concrete plans to quit (Saraiva, 2011). Alternatively, the fact that well over half of the sample had made a quit attempt is encouraging and further speaks to the utility of proactively offering free NRT to smokers, versus placing the onus on individuals to call a mass distribution initiative's toll-free phone number.

Exploring predictors of nicotine patch use we found that in contrast to factors that are associated with the use of NRT purchased over-the-counter, relatively few variables predict the use of mailed-out free nicotine patches, in absence of behavioral support. Most notably, those who were unemployed were more likely to take advantage of the free nicotine patches and use at least some of the 5-week regimen. These findings support previous indications that cost of interventions remains a considerable barrier in accessing smoking cessation interventions for individuals interested in quitting (Kozlowski et al., 2007; Land et al., 2010; Leatherdale & Shields, 2009), and that treatment acceptance and utilization is more likely when cost is minimized or is no longer a factor. Certainly, smokers express considerable interest in the availability of free NRT (Cunningham & Selby, 2008; Tinkelman et al., 2007), however its value may be even more pronounced among more disadvantaged groups or those who face financial hardships.

Previous NRT use was also predictive of some nicotine patch use, in line with population survey data (Bondy et al., 2012). As past users of NRT may have had some quit success, this group of smokers may have had more positive outcome expectations with using the provided nicotine patches, whereas misconceptions about nicotine patch effects and lack of experience

among previous non-users of NRT may have contributed to reduced likelihood of using the provided nicotine patches (Gross et al., 2008; Hammond et al., 2004; Willems et al., 2013). Indeed, those who had used NRT in the past expressed significantly higher mean ratings of importance to quit (M = 7.6, SD = 2.1), compared to participants that had not used NRT in the past (M = 7.0, SD = 2.5) (t(350) = 2.52, p = 0.012), and were further less likely to endorse not being knowledgeable about nicotine patch effects as a reason for not using all nicotine patches (28% vs. 72% among those with no history of past NRT use). The largest determinant of using some or all of the nicotine patches provided however, was intent for change, which is supported by previous findings in clinical settings that motivation to quit is a significant determinant of cessation intervention adherence (Hyland et al., 2006; Jackson et al., 1989; Vangeli et al., 2011). As additional motivational stage-based personalized letters or self-help material would have likely further increased compliance with the supplied NRT as well as odds of cessation (Borland et al., 2004; Velicer et al., 1999), further research is warranted to examine the impact of personalized stage-based brief interventions as part of similar mass distribution models.

Our findings also build on the recently published study by Voci and colleagues (Voci et al., 2016), which identified that poor adherence to 10 weeks of free NRT (combined with a one-time psychoeducational workshop session) provided through community treatment centers, was predicted by having a current psychiatric diagnosis, female gender, and using nicotine gum or inhaler, compared to the patch. Using less than most or all of the NRT provided was also associated with reduced quit success. The study was limited however in having a low follow-up rate (32%) and not accounting for the role of motivation or readiness to quit as a robust predictor of NRT use and attempts at cessation (Hyland et al., 2006; Jackson et al., 1989; Vangeli et al., 2011), therefore restricting the generalizability of those findings and warranting replication and

further examination. Overcoming those limitations, our findings on the association between amount of nicotine patches used and smoking cessation at 6-month follow-up are nonetheless similar, demonstrating that use of entire 5-week supply of patches was associated with increased odds of cessation compared to non-users. They are further consistent with population-based studies as well as those employing standardized treatment programs, that it is a minimum of 4 to 5 weeks of NRT use that is necessary to improve the chances of quitting (Raupach et al., 2008; Zhang et al., 2015), and that the provision of more free NRT does not necessarily translate to greater cessation rates (Burns et al., 2016; Cummings et al., 2010). Even in the absence of any additional support, this duration of NRT use delivers significant benefit and should be encouraged. As this benefit can also be realized through a mass distribution of NRT approach (Cummings et al., 2010), compliance with using this recommended amount can potentially be enhanced by the provision of additional information on stress management and dealing with cravings, as well as supportive calls within the first few weeks to ensure program participants' questions or concerns regarding NRT use can be addressed.

4.1 Limitations

The present study has several limitations that need to be acknowledged. First, we used only one broad category to measure incomplete use of the provided nicotine patches and either more categories or specific questions on the precise amount and duration of nicotine patches used may have provided additional information given the results of this analysis. Second, biochemical validation of smoking abstinence could not be effectively executed (Cunningham et al., 2016),

therefore cessation outcomes are based on self-report data. Finally, while all recruitment and follow-up surveys were conducted by trained interviewers, better probing of reasons for discontinuation of nicotine patch use may have revealed a more accurate temporal relationship between resumption of smoking and incomplete use of recommended nicotine patches. While some studies have controlled for reverse causality – the assumption that non-adherence is the consequence of relapse, rather than the cause (Raupach et al., 2014), as a potential confound in the association between adherence to NRT and abstinence, we felt that doing so as part of the present study would be inappropriate. Relapse to smoking while using patches and subsequently discontinuing, or experiencing cravings and discontinuing patch use prior to resumption of smoking, both underscore ineffectiveness of nicotine patches and are valid reasons for stopping patch use. Most NRT users who relapse in fact cease aid use simultaneously (Pierce et al., 1987). Excluding all those who relapsed from all analyses would therefore overestimate the association between patch use and cessation, particularly so when conservative intent-to-treat analyses are employed.

4.2 Conclusions

The mailed distribution of free nicotine patches to smokers at large can be effective at promoting cessation, particularly among financially disadvantaged groups, those with previous experience in using it and among individuals with already advanced intent to quit. As quitting smoking is more likely among those who use the full 5-week supply of free nicotine patches, strategies aimed at encouraging greater compliance with the advised treatment regimen, by way of offering

additional support or highlighting self-help strategies, may improve cessation outcomes as well as enhance the value of real-world mass distribution programs.

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Chapter 4: Unassisted Smoking Cessation: The Role of Motivation and Personality Factors (Manuscript 3)

Preamble:

The idea for this study was in part, borne out of findings from Manuscript 2, which demonstrated that despite the provision of free nicotine patches to help smokers quit, a small proportion of individuals opted for quitting (and successfully achieved self-reported cessation) without the use smoking cessation aids. These findings spurred interest to examine whether there are certain traits or intrinsic motivational reasons that drive smokers to select and ultimately quit without the use of formal cessation assistance.

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Unassisted Smoking Cessation: The Role of Motivation and Personality Factors

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Abstract

Introduction: Qualitative research has identified that quitting smoking without formal assistance requires greater motivation for change, dedication, and willpower. However, as these concepts have not been quantitatively examined, we aimed to evaluate how motivational reasons for quitting and personality factors predict quitting smoking unassisted.

Methods: Former smokers (quit between 1 - 12 months ago; n=319) recruited through the online crowdsourcing platform MTurk were retrospectively surveyed on their quitting methods, motivational reasons for quitting, the five-factor personality traits (extraversion, neuroticism, agreeableness, conscientiousness and openness to experience), as well as perception and knowledge of smoking cessation aids. A logistic regression model was used to investigate the predictive role of these variables on quitting smoking unassisted.

Results: Of the sample, 56.7% (n=181) reported to have quit with the use of smoking cessation aids or health professional assistance, whereas 43.3% (n=138) quit unassisted. Successful unassisted cessation was associated with higher conscientiousness scores (OR = 1.71; 95%CI 1.07-2.73), and perceptions of greater drawbacks (OR = 1.87; 95%CI 1.42-2.45) and reduced advantages (OR = 0.41; 95%CI 0.25-0.67) of nicotine replacement therapy. Neither autonomous nor controlled motivational reasons for quitting predicted quitting unassisted.

Discussion: The findings are consistent with smokers' views from qualitative research that aspects of the conscientiousness personality trait (i.e., self-discipline) are important for successfully quitting unassisted. Motivational reasons for quitting however, do not seem to play a role in precisely how a smoker achieves cessation.

Introduction

Smoking continues to be the leading cause of preventable disease and premature death, claiming the lives of 6 million people annually, and placing a significant economic burden on countries worldwide (World Health Organization, 2011). In response to this epidemic, smoking cessation research has primarily focused on developing and evaluating interventions to improve smokers' odds of cessation. Overall the results have been promising, with systematic reviews and clinical guidelines suggesting that even brief interventions such as physician advice can increase the chances of quitting by up to 30% (Fiore et al., 2008). Stop-smoking medications also contribute to over two times greater odds of cessation compared to placebo control (Cahill et al., 2013). However, despite the proven efficacy of smoking cessation interventions, and their increasing availability worldwide, the majority of smokers quit unassisted (World Health Organization, 2009). In fact, systematic reviews of the literature have indicated that the prevalence of unassisted quit attempts over the past 30 years has ranged from 40.6% to 95.3% among current and former smokers, and that unassisted cessation rates are as high as 69% among some population samples (Edwards et al., 2014; Hung et al., 2011; Smith et al., 2015c). These findings have garnered considerable interest and debate regarding the effectiveness and appropriateness of promoting cessation aids over unassisted quitting in real-world settings. Some have argued that public health and pharmaceutical industry-sponsored campaigns advocating for medically assisted smoking cessation often undermine those who attempt to quit unassisted, and a greater understanding of why and how smokers quit without help is necessary for improving public initiatives (Chapman & Wakefield, 2013; Smith et al., 2015c). However, despite the growing

discussions, little is known about what distinguishes smokers who quit unassisted from those who seek help.

Few studies have examined this phenomenon directly, identifying that some demographic and clinical characteristics appear to play a role in the preference for quitting without assistance. Consistent evidence suggests that those who successfully quit unassisted are more likely to be male, younger, of an ethnic minority, less addicted to nicotine, and report higher levels of self-efficacy and confidence at the time of quitting (Mikkelsen et al., 2014; Smith et al., 2015c; Zhu et al., 2000). Discrepancies are present, however, in the association between unassisted quitting and education level, income, and socio-economic status (Hung et al., 2011; Smith et al., 2015c), which may, in part, be attributed to the various definitions offered for unassisted quitting. Other factors contributing to the incongruence in findings may be systematic recall biases among stop-smoking medication users, who have been documented to remember their quit attempt for a longer duration than those who attempt to quit unassisted, as well as differences in the quit attempt in question (any previous quit attempt vs. final quit attempt) (Borland et al., 2012; Smith et al., 2015c). It is important to highlight that no quantitative studies have investigated how personal characteristics, such as motivational reasons for change or personality traits, may influence one's choice and ultimate success in quitting without the use of aids or formal help. While quantitative research has been conducted on the predictive role of motivation and personality factors in quitting smoking in general among treatment seeking samples (Hakulinen et al., 2015; Munafo et al., 2007), how these factors drive smokers' preference for different quit methods has remained unexplored.

Qualitative research provides preliminary evidence, identifying that past experiences, personality, individual circumstances and other personal characteristics best guide how ex-

smokers chose to quit (Morphett et al., 2015; Smith et al., 2015b; Willems et al., 2013). A common belief among ex-smokers and smokers alike is that unaided cessation requires greater motivation for change, autonomy, dedication, readiness and commitment, whereas formal treatment is perceived as a "sign of weakness" (Balmford & Borland, 2008; Morphett et al., 2015; Smith et al., 2015b). In other words, unassisted quitting is perceived as more self-reliant and in turn more successful overall, whereas formal treatment is often viewed as better suited to those who exhibit greater tobacco dependency and less commitment/desire for change (Morphett et al., 2015). A recent systematic review of the literature on ex-smokers who quit unassisted further supports this view, as most ex-smokers who quit unassisted cited motivation (i.e., one's reason for quitting), commitment and willpower as the most important determinants of their success (Smith et al., 2015a). Although these findings suggest that personality and motivation may play a role in smokers' choice to quit unassisted, many of the qualitative studies conducted only address the attitudes of current and former smokers towards cessation methods, rather than explicitly exploring the roles of these factors in successful cessation. In addition, studies that have examined ex-smokers' experience with quitting, have only provided the one-sided view of unassisted ex-smokers.

To gain a more comprehensive understanding of why some smokers successfully quit without assistance, whereas others quit with the help of cessation aids or formal treatment, the present study surveyed ex-smokers to retrospectively examine how motivational reasons for quitting smoking and personality factors are associated with how they quit. Consistent with qualitative data on unassisted smoking cessation, it was hypothesized that participants who report greater autonomous motivation for quitting smoking would be more likely to have quit unassisted compared to those who report more controlled reasons for change. As the association

between unassisted smoking cessation and personality traits was previously unknown, it was exploratory in nature.

Methods

Participants

Participants were recruited via Amazon's crowdsourcing web service Mechanical Turk (MTurk), an online platform that allows individuals (i.e. requestors) to post tasks such as surveys that can be completed in exchange for monetary compensation. This platform has become popular among researchers for recruiting participants into behavioral health studies, largely due to its cost-effectiveness and efficiency in reaching demographically diverse and hard-to-reach samples (Buhrmester et al., 2011; Smith et al., 2015d). Participants were initially screened for eligibility using their answers to a short screener survey, which restricted participation to only those who were 19 years of age or older, reported smoking at least 10 cigarettes per day prior to quitting, and had successfully quit smoking within the past year, but not within the last 30 days. Limiting the last successful quit to have taken place within the past year but not in the last 30 days was purposefully selected to minimize recall bias, while also ensuring that the cessation attempt is not transient. Recruitment of participants was further restricted to individuals living in the United States or Canada, who had completed more than 100 tasks successfully with above 95% approval ratings, as these cut-offs have been found to ensure greater data integrity (Peer et al., 2014).

Design and Procedure

The survey was posted as a task on MTurk and advertised as a 15-20-minute survey for those who self-identified as having recently quit smoking. Individuals who accepted the task were directed to a more in-depth description of the study and brief online screener to determine eligibility. Those who were found eligible proceeded to an electronic consent page further detailing the research, their rights, as well as the researchers' and ethics board contact information in case of any questions. Participants were asked to carefully read the consent form and confirm their willingness to participate by accepting to have understood the research and their rights and click on a link to proceed to the main survey. Obtaining written or verbal consent was not possible since the study was conducted exclusively online on the MTurk platform, using functionally anonymous participants (Paolacci et al., 2010). The study and its consent process were approved by the standing research ethics board of the Centre for Addiction and Mental Health.

The survey was hosted by DatStat (Seattle, WA). Overall, the survey assessed: a) demographic characteristics; b) cessation methods employed during the last quit attempt; c) personality traits using the Big Five Inventory (John et al., 1991); d) level of autonomous and controlled forms of motivation using the Treatment Self-Regulation Questionnaire (Deci & Ryan, 1985; Deci & Ryan, 2000) adpated for smoking; e) past cessation attempts; f) perceptions of cessation aids and interventions using the Attitudes Towards Nicotine Replacement Therapy (ANRT-12) (Etter, 2001); and g) history of smoking behavior using the Fagerstörm Test of Nicotine Dependence (FTND) modified for past smoking behavior (Heatherton et al., 1991;

Hudmon et al., 2005). All participants who completed the survey were compensated with a $US 1.50 honorarium. The survey was active September 2 - 7, 2016.

Measures

Demographic characteristics. Information gathered on demographic characteristics included gender, age, marital status, level of education, personal income, self-reported mental health diagnoses, and past and current use of substances.

Employed cessation methods. Participants were asked to select if they used any of the following in their most recent quit attempt: (1) stopped suddenly without a plan (cold turkey); (2) used a self-help book/booklet to guide you; (3) tapered down until you quit; (4) used zyban / bupropion / wellbutrin; (5) used varenicline / champix / chantix (6) used a nicotine replacement therapy (e.g. nicotine patch, gum, lozenge or inhaler); (7) combined 2 forms of medication to stop (i.e. zyban and patch together); (8) used e-cigarettes and cut down on the amount smoked; (9) natural or alternative therapies (e.g. hypnotherapy, acupuncture, laser therapy); (10) individual or group counseling; (11) other (please specify). To further determine if ex-smokers used any formal treatment or professional assistance to quit, participants were asked if they discussed smoking cessation with a medical professional (e.g. doctor, pharmacist, dentist, naturopathic doctor, psychiatrist), and if so, what type of assistance they received (e.g. brief advice, pamphlet, referral to a smoking cessation specialist, counseling, or prescribed medication). Consistent with Smith et al. (Smith et al., 2015c) and the stance taken by the Cochrane Collaboration, unassisted cessation was defined as not using ongoing formal help from a health professional or pharmacological support, specifically including only those who quit

smoking suddenly without a plan, by gradual reduction, or using self-help material. This definition also included those who discussed smoking cessation with a medical professional but only received brief intervention assistance in the form of brief advice or a pamphlet.

BFI. The Big Five Inventory (BFI) is a well-validated multidimensional personality inventory that measures five personality domains (extroversion, agreeableness, conscientiousness, neuroticism, and openness), as defined by the Five Factor Model (John et al., 1991; John et al., 2008). The inventory was engineered to be a brief self-report measure of temporally stable individual differences and has been widely used in addictions research to identify associations between personality traits and addictive behaviors such as gambling, smoking, and substance use (Livingston et al., 2015; McCann, 2010; Miller et al., 2013). With strong reliability and convergent validity to the NEO personality inventory (John & Srivastava, 1999), the 44-item BFI was purposefully selected for its brevity and ease of understanding to be used in an online survey.

TSRQ. The Treatment Self-Regulation Questionnaire (TSRQ) is a validated scale that assesses the degree of self-directed motivation for engaging in a healthy behavior or behavioral change, as defined by Self-Determination Theory (Deci & Ryan, 1985; Deci & Ryan, 2000). Designed to be readily modifiable, it has been employed across various health change behaviors, including smoking cessation (Levesque et al., 2007; Williams et al., 2006a). Although the objective of the tool is to assess motivational reasons for engaging in current or future behaviors, variations of the scale have also been used to retrospectively measure motivation for engaging in past behaviors (Katz et al., 2015). In general, the scale measures motivation on a continuum that ranges from more self-regulated reasons for change (i.e. autonomous) to more controlled reasons for change (i.e. introjected, external), as well as the absence of motivation (i.e. amotivation). To

measure past motivation for smoking cessation, participants were presented with the statement "The reason I quit smoking was…", and then asked to rate their agreement with different reasons for change on a 7-point Likert scale that ranges from 1 (*not at all true*) to 7 (*very true*). Composed of 15 items, the tool measures five different motivational constructs: integrated motivation (e.g., "Because stopping smoking was an important choice I really wanted to make."); identified motivation (e.g., "Because I carefully thought about it and believed stopping smoking was very important for many aspects of my life"); introjected motivation (e.g., "Because I would have felt bad about myself if I smoked"); external motivation (e.g., "Because I felt pressure from others to stop smoking permanently."); and amotivation (e.g.," I really didn't think about stopping smoking"). Each construct is scored by computing the mean of the responses that comprise it; however motivations which are more self-regulated and internal (i.e., identified and integrated) have typically been combined to represent autonomous motivation, whereas more external motivations (i.e., introjected and external) collectively represent controlled reasons for change (Deci & Ryan, 1985; Deci & Ryan, 2000; Levesque et al., 2007). Amotivation however, is traditionally viewed as a stand-alone construct that describes the lack of or absence of motivation (Deci & Ryan, 2000).

History of smoking behavior. Past smoking behaviors and previous tobacco dependence were measured retrospectively using questions on smoking onset, previous cessation attempts, as well as a modified version of the FTND for past smoking behavior, which has been shown to demonstrate good reliability when compared to FTND scores assessed prior to treatment (Heatherton et al., 1991; Hudmon et al., 2005).

Perceptions and knowledge of cessation aids. Perception and knowledge of cessation aids was assessed using the Attitudes Towards Nicotine Replacement Therapy (ANRT-12) scale

(Etter, 2001). Composed of 12 items, this tool asked participants to rate their agreement with 8 statements that reflect the advantages to using NRT (e.g., "The products help people to feel less irritable when they quit smoking"), and 4 statements that reflect the drawbacks (e.g. "There is a risk of becoming dependent on these products"), on a 5-point Likert scale ranging from 1 (*strongly disagree*) to 5 (*fully agree*). Each subscale was scored by computing the mean of responses that comprise it, however a minimum of two valid answers were required for this calculation. Further, an additional knowledge subscale was computed as the number of correct responses (i.e., an answer of 4: *generally agree* or 5: *fully agree*) to items that are related to factual knowledge about NRT (e.g., "These products help people to feel less depressed when they quit smoking").

Validity measures. Consistent with techniques employed by Kim and Hodgins (Kim & Hodgins, 2016), both overt and subtle measures of response validity were included in the survey to determine whether participants provided honest and accurate answers. Specifically, at the end of the survey participants were asked to indicate their agreement with the following questions on a Likert scale ranging from 1(strongly disagree) to 7 (strongly agree): "*I answered all questions truthfully*", and "*I paid close attention to all questions*". Participants were also asked a face validity question to indicate whether they thought their answers should be kept or discarded, however, were informed that their answer would not affect their reimbursement. In addition, an attention check question was also embedded within the BFI items, prompting subjects to select the '*strongly agree*' option. Participants who failed to provide the desired response (indicating inattention) were excluded from all analyses.

Data Analysis

A priori power and sample size calculations were conducted based on the estimate that 50% of the sample would have quit smoking unassisted. Primary analyses were designed to employ a binary logistic regression model to investigate the role of 14 variables (age, gender, level of nicotine dependence prior to quitting (FTND), 5 personality factors, autonomous motivation, controlled motivation, amotivation, and perception and knowledge of smoking cessation aids (3)) as predictors of unassisted smoking cessation among former smokers. In keeping with an acceptable 10 outcome events per predictor variable (EPVs; unassisted cessation) (Vittinghoff & McCulloch, 2007), it was estimated that a minimum of 280 subjects would be required for the survey. With 10 EPVs and a total of 280 subjects in the study, the analyses would yield 95% confidence interval coverage, type I error $< 5\%$, and minimal relative bias.

In total, 403 participants were found eligible and completed the survey. Data cleaning efforts identified that 35 individuals were falsely eligible as they were initially ineligible to participate but met eligibility criteria after repeated screener completion attempts. Data from an additional 46 individuals was excluded due to negative endorsement of the face validity question (n=3), failed attention check question (n=23), and whose mean time to completion was less than half of the remaining sample (mean: 15.10min, SD = 7.22) (n=20). Of the remaining 322 participants, outlier analyses were subsequently performed by calculating the multivariate distances (i.e. Mahalanobis D) for both the tool items and response frequencies of the BFI and TSRQ, in line with the recommendations of Godinho et al. (2016) Participants with outlier data on two or more measures were excluded (n=3). All analyses were therefore conducted using data of the remaining 319 participants.

Demographic and smoking characteristics were compared between ex-smokers who quit unassisted vs. assisted using one-way analyses of variance for continuous variables and chi-square tests for categorical variables. To minimize bias due to missing data on the ANRT-12 advantages subscale (4.1%) and drawbacks subscale (1.9%), multiple imputations analyses were used to generate 10 imputed datasets with the 14 predictor variables of the primary analyses (discussed above) acting as auxiliary variables in the imputation model (Graham et al., 2007). Primary analyses employed a binary logistic regression model to investigate the role of the 14 variables as predictors of unassisted smoking cessation among former smokers, using the multiple imputed data. All analyses were conducted using IBM SPSS v.24.0.

Results

Demographic and smoking history characteristics of our sample are presented in Table 1. Of the entire sample, 56.7% (n=181) of former smokers reported to have quit with the use of smoking cessation aids or health professional assistance, whereas 43.3% (n=138) quit unassisted. Approximately three quarters of the entire sample (74.0%, n=236), regardless of quit method, had quit for longer than 3 months. Differences in demographic and smoking history characteristics were observed between the samples who had quit using assisted vs. unassisted methods, such that unassisted quitters were less likely to be students, had lower levels of nicotine dependence (FTND scores) prior to cessation, and started smoking daily at a later age, compared to assisted quitters.

Table 1. Demographic and smoking history characteristics by quit method.

	Assisted quitters (n=181)	Unassisted quitters (n = 138)	p-value
Demographic Characteristics			
Age, mean (SD)	35.9 (9.7)	35.5 (9.6)	0.697
Female, % (n)	56.9 (103)	55.1 (76)	0.744
Marital Status, % (n)			0.869
Married/Common-law/same sex partner	53.1 (95)	52.1 (73)	
Single/divorced/separated/widowed	45.9 (84)	47.9 (67)	
Employment status, % (n)			0.066
Full-time	66.9 (121)	74.6 (103)	
Part-time	13.8 (25)	10.9 (15)	
Student	6.1 (11)	0.7 (1)	
Not Employed	13.3 (24)	13.8 (19)	
Education Level, % (n)			0.741
Less than high school diploma	0 (0)	0 (0)	
High school diploma	28.2 (51)	31.9 (44)	
Community college or university degree	64.1 (116)	61.6 (85)	
Professional or Master's degree or higher	7.7 (14)	6.5 (9)	
Household Income, % (n)			0.388
Under $20,000	14.9 (27)	10.1 (14)	
$20,000 - $39,999	25.4 (46)	22.5 (31)	
$40,000 - $59,999	23.2 (42)	26.1 (36)	
$60,000 - $79,99	18.8 (34)	23.2 (32)	
$80,000 - $99,999	8.3 (15)	12.3 (17)	
$100,000 +	9.4 (17)	5.8 (8)	

Smoking Characteristics

Cigarettes/day, mean (SD)	18.8 (7.9)	17.5 (7.5)	0.129
FTND score, mean (SD)	4.1 (1.3)	3.8 (1.3)	**0.021**
Age at first smoking, mean (SD)	16.3 (4.2)	16.7 (4.8)	0.423
Age at daily smoking, mean (SD)	18.8 (4.3)	19.9 (5.7)	**0.050**
Number of previous quit attempts, % (n)			0.211
0	0.6 (1)	0.7 (1)	
1 – 2	30.4 (55)	38.4 (53)	
3 – 5	39.8 (72)	41.3 (57)	
6 +	29.3 (53)	19.6 (27)	
Duration since quitting			0.752
1 to 3 months ago	27.6 (50)	23.9 (33)	
3 to 6 months ago	34.3 (62)	35.5 (49)	
6 to 12 months ago	38.1 (69)	40.6 (58)	
Number of times previously successful at quitting smoking for more than 1 month, % (n)			0.538
0	1.7 (3)	1.4 (2)	
1 – 2	71.8 (130)	79.0 (109)	
3 – 5	22.7 (41)	16.7 (23)	
6 +	3.9 (7)	2.9 (4)	

Note: Bold denotes significant findings ($p < 0.05$).

Table 2 displays the proportion of quit methods used by smokers who quit with the help of cessation aids or formal treatment, identifying that three quarters (75.7%) of assisted quitters had used electronic cigarettes in their latest quit efforts, followed by nicotine replacement therapy in approximately 40% of cases. Evaluating whether quitting smoking was discussed with a medical

professional, a significantly greater proportion of assisted quitters discussed cessation with a general family practitioner (54.7%; n=99), compared to unassisted quitters (33.3%; n=46) (χ^2 (1, N = 319) = 14.41, $p < 0.001$). Of those that discussed quitting, 44.4 % (n=44) of assisted quitters were provided with any form of support, while 2.2% (n=1) of identified unassisted quitters received either brief advice to quit or a pamphlet (χ^2 (1, N = 145) = 26.22, $p < 0.001$). No differences were observed between the two groups in discussing cessation with a pharmacist (5.5% assisted vs. 2.2% unassisted), dentist (6.1% assisted vs. 3.6% unassisted), naturopathic doctor (3.3% assisted vs. 0.7% unassisted), or medical specialist (9.4% assisted vs. 4.3% unassisted) ($p > 0.05$).

Table 2. Proportions of quit methods used by smokers who quit using cessation aids or formal treatment (n=181).

	Proportion of Assisted Quitters %, (n)
Electronic cigarettes	75.7 (137)
Nicotine Replacement Therapy	39.8 (72)
Tapered down	39.2 (71)
Bupropion	8.8 (16)
Varenicline	7.2 (13)
Natural or alternative therapies	6.6 (12)
Smokers' helpline	6.1 (11)
Counseling (individual or group)	3.9 (7)
Self-help resources (i.e. books, online)	3.3 (6)
Combined 2 forms of medication	2.2 (4)

Note: Endorsement of any particular quit method was not mutually exclusive.

Evaluating predictors of unassisted smoking cessation, pooled estimates of the logistic regression analyses (Table 3) revealed that former smokers who had lower pre-cessation nicotine dependence levels were more likely to have quit without using smoking cessation aids or formal

medical intervention. Individuals who perceived greater drawbacks of smoking cessation aids (specifically NRT) and scored higher on the conscientiousness personality domain were close to 2 times more likely to have quit unassisted. Conversely, those who endorsed greater advantages of smoking cessation aids were significantly less likely to have quit unassisted. No issues of multicollinearity were found between any of the predictor variables. For the entire sample, each personality domain and motivation construct mean (standard deviation) scores were as follows: Extraversion, 3.20 (0.95); Agreeableness, 3.94 (0.69); Conscientiousness, 4.02 (0.72); Neuroticism, 2.69 (1.06); Openness, 3.77 (0.68); Autonomous motivation, 6.00 (1.07); Non-autonomous motivation, 3.70 (1.61); Amotivation, 1.96 (1.18); perception of NRT advantages, 3.65 (0.90); perception of NRT drawbacks, 3.26 (1.07); accurate knowledge of NRT effectiveness, 2.99 (2.34).

Table 3. Predictors of unassisted smoking cessation (n=319).

	OR	95% CI	*p*-value
Age	0.99	0.96 – 1.02	0.351
Gender			
Male	1.00	Reference	
Female	0.90	0.52 – 1.55	0.695
FTND Score	0.84	0.69 – 1.03	0.096
BFI			
Extraversion	1.06	0.76 – 1.47	0.727
Agreeableness	0.72	0.46 – 1.13	0.154
Conscientiousness	**1.71**	**1.07 – 2.73**	**0.024**
Neuroticism	1.06	0.75 – 1.50	0.740
Openness	0.99	0.67 – 1.50	0.995
Motivation			
Autonomous	0.97	0.73 – 1.29	0.850
Non-autonomous	0.99	0.83 – 1.19	0.924
Amotivation	1.22	0.96 – 1.57	0.112
Perception and knowledge of cessation aids			
Perceived advantages	**0.41**	**0.25 – 0.67**	**<0.001**
Perceived drawbacks	**1.87**	**1.42 – 2.45**	**<0.001**
Knowledge	1.14	0.95 – 1.37	0.159

Note: Bold denotes significant findings (p<0.05). OR, odds ratio; CI, confidence interval.

Discussion

This exploratory retrospective analysis of a cohort of recent quitters revealed that higher conscientiousness, but not motivation, predicted whether a smoker successfully quits unassisted. While studies have previously focused primarily on identifying personality factors associated with smoking cessation in general, finding that lower neuroticism predicts cessation (Hakulinen et al., 2015; Munafo & Black, 2007), the association between personality traits and smoking cessation methods presents another layer of complexity to the interplay between personality and smoking behaviors. The findings are conceptually consistent with smokers' views about quitting methods from qualitative research, citing tenets of the conscientiousness trait as being important for unassisted quitting - willpower, strong desire, and determination (Morphett et al., 2015). They suggest that individuals scoring high on this trait who attempt to quit unaided are likely to have the self-discipline and commitment to resist smoking urges and adhere to a self-help program (del Río., et al., 2015). It is notwithstanding however, that the choice of utilizing and ultimately quitting with cessation aids may also be governed by both positive and negative perceptions that smokers hold towards them. Controlling for the contribution of both negative and positive perceptions towards smoking cessation aids in our model, the role of conscientiousness is robust in spite of these factors.

Contrary to our hypothesis, autonomous reasons for quitting smoking did not predict unassisted smoking cessation. We suspect that this null finding may be reflective of a collective tendency among former smokers to recall the desire to quit smoking as intrinsically motivated and volitional, regardless of the method by which smokers quit. Indeed, mean ratings of

autonomous reasons for quitting among participants in the current study were 6 on a 7-point scale, and are consistent with other reports that the most predominant reasons for quitting among ex-smokers are intrinsic health concerns, while those least influential are extrinsic social pressures and reinforcement (Cuc et al., 2014; Curry et al., 1997; McCaul et al., 2006). It is therefore plausible that among current smokers who are intent on quitting and have already set a quit date, their reasons for doing so may not play a role in precisely how they plan to achieve cessation. In contrast, for smokers with reduced intent to quit or those contemplating quitting, autonomy support can be beneficial in motivating them to use medications and achieve cessation (Williams et al., 2006b). Further, the notion that unassisted quitters are 'more motivated' than those opting to use cessation aids or behavioral support does not seem to have empirical support. While the concept of motivation or reasons for quitting are central to undertaking and persisting through a quit attempt, these reasons may not be discernable between quitting methods, and it is perhaps belief in the ability to quit and self-efficacy which are better predictors of unassisted cessation (Myers et al., 2015; Willems et al., 2013).

We further identified that a lower proportion of unassisted quitters had discussed smoking cessation with their physician, consistent with other reports. Although over one third of unassisted quitters discussed smoking with a general family practitioner, fewer than 3% of these had received brief advice or a pamphlet, suggesting that physician contribution in those quit efforts was minimal. It has been noted that the reluctance to consult a physician among smokers making an unassisted quit attempt is rooted in the belief that smoking is not an illness and that quitting is a personal responsibility (Smith et al., 2015b), which may be further reinforced if the smoker holds negative views about cessation aids or perceives that general practitioners have little to offer. Negative health-related events (i.e., particularly those requiring hospitalization)

may also precipitate the use of smoking cessation aids and physician support, thus mediating the likelihood of successful assisted quitting. Indeed, many hospital-based smoking cessation programs, in-line with clinical practice guidelines (Fiore et al., 2008), position papers (Pipe et al., 2011), and hospital smoke-free policies (Reid et al., 2010), help smokers manage their nicotine withdrawal and cravings during hospitalization usually through the provision of free NRT with brief or intensive counseling support (see Rigotti et al. 2012 for review). Pooled estimates of these programs' effectiveness have revealed that the combination of hospital-based pharmacotherapeutic and counseling interventions can increase quit rates by 37% at six to 12 months following discharge, and up to 71% in rehabilitation centers (Rigotti et al., 2012). Experiencing a serious medical illness requiring physician support or hospitalization (whether smoking-related or not) therefore may have contributed to the likelihood of assisted cessation in our sample, however this was not examined as part of our primary outcomes model.

The results of the present study should be considered in the context of several limitations. First, while addiction populations recruited through the MTurk platform provide self-report data which exhibits both good concurrent and convergent validity (Kim & Hodgins, 2016), participants in the present study were not representative of the general ex-smoker population and could not be confirmed for smoking abstinence via biochemical means. Second, the retrospective nature of the present study could have made participant responses subject to recall bias and thus prospective designs are necessary to confirm the present findings. Third, we acknowledge that the Five Factor Model has been subject to criticism, primarily for not providing a complete theoretical framework of personality and limiting the personality domain to five broad descriptors (John & Srivastava, 1999; Smith & Williams, 1992). However, the model has also been praised for its external validity and predictive utility of life and health outcomes. Given its

commonality with other personality constructs and the brevity of the BFI (John & Srivastava, 1999), it presented a scalable way of exploring how personality traits interact with health-change behavior choices. Fourth, attitudes towards NRT may not have been representative of participants' perception towards all smoking cessation aids. Particularly in light of recent evidence that e-cigarette use is becoming the most dominant cessation method (Beard et al., 2016), a finding also identified in the present study, their perceived harms and helpfulness in quitting smoking may differ from conventional pharmacotherapies (Barbeau et al., 2013). Further, these attitudes towards cessation aids were also assessed after individuals had quit smoking and may have changed from prior to their last quit attempt.

Overall, findings from this study provide support for the role of individual personality trait differences in predicting the likelihood of successful unassisted smoking cessation. Future research is warranted to prospectively examine whether personality traits predict smoking cessation success, as part of both integrated cessation programs and unassisted quit efforts.

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Chapter 5: Impact of Large-Scale Distribution and Subsequent Use of Free Nicotine Patches on Primary Care Physician Interaction (Manuscript 4)

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Impact of Large-Scale Distribution and Subsequent Use of Free Nicotine Patches on Primary Care Physician Interaction

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Abstract

Background: Large-scale distribution efforts of free nicotine replacement therapy (NRT) have been documented to be cost-effective interventions for increasing smoking quit rates. However, despite nearly a dozen studies evaluating their effectiveness, none have examined whether free NRT provision promotes further primary care help-seeking and the impact that it may have on cessation efforts.

Methods: In the context of a randomized controlled trial, a secondary analysis was conducted on 1000 adult regular smokers randomized to be mailed a 5-week supply of nicotine patches or to a no intervention control group. Recipients and users of free nicotine patches at an 8-week follow-up were successfully case matched to controls based on age, gender, and baseline level of nicotine dependence and intent to quit (n=201 per group). Differences in physician interaction between the two groups were evaluated at both 8-week and 6-month follow-ups. The impact of physician interaction on self-reported smoking abstinence at each follow-up was also examined.

Results: Although no differences in physician interaction were noted between groups at the 8-week follow-up, at the 6-month follow-up, nicotine patch users reported greater frequency of discussing smoking with their physician (43.9%), as compared to the control group (30.3%) (p=0.011). Across both groups, over 90% of those that discussed smoking with a physician were encouraged to quit and approximately 70% were provided with additional support. Separate ANOVAs revealed no significant impact of physician interaction on

cessation ($p>0.05$), regardless of group or follow-up period, however, at the 6-month follow-up, nicotine patch users who discussed cessation with a physician had made serious quit attempts at significantly greater rates (72.6%), compared to controls (49.1%) ($p=0.007$).

Conclusions: Irrespective of group, the majority of smokers in the present study did not discuss cessation with their physician. Recipients and users of nicotine patches however, were more likely to discuss smoking with their physician, suggesting that the provision of free NRT particularly to those who are likely to use it may facilitate opportunities for benefits beyond the direct pharmacological effects of the medication.

Trial registration: clinicaltrials.gov, NCT01429129. Registered: 2 September 2011.

Key Words: Smoking Cessation, Nicotine Replacement Therapy, Primary Care Physicians, Tobacco, Health Professionals

Introduction

Physicians are thought to play a critical role in the provision of smoking cessation assistance to patients (Davis, 1988). As more than 70% of smokers visit a physician annually (Leatherdale & Shields, 2009), medical practitioners are seen to have optimal opportunity to promote smoking cessation to their patients. Primary care practitioners in particular are visited on average more than 4 times per year by patients that smoke, and have thus been directed by clinical practice guidelines to identify and offer support to smokers at every visit. The Clinical Practice Guidelines for Treating Tobacco Use and Dependence, originally developed in 1996 by the United States Department of Human Health Services, stress that primary care physicians should treat tobacco dependence as a chronic disease and follow the 5A's model of: asking about smoking, assessing readiness to quit, advising smokers to stop, assisting patients with treatment, and arranging follow-up. These forms of intervention have been shown to be quite effective in motivating and driving smokers to quit, where even brief advice increases the odds of cessation (Aveyard et al., 2012; Stead et al., 2008). Combined behavioral counseling and pharmacotherapy however, has been shown to be the most effective at treating tobacco dependence, producing the highest odds of quitting and progressively higher quitting estimates with increased number of counseling sessions (Fiore et al., 2008).

Despite evidence showing that smoking cessation intervention in primary care is effective at helping smokers quit and offers a cost-effective option of reaching most smokers (Cummings et al., 1989), studies have shown that physicians have not been active in providing such assistance. Population-based surveys of smokers have revealed that between

44% and 71% were ever advised to quit, and even fewer received any form of intervention (Anda et al., 1987; Goldstein et al., 1997; Quinn et al., 2005). One telephone-based population survey had further documented that discussion about smoking was largely dependent on whether smokers were women, in the preparation stage of change, in fair or poor health, and smoked for a greater number of years (Goldstein et al., 1997). With follow-up care also arranged in less than 10% of all visits (Goldstein et al., 1997; Quinn et al., 2005), these practice gaps confirm findings from physician surveys that report physician behavior is below recommended guidelines (Goldstein et al., 1998; Schnoll et al., 2006; Thorndike et al., 1998).

To address such gaps, researchers have called for specific strategies aimed at enhancing the integration of clinical smoking cessation interventions into primary care settings. Some of these strategies include advanced training initiatives for physicians, enhanced use of established interventions, establishing performance feedback for practitioners, as well as the provision and combined use of low-cost or cost-free pharmacotherapy for patients (Papadakis et al., 2010; Schnoll et al., 2006). While several trials have evaluated the effectiveness of multi-component interventions in primary settings, to date, only one investigated the provision of cost-free medication. The trial revealed that the provision of cost-free nicotine replacement therapy (NRT) or bupropion in combination with general practitioner training strongly increases the odds of cessation (odds ratio of 4.77) and is markedly cost-effective in reducing smoking-related morbidity (Salize et al., 2009; Twardella & Brenner, 2007). As these findings suggest that smoking cessation support and provision of free pharmacotherapy in primary practice is an effective strategy of reducing

smoking prevalence in the general population, cost-free medication provision appears to be an important component of achieving higher abstinence rates.

Over the past decade, many giveaway programs outside of clinical settings have provided NRT to large samples of smokers as part of a telephone quitline or large-scale distribution program. Studies evaluating these programs have generally revealed that compared to non-treatment cohorts, smokers receiving NRT were able to achieve higher quit rates, and that offering free NRT is an effective intervention in encouraging program participation, improves treatment satisfaction, and is cost-effective (Bush et al., 2008; Cummings et al., 2006; Miller et al., 2005; Swartz et al., 2005; Tinkelman et al., 2007). Direct causal evidence on the efficacy of large-scale distribution of free NRT has also been recently established, documenting that despite concerns over the 'real-world' effectiveness of NRT (Kotz et al., 2014a, 2014b), the mailed distribution of free nicotine patches in absence of behavioral support more than doubled the odds of cessation at a 6-month follow-up (Cunningham et al., 2016). Nonetheless, no previous studies had evaluated whether the provision of free NRT had promoted further help-seeking and what impact that interaction may have had. As mass distribution of NRT is being considered in many jurisdictions across the United States and Canada, it is important to identify whether this form of intervention drives smokers to seek out additional front-line support.

In the context of a randomized controlled trial evaluating the efficacy of mass distribution of free NRT to smokers, the aim of this study was to examine whether and to what extent the provision of free NRT impacts smokers' interaction with primary care physicians. In particular, the research attempted to answer the question: does the provision and subsequent use of free nicotine patches to smokers interested in quitting promote

interaction with their primary care physicians, and whether that interaction has a role in

quitting smoking?

Methods

Study Design and Participants

A detailed research protocol of the overall trial design and primary outcomes are published

elsewhere (Cunningham et al., 2016; Cunningham et al., 2011). Briefly, the trial employed a

single blinded, panel survey design with random assignment to an experimental and a control

group. Random digit dialing of Canadian telephone numbers and an initial interview was

used to identify households with adult (age 18 or over) smokers who smoke 10 or more

cigarettes per day. One individual from each household who was willing to take part in a

smoking study that involves three interviews (baseline, 8-week and 6-month follow-ups) was

randomly selected (according to most recent birthday). Of 43,785 households contacted,

2,737 contained at least one adult daily smoker, and 2,093 consenting individuals were

interviewed (response rate of 76.5%) in English or French.

As part of the baseline survey, eligible participants (n=1000) were identified and randomized

into experimental and control groups to receive versus not receive free nicotine patches.

Eligibility was determined by a series of questions regarding hypothetical interest in nicotine

patches to quit smoking (including willingness to have nicotine patches sent to their home)

and having no contraindications for using NRT. A randomized half of eligible participants

were assigned to the experimental group and asked for their permission to have nicotine

patches sent to their home. These participants were sent a package of 5 weeks of nicotine patches (tapered regimen of 3 weeks 21mg patches, 1 week 14mg patches, and 1 week 7mg patches) to their homes via expedited postal mail to help them quit smoking. The package also contained a cover letter instructing them on the use of the patches, a list of answers to frequently asked questions, as well advice to talk to their physician or pharmacist if they had further questions. Participants in the control group were not offered nicotine patches or any other form of support, and were not aware that nicotine patches were offered to others.

Baseline and Follow-up Measures

All baseline and follow-up surveys were conducted by trained interviewers from the University of Waterloo Survey Research Centre. In addition to assessing eligibility for the randomized controlled trial, the baseline survey assessed participants' level of nicotine dependence using the Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991), intent to quit using the Transtheoretical Model's stages of change (precontemplation, contemplation, and preparation stages) (Prochaska & Velicer, 1997; Velicer et al., 1992), number and duration of past quit attempts, past use of NRT, motivation to quit smoking, a series of demographic characteristics, and the presence of a family practitioner. Those expressing intent to quit in the next 30 days and 6 months (preparation and contemplation stages, respectively) were further asked of their comfort in discussing smoking cessation with their primary care practitioner and whether they perceived their physician was aware of their interest in quitting.

Follow-up surveys conducted at both 8 weeks and 6 months post-baseline assessed smoking status, where abstinence at each of the follow-up periods was measured as positive endorsement of 'not smoking even a puff' for at least 7 days or 30 days, respectively. At 8 weeks, participants in the experimental group were asked if and how much of the nicotine patches sent to them were used (assessed using response options of "none", "some" and "all"), whether they had informed their physician of NRT use, their reasons for and against informing their physician, as well as having received additional support from their physician. Participants in the no-intervention control group were asked whether they had purchased and used any nicotine patches over-the-counter (OTC), had discussed smoking cessation with their physician post-baseline and the support, if any, they had received. At 6 months, all participants regardless of their randomly allocated group were asked if they had talked to their physician about smoking since they were last interviewed, whether they were encouraged by their practitioner to quit, and what forms of smoking cessation intervention were provided to them to help them quit. Discussion of smoking cessation with a primary care practitioner at 6 months post-baseline was the primary outcome measure.

Analyses

To investigate the impact of free NRT provision and use on physician interaction and smoking cessation, participants in the experimental group who endorsed using at least some of the provided nicotine patches by the 8-week follow-up (n=246) were case matched to participants in the control group based on age, gender, severity of nicotine dependence, stages of change (precontemplation, contemplation, and preparation stages) and the

completion of the 8-week follow-up survey. Both age and severity of nicotine dependence as determined by FTND were recoded into categorical values to facilitate optimal case matching. The age variable was recoded into five categories of 18 -24, 25-34, 35-44, 45-54, and 55+, while FTND scores of 1 or 2 corresponded to low dependence, scores of 3 or 5 – low to moderate dependence, scores of 5 to 7 – moderate dependence, and scores of 8 to 10 – high dependence. A total of 201 nicotine patch users were case matched to 201 no-intervention control participants.

Group differences in baseline demographic and smoking characteristics were evaluated using one-way analysis of variance (ANOVA) analyses for continuous variables and Pearson's chi-square tests of independence for categorical variables. In line with recommendations for outcomes analysis of matched case-control data (Breslow & Day, 1980; Niven et al., 2012), McNemar's tests were used to evaluate differences in physician interaction at each follow-up, defined as discussing smoking with a physician. These analyses restricted the data to case-controlled pairs and were thus conducted only among those who were followed up and had a family physician at the respective follow-up (8 weeks: 177 matched pairs; 6 months: 155 matched pairs). Among specifically nicotine patch users in the experimental group, within group analyses further used chi square analyses to examine the impact of amount of nicotine patches used on physician interaction. To investigate the impact of physician interaction on cessation outcomes at 8 weeks and 6 months, separate univariate ANOVAs were conducted with group (experimental group nicotine patch users vs. control) as the between subjects factor, physician interaction at each follow-up as the within subjects factor, and making a serious quit attempt (defined as stopping smoking for one day or longer) and self-reported smoking abstinence (7-day point prevalence abstinence at 8

Health satisfaction, mean (SD)[b]	3.2 (1.2)	3.2 (1.1)	0.764
Smoking Characteristics			
Cigarettes/day, mean (SD)	18.0 (7.2)	17.9 (6.8)	0.820
FTND score, mean (SD)	5.0 (1.7)	5.0 (1.8)	0.822
Level of Nicotine Dependence, % (n)			1.000
Low	8.0 (16)	8.0 (16)	
Low to Moderate	29.4 (59)	29.4 (59)	
Moderate	56.2 (113)	56.2 (113)	
High	6.5 (13)	6.5 (13)	
Age at first smoking, mean (SD)	14.4 (4.2)	14.8 (3.8)	0.307
Years as smoker, mean (SD)	25.9 (13.3)	24.2 (13.0)	0.199
Number of previous quit attempts, % (n)			0.142
0	5.0 (10)	3.0 (6)	
1-5	63.2 (127)	72.1 (145)	
6 +	31.8 (64)	24.9 (50)	
Past quit methods or aids used, % (n)			
Nicotine replacement therapy (patch/gum/inhaler)	68.6 (131)	64.1 (125)	0.351
Bupropion	34.0 (65)	31.3 (61)	0.565
Varenicline	33.0 (63)	24.6 (48)	0.069
Counselling (individual or group)	7.3 (14)	5.1 (10)	0.370
Acupuncture/hypnosis/herbal remedies	16.2 (31)	16.4 (32)	0.962
Self-help materials	17.3 (33)	17.9 (35)	0.863
Stage of Change			1.000
Precontemplation, % (n)	20.4 (41)	20.4 (41)	
Contemplation, % (n)	39.3 (73)	39.3 (73)	
Preparation, % (n)	40.3 (81)	40.3 (81)	
Confidence in ability to quit, mean (SD)	5.8 (2.6)	5.6 (2.4)	0.428
Importance of quitting now, mean (SD)	7.6 (2.2)	7.7 (2.4)	0.768
Comfort in discussing smoking cessation with family doctor, mean (SD)[c]	8.5 (2.5)	8.7 (2.3)	0.623

Note: SD = standard deviation; FTND = Fagerström Test for Nicotine Dependence.
Age, Gender, FTND, and Stage of Change were used to case match control participants to recipients and users of nicotine patches in the experimental group.
[a] Sample sizes vary due to missing data on some variables.
[b] Health satisfaction was assessed by way of the World Health Organization Quality of Life Instrument (WHOQOL-BREF)(Skevington et al., 2004) question on health satisfaction over the past 2 weeks, where participants were asked to rate how satisfied they are with their health on a 5-point Likert scale of 1 (very dissatisfied) to 5 (very satisfied).

[c] Comfort in discussing smoking cessation with family doctor was assessed on a Likert scale of 1 (not at all comfortable) to 10 (very comfortable). This question was asked only of those in the preparation and contemplation stages of change.

At baseline, individuals in the preparation and contemplation stages of change (n=320) were asked whether they thought their doctor was aware of their interest in quitting smoking. Of this subgroup, 88.1% (n=141) of eventual nicotine patch recipients and 90.0% (n=144) of those in the control group had a family physician. Across both groups, three quarters (75.1%) had endorsed that their family doctor was aware, and of those, an average of 87.7% reported that their doctor encouraged them to quit. No differences in rates were noted between groups.

Physician interaction

Among those with a family physician at the 8-week follow-up (n=177 per group; 88% of entire sample), 26.0% of nicotine patch users had informed their physician they had started using their nicotine patches, while 25.4% of control participants had talked to their doctor about smoking ($p=1.00$). At the 6-month follow-up, among those contacted with a family physician (n=155 per group; 77% of entire sample), nicotine patch users reported greater frequency of discussing smoking with their physician (43.9%), as compared to the control group (30.3%) ($p=0.011$).

Of nicotine patch users at 8 weeks, 82.1% (n=165) reported to have used some but not all of the nicotine patches provided and 17.9% (n=36) reported to have used all the patches. No differences in physician interaction were observed between those who used all or

just some of the provided nicotine patches at both 8 weeks (χ^2= 0.96, *p*=0.327) and 6-month follow-ups (χ^2= 0.91, *p*=0.341).

Nicotine patch users' reasons for and against informing physicians of patch initiation

Among individuals in the experimental group, reasons for informing a physician of nicotine patch use were evaluated at the 8-week follow-up (n=48). While a large majority (62.5%) informed their physician of nicotine patch use as part of a visit for an unrelated issue, 39.6% had sought additional support, 18.8% felt obligated, 12.5% had concerns about possible interactions between the patches and other medication or health conditions, 8.3% were advised by a friend or family member, and 8.3% other reasons. Among nicotine patch users who had not informed their physician at 8 weeks of their nicotine patch use (n=133) on the other hand, the top-rated reason for not informing a physician of nicotine patch use was that they did not think they should have or needed to (56.2%). Other reasons were that it is time consuming to visit a doctor (52.6%), smoking is not a serious medical problem (27.8%), felt they could quit without physician help (26.3%), did not want to use prescription drugs (24.8%), have not seen a doctor (13.5%), believed that doctors can't help quit smoking (11.3%), and other (15.8%). Separately, reasons for and against informing a family physician of nicotine patch use were not mutually exclusive.
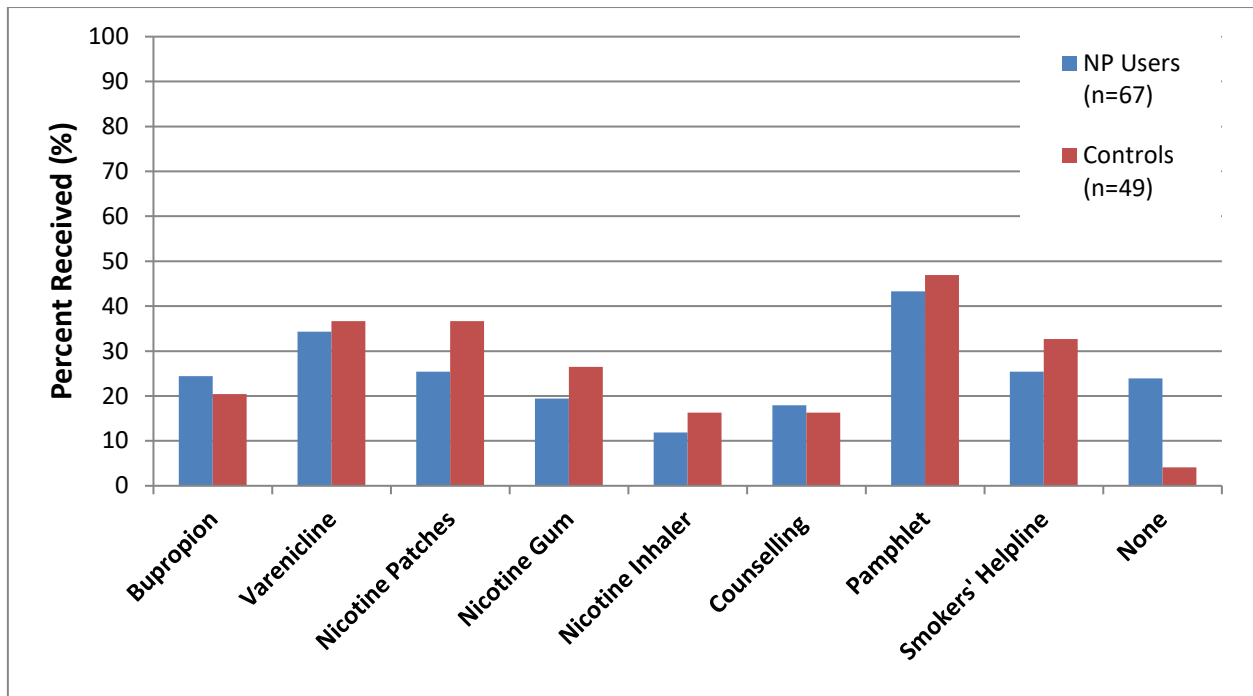
Physician assistance offered

Of participants who used the freely provided nicotine patches and informed their physician of doing so by the 8-week follow-up (n=48), 39.8% were offered additional support by way of a prescription for varenicline or bupropion, 35.4% were given a brief intervention in the form of a smokers' helpline number or pamphlet, 25% were provided with or offered counselling, 18.8% were encouraged to use nicotine gum or inhaler, and 31.3% received none of the above.

Of participants in the control group who had talked about smoking with their doctor by the 8-week follow-up (n=48), 83.3% (n=40) were encouraged to quit. Of these, 50% were offered varenicline or bupropion, 42.5% were given a brief intervention in the form of a smokers' helpline number or pamphlet, 32.5% were encouraged to use NRT (nicotine patch, gum or inhaler), 15% received or were referred to counselling, and 22.9% received none of the above.

At the 6-month follow-up, 91.8% (n=67) of nicotine patch users and 92.5% of (n=49) of controls who had talked to their family physician about smoking reported they had been encouraged to quit. Figure 1 depicts proportions of assistance offered by group among those who have talked to their physician about smoking.

Figure 1. Physician assistance offered between 8-week and 6-month follow-ups.

Note: NP, nicotine patch

Impact of physician interaction on smoking cessation

Separate univariate ANOVAs tests were conducted to evaluate the effect of group, physician interaction and physician interaction by group on quitting smoking at both 8 weeks (7-day point prevalence abstinence) and 6 months (30-day point prevalence abstinence) and making a serious quit attempt (quitting for one day or longer), using an intent to treat approach (Table 2). A main effect of Group was evident for abstinence and making a serious quit attempt at both follow-up periods, such that nicotine patch users exhibited greater cessation rates and serious quit attempts compared to case matched controls. A significant interaction effect between group and physician interaction was observed for making a serious quit

attempt at 6-month follow-up. Post-hoc analyses revealed that this interaction effect was driven by two observations: a) nicotine patch users who had discussed cessation with a physician had made serious quit attempts at significantly greater rates (72.6%), compared to controls (49.1%) (χ^2= 7.28, p=0.007); and b) within the control group, frequency of making serious quit attempts was higher among those that discussed smoking cessation with a physician at 6 month follow-up (49.1%), compared to those who did not speak with a physician (24.4%) (χ^2= 10.39, p=0.001).

Table 2. Impact of physician interaction on quitting smoking.

8-week Follow-up	Abstinence (7-day pp)		Serious Quit Attempt	
	F	p-value	F	p-value
Main effect of Group	5.69	**0.018**	160.11	**<0.001**
Main effect of Physician Interaction	1.93	0.165	1.97	0.161
Interaction between Group and Physician Interaction	2.96	0.086	0.442	0.506

6-month Follow-up	Abstinence (30-day pp)		Serious Quit Attempt	
	F	p-value	F	p-value
Main effect of Group	3.99	**0.047**	59.92	**<0.001**
Main effect of Physician Interaction	0.29	0.594	3.74	0.054
Interaction between Group and Physician Interaction	0.77	0.382	4.14	**0.003**

Evaluating quitters at 6 months (using 30-day abstinence point prevalence), no differences were observed between the two groups in physician interaction throughout the study, such that 45% (n=9) of abstainers in the nicotine patch use group had talked to their doctor at any

point throughout the study, compared to 62.5% (n=5) of those in the control group (Fisher's Exact Test, $p = 0.678$).

Discussion

To our knowledge, this is the only intervention study to date to evaluate the impact of free (to the end user) NRT provision on further help seeking and its associated smoking cessation implications. The study identified that while smokers are generally comfortable in turning to their primary care physicians for smoking-related support, most participants, regardless of whether they received and used nicotine patches, did not discuss cessation with their physician by either the 8-week or 6-month follow-ups. Among nicotine patch users at the 8-week follow-up, predominant reasons for not seeking support were beliefs that they did not need to visit a physician, it is time consuming to do so, and the perception that smoking is not a serious medical problem. Such reluctance to proactive support seeking suggests that most smokers generally hold passive views towards primary care physicians' role in smoking cessation when considering or initiating quitting. Other research has also documented that while some reluctance to consult a practitioner stems from individuals not seeing smoking as an illness (Fu et al., 2007; Levinson et al., 2006), others do not seek physician support due to the perception that they have little to offer or the belief that smoking is not a condition that requires medical help (Smith et al., 2015).

Of those that did visit their physician however, an overwhelming majority reported that their doctors were active in encouraging them to quit. Again, regardless of whether smokers had received and used free nicotine patches, between 83% and 93% of those that

discussed smoking cessation with their doctor throughout the 6-month duration of the study were advised to quit, and over 70% were offered additional or alternative support. While the provision and use of nicotine patches, and possibly just surveying about smoking habits, may aid in stimulating patient-initiated discussion of smoking cessation with primary care physicians, these findings point to an encouraging trend of greater physician compliance with the *advise* and *assist* components of the 5A model, as seen in recent representative U.S. population surveys (King et al., 2013; Kruger et al., 2016). They may also be indicative of a shift in practice guideline adherence among specifically Canadian physicians, which were reported in 2012 to offer advice to quit to merely 56% of smokers who had visited them in the past year, and fewer than 30% of surveyed smokers received information about assistance (Reid et al., 2014). As recipients and users of nicotine patches in the current study were more likely to discuss smoking with their physicians compared to the no intervention control group, the findings suggest that the provision of free NRT particularly to those who are likely to use it may facilitate opportunities for benefits beyond the direct pharmacological effects of the medication, such as the receipt of physician-assisted brief or supplementary intervention. Indeed, nicotine patch users who had discussed cessation with a physician between the 8-week and 6-month follow-ups were more likely to make a serious quit attempt compared to controls. From a public health perspective, the mailed-out provision of free nicotine patches may therefore be effective in not only promoting cessation but also in stimulating conversations and support from health professionals that help towards achieving that goal.

It is important to note that approximately 70% of participants who had used the freely provided nicotine patches by 8 weeks and informed their physicians of doing so, were provided with supplementary support, the most common being prescribed varenicline or

bupropion. The majority (73.7%) of nicotine patch users had used only some of the provided NRT, therefore it is most likely that the medications were prescribed subsequent to their discontinuation of nicotine patches. The remaining 26.3% however, reported to have used all their nicotine patches by 8 weeks, in which case it is plausible to suspect that these participants were prescribed the medications while they were still using the nicotine patches, contrary to the recommendations of the National Institute for Health and Care Excellence (NICE) ("Smoking Cessation Services. NICE public health quideline 10.," 2013) and US Public Health Clinical Practice Guidelines for Treating Tobacco Use and Dependence (for varenicline only) (Clinical Practice guideline Treating Tobacco Use and Dependence 2008 Update Panel, 2008). Nearly one half (45.5%) of those who used all their nicotine patches and informed their physician of doing so were prescribed varenicline or bupropion. The combination of bupropion and NRT has been reported to provide similar benefit as either therapy alone (Stapleton et al., 2013), and only until a recent systematic review and meta-analysis (Chang et al., 2015), combination therapy of varenicline and NRT produced favorable, albeit non-significant effects on cessation (Hajek et al., 2013; Ramon et al., 2014). However, in the event that the prescribed cessation medications were utilized, it is unclear what role, if any, that would have had on the observed effects in this study. Further research is necessary to evaluate the effectiveness of combination therapy on cessation outcomes in primary care settings, as well as directly contrast the effectiveness of nicotine patches and combination nicotine patch and varenicline in an open label design.

Several limitations of the current study should be noted. First, as nicotine patch users in the experimental group were asked specifically whether they had informed their physician of patch use at 8 weeks, as opposed to whether they had discussed smoking cessation with

their physician, direct comparisons between this group of smokers and control participants could not be made. Second, as we were intent on examining how the receipt and specifically use of free nicotine patches is associated with physician interaction, thus necessitating case control matching, the employed random assignment to condition was compromised and placed limits on our ability to infer causality of intervention. Third, the temporal order of nicotine patch use and physician interaction was not captured, therefore nicotine patch use could have either preceded and caused participants to visit their physician (whether due to side effects or additional support), or some participants may have sought physician advice prior to initiating patch use. It is therefore important to emphasize again that the present findings pertain specifically to an association between use of freely provided nicotine patches and physician support, and are not causal in any regard. Third, recipients of the 5-week course of nicotine patches were advised to talk to their physician or pharmacist if they had additional questions to the included instructions on how to use the patches, in compliance with common pharmacotherapy distribution practices and our research ethics board recommendations. Some individuals however, may have perceived this as direct instructions to seek out physician support. Fourth, asking whether participants had visited a physician and discussed smoking cessation could have been subject to recall bias. Finally, biochemical verification of smoking status could not be effectively executed (Cunningham et al., 2016), therefore cessation outcomes are based on self-report data.

Conclusions

Use of freely distributed nicotine patches promoted further smoking cessation centered discussion with family physicians, compared to non-recipients of NRT. Although this was associated with increased likelihood of making a quit attempt, nicotine patch users as a whole generally did not turn to their physicians for cessation assistance, expressing reluctance in seeking their support. In line with grater adherence to clinical practice guidelines of following the 5A model, promotion of physician capacity in addressing tobacco dependence with patients could be enhanced through non-judgmental, stage-based brief motivational interviewing methods. Future research is warranted to examine whether the free NRT distribution as part of smokers' helplines also mobilizes additional health-care provider support, in particular among pharmacists, who are generally more easily accessible than physicians.

Abbreviations

NRT, nicotine replacement therapy

FTND, Fagerström Test for Nicotine Dependence

OTC, over-the-counter

ANOVA, analysis of variance

Declarations

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Chapter 6: Discussion and Conclusions

The present body of work was embarked upon to gain a deeper understanding of individual

and treatment-level factors that may influence the effectiveness of the mailed free NRT

intervention for smoking cessation. In doing so, results from Manuscript 1 demonstrate that

not only is the mailed distribution approach of free nicotine patches effective in helping

smokers quit, it is similarly effective among a population of smokers with presumed

difficulty in quitting smoking – those with a lifetime history of depression or anxiety, two of

the most prevalent mental health comorbidities among smokers. The study underscored that

that the lifetime diagnostic status of depression or anxiety does not affect quit outcomes

when NRT is provided for free via the mailed approach and further supported the inherent

effectiveness of nicotine patches in the real-world setting as a viable treatment option for

tobacco dependence. These findings are particularly notable given that over 50% of

participants with the lifetime diagnosis of depression or anxiety also endorsed a current

diagnosis of these disorders. Despite the presupposed lower likelihood in quitting smoking

within this subgroup however, those with lifetime/current depression or anxiety were not

disadvantaged from the impact of the intervention. Thus, the study had demonstrated that the

effectiveness of mailed nicotine patches is stable in the face of lifetime mental health status,

a known moderator of smoking cessation success, and that it is not driven primarily by

smokers who possess the most optimal characteristics for success in their cessation efforts.

Evaluating which demographic and smoking history characteristics predict the

likelihood of using NRT when it is offered and provided for free, Manuscript 2 documents

that those who were unemployed, previously used NRT, and expressed greater intent for change at baseline were more likely to take advantage of freely provided nicotine patches and use at least some of the 5-week patch regimen to make a quit attempt. Relative to independent predictors of OTC purchase and use of NRT, the number of factors associated with NRT use as part of the mailed distribution model was limited. Further, the fact that approximately 60% of the sample had used the supplied nicotine patches is below NRT utilization rates found when NRT is provided via smokers' helpline-affiliated distribution efforts. Nonetheless, the findings can be considered as encouraging, given that the study proactively recruited a non-treatment-seeking sample and with the offer and provision of free nicotine patches may have driven a proportion of smokers unmotivated to quit or merely considering quitting, to make a quit attempt. Indeed, prior studies have documented that providing free nicotine medications to smokers (even those not motivated to quit) can be beneficial in enhancing readiness to quit, promoting quit attempts, as well as contributing to reductions in cigarette consumption (Carpenter, Hughes, Gray et al., 2011; Jardin, Cropsey, Wahlquist et al., 2014). While a greater understanding of factors that contribute to smoking cessation (i.e., making a quit attempt using NRT) was developed, the study also uncovered that of the multitude of demographic and smoking history characteristics examined, only past NRT use was highly associated with the likelihood of cessation at 6 months. In addition, the study determined that use of all 5 weeks of nicotine patches was associated with approximately a three-fold increased likelihood of cessation compared to those not using any. These findings provide support to other research documenting that, irrespective of setting, adherence to the treatment regimen is critical in increasing the chances of cessation success and that a minimum of 4 to 5 weeks of NRT use is necessary for realizing the most

optimal odds of success (Raupach, Shahab, Neubert et al., 2008; Zhang, Cohen, Bondy et al., 2015).

Recognizing that a large proportion of smokers opt to quit on their own, in absence of formal cessation assistance and even when medication such as NRT is provided free of charge to the individual, Manuscript 3 documents the role of personality traits and motivational reasons for quitting smoking in the methods with which smokers quit. The retrospective study of recent quitters revealed that those with higher conscientiousness levels and negative perceptions of smoking cessation aids were more likely to have quit in absence of formal cessation assistance. Conversely, individuals with lower conscientiousness ratings and who perceived advantages of smoking cessation aids were more likely to have quit smoking using formal treatment/cessation assistance methods. Motivational reasons for quitting smoking were not found to predict precisely how individuals quit. Consistent with findings from qualitative research, the study quantified the contributing role of inter-individual traits and perceptions towards medications for smoking cessation that guide how smokers ultimately quit. These findings can be extrapolated to suggest that such individual-level factors may also affect the uptake and successful cessation via a mailed NRT distribution program. Given several methodological limitations in the study design however, caution must be exercised in overextending the findings. Most notably, participants in Manuscript 3 were recruited from a select sample of former smokers (without biochemical confirmation of smoking abstinence), who also had considerable experience in completing surveys, thus selection bias may have played a role in the study findings. Notwithstanding these limitations, the contributing variance of the conscientiousness personality trait in predicting NRT effectiveness is also difficult to quantify amidst other mass distribution of

NRT program mediators, particularly the presence or quality of a supportive smoking cessation assistance (akin to the often provided behavioural support through smokers' helpline-affiliated mailed NRT distribution programs) and perceptions that smokers hold towards smoking cessation aids.

It is plausible to suspect that when smokers hold misconceptions on the contraindications and proper utilization practices of NRT and subsequently discontinue treatment due to these misconceptions, reinforcement of these beliefs prevents these individuals from using cessation medications in the future. As reported in Manuscript 2, one of the most common reasons for discontinuing use of the provided 5-week nicotine patch treatment regimen was relapse, which for some individuals stemmed from the belief that using the patch while smoking could lead to a 'nicotine overdose' and transpire in cardiac problems (qualitative data not reported). This observation has been also recognized by other research, noting that the reason for discontinuing NRT use during a lapse may be driven by strong warnings in NRT product monographs against using NRT while smoking (Balmford, Borland, Hammond et al., 2011; Burns & Levinson, 2008). The product monograph of nicotine patches used in the present study also contained such warnings (Novartis Consumer Health Canada Inc., 2005). On the contrary, continued use of NRT during a lapse is safe and should be encouraged (Coleman, 2013; Ferguson, Docherty, Bauld et al., 2012; McNeill, Foulds & Bates, 2001). Side-effects are mild to moderate (Hays & Ebbert, 2010), and given the benefits of cessation, strategies can be given to manage them. Mass distribution of free NRT programs therefore have an opportunity to quell some of those misconceptions by incorporating messaging as part of a program's advertising strategy, and hopefully encouraging those previously resistant to using NRT to consider it. Programs that offer

supplementary behavioural support have the added benefit of addressing smokers' questions and concerns as well as proactively offering accurate information on the commonly held misbeliefs.

Manuscript 4 examines the impact of the mailed NRT distribution model on stimulating further help-seeking from primary care physicians and the effect that that interaction has on cessation outcomes. It demonstrates that the mailed distribution approach encourages users of nicotine patches to seek additional primary care support, at least more so than those not receiving free NRT, suggesting that it facilitates opportunities for additional intervention from primary care physicians. Nicotine patch users who had discussed cessation with their physician were also more likely make a serious quit attempt, thus increasing the odds of future cessation (Hyland, Borland, Li et al., 2006). From a public health perspective, the mailed distribution of free NRT can have compounded benefits in not only helping a small percentage of smokers quit, but also increasing follow-up care in primary practice and improving the chances of successful future cessation among those who did not quit.

Most participants in the study however, irrespective of group, did not discuss cessation with their primary care physician. This finding is supported by previous research demonstrating that smokers generally believe primary care physicians have little to offer in assisting with smoking cessation. As most smokers are aware of the need to quit smoking, many may also view quitting as a personal responsibility (Smith, Carter, Chapman et al., 2015). Nonetheless, with more education for primary care professionals on effective smoking cessation treatment (Centre for Addiction and Mental Health, 2017; U.S. Department of Health and Human Services, 2017), its effectiveness in promoting smoking cessation (Anderson & Jane-Llopis, 2004; Lancaster, Stead, Silagy et al., 2000), and the suggested

greater compliance with the 5A model as observed in the present study, promotion and encouragement of primary care support to mailed distribution of NRT program participants can and should be standardized.

It is important to acknowledge that the present body of work should be interpreted in the context of several limitations, most of which have been reviewed in the individual studies. A common theme across all studies however, is the reliance of outcomes on self-reported smoking abstinence, which can be prone to participant misreporting and result in inflated cessation rates. While biological confirmation of smoking abstinence would have strengthened confidence in this work, considerable stock is present in the findings given that self-reported cessation rates among treatment arms were similar or lower than seen in other mass distribution initiatives and cessation rates of control arms were in-line with those reported in general population surveys (Hughes, Keely & Naud, 2004; Statistics Canada, 2008; Zawertailo, Dragonetti, Bondy et al., 2013). Further, as reported in the primary outcomes of the core RCT (Cunningham, Kushnir, Selby et al., 2016), saliva sample return rates and verification rates were similar across both study arms, suggesting that both the self-reported and biochemically confirmed treatment effects were subject to minimal bias. The possibility of a demand characteristic among recipients of free nicotine patches however, may have contributed to the observed treatment effect and is a limitation that merits recognition.

Taken together, the present body of work assists in formulating a conceptual framework of factors that may influence the effectiveness of mailed free NRT as a population-level smoking cessation intervention. Depicted in Figure 1, the framework

summarizes the role of known individual-level predictors, smoking history factors, type of support, program mediators, and community/social-level indicators and norms, that can guide the effectiveness of a mailed-nicotine replacement therapy program. While by no means exhaustive and likely to be informed by future research, the conceptual framework sets a foundation of factors that should be considered when designing mass distribution programs, as well as helps identify which individuals are likely to gain most from such interventions.   Factors identified by the present line of work are marked in yellow.

Figure 1. Conceptual framework of factors influencing the effectiveness of mass distribution of free NRT
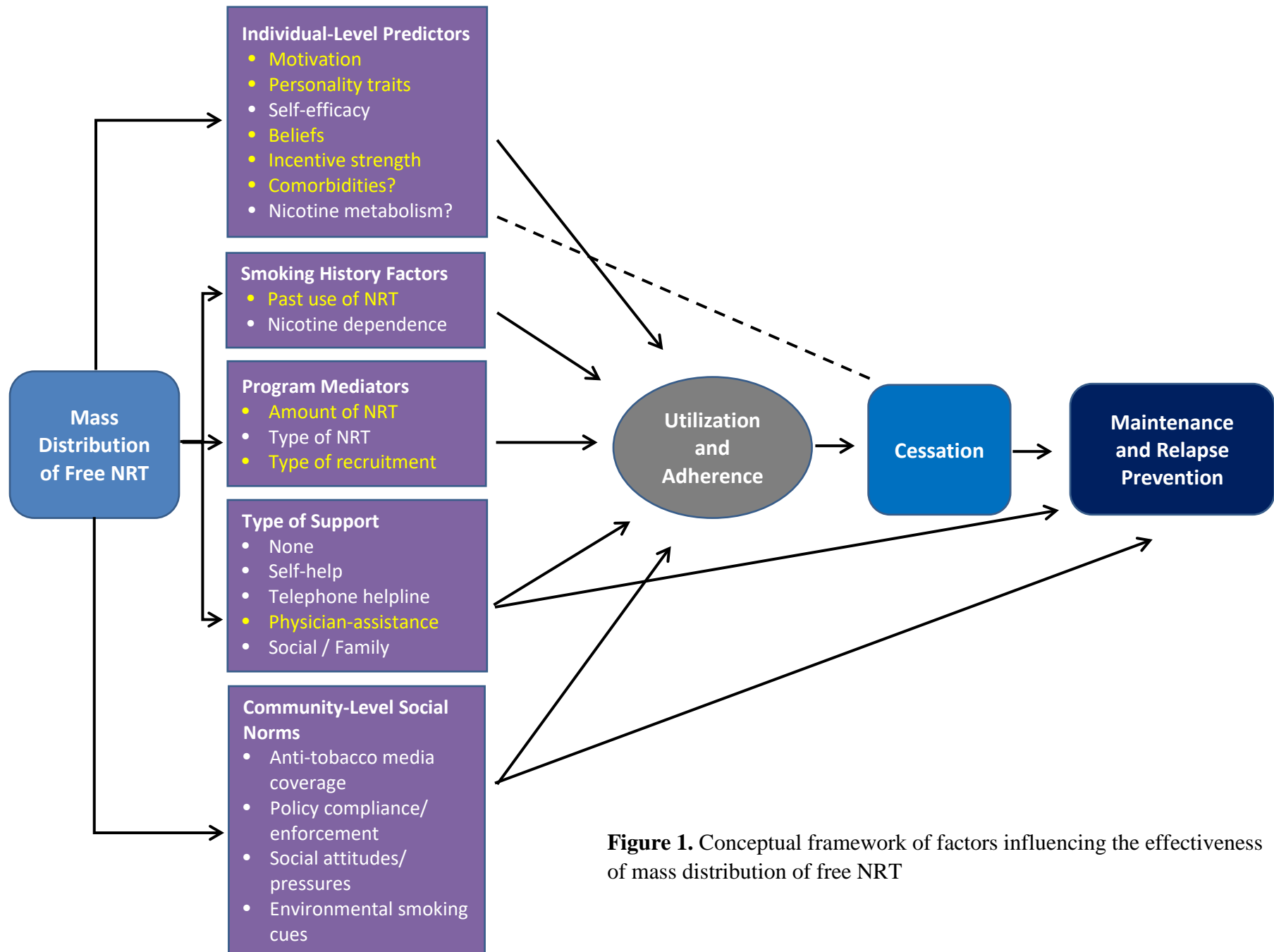
Focusing on individual-level predictors, the framework recognizes the role of motivation/readiness to quit, self-efficacy, confidence, and personal beliefs/perceptions of NRT and smoking cessation aids that have been both previously, and through the present research, shown to influence cessation medication use and success in abstaining from smoking via a smoking cessation program. While those who are intent on quitting smoking in the more immediate future, or have already set a quit date, are more likely to be successful in a quit attempt, the offer of free NRT to 'less motivated' smokers has potential benefit. In particular, the availability of free NRT has been recognized as an important 'cue to action', similar to mass media campaigns and health scares that can trigger movement towards receiving help and ultimately quitting. Based on evidence that free NRT offers engages both motivated and unmotivated smokers into the quitting process, Jardin et al. (2014) had proposed that access to cessation medication should not be restricted only to those who demonstrate an immediate readiness to quit, and that making cessation medication more readily available could propel smokers who are considering quitting towards an actual cessation attempt. The present research further identified a possible role of personality traits in determining quitting using cessation aids in general, and underscored a limited impact of certain lifetime mental health comorbidities (namely, depression and anxiety disorders) on the likelihood of quitting smoking via the mailed free NRT paradigm. Conclusions on the effectiveness of the cessation paradigm among those with current self-reported anxiety or depression however, could not be drawn, primarily due to small sample size and observed small effect size among this subgroup of participants. Nonetheless, there is strong suggestive evidence that smokers with current or recurrent mental illness, such as schizophrenia as well as mood and anxiety disorders, which have been reliably shown to be linked with reduced

odds of quitting smoking, are likely to experience poorer quit outcomes as part of a standardized mailed-out free NRT program (Lasser, Boyd, Woolhandler et al., 2000; Smith, Mazure & McKee, 2014; Zawertailo, Voci & Selby, 2015). However, that is not to say that free NRT distribution programs have no role to play in helping smokers with current mental illness. On the contrary, for some, free NRT programs accompanied by counselor-facilitated cognitive/behavioural support can promote cessation, link individuals with appropriate and personalized mental health care resources, and in and of themselves be used as a vital resource in areas lacking easy access to personalized tobacco and mental health treatment. It is important to be realistic however, that for this segment of the smoker population a personalized, face to face, therapist-assisted treatment regimen involving a combination of cessation medications would still provide the best chances of achieving cessation (George, Vessicchio, Sacco et al., 2008).

The nicotine metabolic ratio has been identified as a genetically informed biomarker of NRT effectiveness in clinical and community settings (Kaufmann, Hitsman, Goelz et al., 2015; Lerman, Tyndale, Patterson et al., 2006), and as such, should be recognized as a possible mediator of the effectiveness of NRT provided via a mailed distribution program. While its predictive value on NRT- affiliated smoking cessation outcomes is yet to be examined in absence of direct, face-to-face behavioral support, this individual-level predictor of NRT effectiveness may not be dependent on the context in which NRT provided. Future research is certainly warranted to examine whether slow nicotine metabolizers exhibit greater cessation rates compared to fast or normal metabolizers as part of a mailed NRT distribution program, while stratified by varying amounts of counselor-assisted support. It should be noted however, that the rate of nicotine metabolism has not been shown to be a predictor of

treatment adherence when NRT was provided as part of a structured, therapist guided program (Kaufmann, Hitsman, Goelz et al., 2015; Schnoll, Wileyto, Leone et al., 2013), therefore its impact on cessation as part of a mass distribution of free NRT program, as depicted in the figure by a dashed line, is also likely to be direct.

With cost of NRT being a significant barrier to attempting cessation for a large proportion of smokers, especially among those facing financial hardship, the incentive value of free NRT provision can also be considered as an individual-level predictor that guides the uptake and ultimate success of a mailed NRT distribution program. Indeed, in Manuscript 2 (Kushnir, Sproule & Cunningham, 2017b), unemployment was identified as a strong predictor of whether nicotine patches were used by participants, suggesting that the null cost of the patches incentivized attempted cessation. Depending on a smoker's financial well-being, the offer of saving approximately $175 - $200 CAD via the freely provided NRT (retail cost of 5 weeks of nicotine patches), plus additional savings associated with not buying cigarettes (approximately $2,000 - $4,000 for those smoking more than 10 cigarettes per day (Non-Smokers' Rights Association, 2017)), may be a large enough financial incentive for smokers to engage in the program and attempt to quit.

With respect to smoking history factors mediating the effectiveness of mailed free NRT, the present research has documented that individuals who are less nicotine dependent and have used NRT in the past are more likely to succeed with cessation. These findings are consistent with those seen in clinical settings, with NRT obtained OTC, and via prospectively evaluated free NRT distribution programs (Hyland, Borland, Li et al., 2006; West, McEwen, Bolling et al., 2001; Zawertailo, Dragonetti, Bondy et al., 2013; Zhu, Sun,

Billings et al., 1999). As such, it is reasonable to attribute the level of nicotine dependence and past use of NRT as stable predictors of mailed free NRT effectiveness.

On a more macro level, higher levels of nicotine dependence and financial difficulty are characteristics representative of smokers in lower SES groups, in addition to lower self-efficacy and intention to quit (Siahpush, McNeill, Borland et al., 2006) Increased accessibility to cost-free intervention, as gained from a mailed distribution of free NRT program, may thus help encourage smokers in lower SES groups to consider and attempt quitting. Although the likelihood of cessation among these subgroups would be expected to be nonetheless lower, as compared to those with higher SES (Reid, Hammond, Boudreau et al., 2010), targeted distribution efforts with greater intensity of support could potentially increase program effectiveness. Specifically, mailed free NRT programs identifying highly dependent smokers and those in low income brackets may opt to offer additional follow-up and counselling to encourage optimal utilization of NRT and reduce the risk of relapse. Additional research is warranted however, to elucidate the impact of free NRT distribution on cessation outcomes among smokers of varying SES, as well as the mediating role of cessation counseling.

The availability and type of cessation support are additional moderators of mailed free NRT program effectiveness. Large-scale NRT distribution efforts through smokers' helplines and specialized distribution programs have utilized a variety of telephone and mobile phone-based support options (i.e., counselor-based support or text-messages) that have ranged in the frequency of interaction and intensity of support (Hollis, McAfee, Fellows et al., 2007; Keller, Schillo, Kerr et al., 2016; Krupski, Cummings, Hyland et al., 2013). The provision of proactive, phone-based counselling sessions lasting 30 to 40-minutes, based on

the motivational interviewing model, following the offer of free NRT has been shown to be superior at helping smokers quit at both short- and long-term follow-ups, compared to a one-time, brief intervention (Hollis, McAfee, Fellows et al., 2007). As counsellors typically develop individual quit plans, provide an opportunity to ask questions on the use of NRT, teach coping skills and relapse prevention, as well as enhance confidence around quitting (Stead, Hartmann-Boyce, Perera et al., 2013; Stead, Perera & Lancaster, 2007; Swartz, Cowan, Klayman et al., 2005), such efforts result in greater medications adherence. In turn, the free NRT distribution efforts via smokers' helplines have yielded quit rates most commonly over 20% at 6-month follow-up. These rates are in stark contrast to those seen in the present line of research (7.6% among all nicotine patch recipients at 6 months), where no supplementary intervention was provided to the 5-week nicotine patch regimen. The availability and provision of therapist-guided support or individual-selected services (for those opting for less-intensive services such as text messaging) thus appear to enhance smokers' chances of quitting and should be considered as highly desirable components of any future mailed NRT distribution programs.

It is not withstanding that physician assisted support outside of the NRT distribution program may also impact the odds of making a quit attempt and quitting smoking. Physicians are highly supportive of their patients' intentions to quit smoking and believe it is their role to help patients quit (Assocciation of American Medical Colleges, 2007). As even brief advice from primary care practitioners has been shown to significantly increase the odds of cessation (Aveyard, Begh, Parsons et al., 2012; Fiore, Jaen, Baker et al., 2008; Stead, Bergson & Lancaster, 2008), healthcare providers can play an important role in encouraging NRT utilization, minimizing the risk of relapse, and overall, improving the likelihood of

quitting. Within the context of the mailed free NRT paradigm, findings from Manuscript 4 (Kushnir, Sproule & Cunningham, 2017a) had suggested grater overall physician compliance with the 5A model of smoking cessation support in recent years, and that the provision of free NRT may help stimulate conversation around smoking cessation. Other healthcare providers may play a similar role in supporting their patients. In particular, pharmacists and community pharmacies are in a unique position to provide effective counselling and support for smokers with their cessation efforts (Brown, Todd, O'Malley et al., 2016; Saba, Diep, Saini et al., 2014). Aside from being one of the most accessible healthcare professionals, pharmacists can provide on-site assessment, cessation counselling, as well as prescribe and dispense prescription and non-prescription smoking cessation medication (Dent, Harris & Noonan, 2007; Wong, Burden, Liu et al., 2015). Community pharmacists can also facilitate important continuity of care for those initially seeking support from a mailed free NRT distribution program. By providing face-to-face counselling for those seeking more information on NRT and smoking cessation products, as well as advising on continued NRT use or alternative therapeutic options beyond the distribution program parameters, pharmacists can be a valuable resource for mailed NRT program and individual cessation effort success.

Canadian pharmacists are firmly supportive of their professional role in motivating and assisting clients who smoke. Approximately 90% of Ontario pharmacists in 2002 believed that it is important for pharmacists to advise their patients about the use of NRT gum or patches, and further 85% perceived their knowledge on the use of NRT in smoking cessation was either good or excellent (Ashley, Victor & Brewster, 2007; Brewster, Ashley, Laurier et al., 2005). A high proportion (79%) of Canadians also trust their pharmacists to

give them helpful and accurate information about different healthcare and lifestyle topics and

75% indicate they would consider going to their pharmacist for smoking cessation advice

(Coletto, 2015). The mass distribution of NRT via community pharmacies has thus been

conceived and tested as an alternative model to the mailed distribution approach.

Preliminary evidence from the very few studies conducted to date revealed that compared to

cohorts receiving comparable amounts of NRT via postal mail, the receipt of free NRT

through a pharmacy in combination with brief counselling from a pharmacist or smokers'

helpline resulted in considerably higher self-reported abstinence rates (Costello, Sproule,

Victor et al., 2011; Cummings, Fix, Celestino et al., 2006). While the mail-out cohorts in

these studies were not randomly assigned and any causal inference on the impact of NRT

distribution via pharmacies is limited, the adoption of a pharmacy-based free NRT

distribution program may have merit. Future research is encouraged to evaluate the

effectiveness of such approaches in a randomized controlled research design.

Of other mailed free NRT program mediators, however, the type and amount of NRT

provided can further affect the likelihood of cessation success. Research has documented a

distinct preference among smokers for nicotine patches over gum, with those receiving free

patches also more likely to quit at short-term follow-up compared to nicotine gum recipients

(Cummings, Fix, Celestino et al., 2006; Zawertailo, Dragonetti, Bondy et al., 2013). While

the nicotine patch has been the most widely used and evaluated NRT option among past and

current distribution programs, those offering only select forms of NRT are likely to

experience reduced enrolment and limited interest compared to programs allowing the

participant to select their preferred medication. Further, given that combined use of short

acting NRT with the long-lasting nicotine patches is superior to either alone (Fiore, Jaen,

Baker et al., 2008; Shah, Wilkens, Winkler et al., 2008; Stead, Perera, Bullen et al., 2012),

offering and recommending both types of NRT to eligible smokers should be considered as

part of future mailed distribution programs.

The amount of NRT provided and more precisely, the amount used, are also

determinants of quit outcomes. With the exception of one trial (McAfee, Bush, Deprey et al.,

2008), accumulating evidence is available that there is little distinction in quit rates between

those receiving between 2 to 8 weeks of NRT at follow-ups of 6 months or longer (Burns,

Hood, Goforth et al., 2016; Cummings, Fix, Celestino et al., 2006; Cummings, Fix, Celestino

et al., 2010; Cummings, Hyland, Carlin-Menter et al., 2011; Smith, Keller, Kobinsky et al.,

2013). While recipients of larger amounts of NRT tend to use more of it (Cummings,

Hyland, Carlin-Menter et al., 2011), the relationship between the amount of NRT provided

and its use in its entirety is inversely proportional. For example, one RCT had found that

moderately dependent smokers who were provided with NRT sufficient for 8 weeks'

duration after calling a quitline used them at significantly lower proportions compared to

those who were provided with 4 weeks of NRT, however no differences in abstinence rates at

a 7-month follow-up were found between the two groups (Burns, Hood, Goforth et al.,

2016).

Considering the reduced program costs associated with the provision of lower

amounts of NRT and limited smokers' helpline budgets, programs opting to offer a one-time

supply of NRT would likely realize most benefit through the provision 4 to 5 weeks' worth

of NRT, while further strengthening efforts to encourage its entire use and adherence. As

suggested in Manuscript 2 (Kushnir, Sproule & Cunningham, 2017b) and by others

(Raupach, Shahab, Neubert et al., 2008; Zhang, Cohen, Bondy et al., 2015), it is a minimum

of 4 to 5 weeks of NRT *use* that offers smokers the most optimal chances of quitting success. Alternatively, programs may consider offering a supplementary supply of NRT to those who request it or upon meeting specific participation requirements, such as partaking in at least 2 therapist-guided counseling calls. Staggering the amount of NRT distributed to each individual would thus provide additional support only to those who are especially committed to quitting, reduce costs associated with NRT self-purchase, and utilize program resources in a conservative manner.

Further, it cannot be discounted that the type of recruitment and relatedly, interest in quitting smoking at time of recruitment, would also have an impact on program participation, NRT utilization, and ultimately quit outcomes. Indeed, it is highly likely that the proactive recruitment strategy used in the present line of research via random digit dialing of Canadian telephone numbers, while in line with recommendations for assessing the effectiveness of OTC NRT (Walsh, 2008), contributed to NRT utilization and quit rates well below those seen in NRT distribution programs facilitated in collaboration with smokers' helplines. Those programs placed the onus on individuals interested in quitting to call a toll-free phone number, and eligibility to receive free NRT was commonly restricted to those willing to set a quit date within 30 days of their intake call (or placed within the preparation stage of change), thus likely enrolling participants with more immediate interest or readiness to quit. In contrast, participants recruited in the present line of research varied in their stage of change (as this was not an eligibility criterion for participation in the core RCT), despite expressing willingness at baseline to use the free NRT to make a quit attempt within one week of its receipt. Taken together it is important to emphasize that the samples used were

not representative of smoker populations commonly accessing free NRT as part of quit lines,

and as such, our ability to directly translate the findings to these settings is somewhat limited.

Further, programs that offer additional incentives beyond the free NRT, such as 'quit

and win' style competitions with monetary prizes upon confirmation of abstinence, may have

the potential to harness greater participation interest, program compliance, and deliver higher

absolute number of quitters. Considerable research has been conducted to date on the

effectiveness of competitions and incentives on smoking cessation (generally in absence of

free NRT provision). A Cochrane review of 19 studies, involving more than 4500

participants, has concluded that while incentivized programs may attract more smokers to

make a quit attempt than would otherwise do so, monetary incentives and competitions do

not appear to enhance long-term quit rates, with early successes often dissipating upon expiry

of the payment schedule (Cahill & Perera, 2011). However, no controlled trials have offered

free NRT in combination with a quit and win contest among a generalizable sample of

regular adult smokers. Such programs may enhance quit rates beyond those offering free

NRT alone, although mindful assessment would need to be conducted on whether cost

increases associated with running them would justify the potential benefits.

Finally, the conceptual framework of factors that may influence the effectiveness of

mailed free NRT recognizes the possible role of community-level social norms as guided by

anti-tobacco/smoking media coverage, jurisdictional tobacco control policies and their

enforcement, as well as social pressures and environment (i.e., smoking cues, smoke-free

homes, etc.). The presence and intensity of all has the potential to either support or hinder the

likelihood of smoking cessation success via a free NRT distribution program. Mass media

campaigns in particular, have used numerous mediums including television, radio, print

media and billboard advertising to inform the public about the health risk factors associated with smoking as well as exposing the tobacco industry's manipulative or unethical tactics. Research evaluating the impact of campaigns disseminating such information has documented that some are effective in changing smokers' attitudes about risk factors as well as directly influencing individuals' smoking behaviour in terms of cigarette consumption and increasing quit rates (Bala, Strzeszynski & Topor-Madry, 2017; Brown, Kotz, Michie et al., 2014). While variability in study quality, scale, and difficulty in quantifying campaign effectiveness exclusively of other influences (i.e., smokers' helpline promotion), have been noted to contribute to an overall low quality of evidence, the wide reach of mass media campaigns, especially those with graphic television imagery, is considered important in shaping motivations and encouraging action to quit smoking (World Health Organization, 2015). It is further foreseeable that in the context of large-scale mailed NRT distribution programs, anti-smoking mass media advertising may drive smokers to persist with their quitting goals, thus strengthening the NRT program effectiveness. Implemented as part of a comprehensive tobacco control programme, mass media campaigns supported by restrictive tobacco control policies that, for example, restrict tobacco advertising and smoking in public places, help also shape social norms around the acceptance of smoking in society. For individuals considering quitting smoking, these measures may make the offer free NRT delivered directly to their homes even more appealing. Following the uptake of NRT, they may further help create a supportive environment that limits the impact of relapse-inducing stimuli.

Taken together, the present research strengthens knowledge on the determinants, impact, and implications of the free distribution of nicotine replacement therapy as an effective *en-masse*, "real-world" smoking cessation intervention. While highlighting the potential benefit of the free distribution of NRT in helping smokers quit, it also underscores the utility of the mail-out approach of OTC smoking cessation aids (not just NRT) as a scalable way of reaching large populations of smokers, effectively increasing accessibility to treatment and promoting cessation in ways that cannot be accomplished through clinical settings alone. As a population-level smoking cessation intervention, the mailed distribution approach has been also adopted in studying the *en-masse* effectiveness of cytisine, a plant-based alkaloid with α4β2 nAChR partial agonist activity similar to varenicline. A comparison of mailed free cytisine versus NRT, with minimal behavioural support, in a New Zealand RCT, in fact revealed cytisine to be superior in promoting self-reported continuous abstinence at 6 months, albeit with significantly greater incidence of adverse side effect (Walker, Howe, Glover et al., 2014). The concept of mailing or mere provision of efficacious smoking cessation aids free of charge has thus gained substantial merit for its inclusion as part of a comprehensive long-term tobacco control strategy. Indeed, recent results from Health Canada's public consultation on the future of tobacco control in Canada have revealed considerable support for free or low cost access to medication and NRTs, in line with the Government of Canada's target to reduce smoking prevalence to less than 5% by the year 2035 (Health Canada, 2017). The present research therefore presents timely and important considerations for both policy makers and funders of service in the development of Canada's pending update to the Federal Tobacco Control Strategy (2018).

6.1   Future Directions

A number of future directions are guided by the described body of research. As delineated in the conceptual framework model of mailed free NRT effectiveness, several known predictors of smoking cessation success in clinical settings are yet to be confirmed as part of the mailed distribution paradigm in "real-world" world settings. These include delineating the predictive role of the nicotine metabolic rate in guiding pharmacotherapeutic response to NRT, elucidating the impact of free NRT provision on smokers of varying demographic, mental health and SES markers, as well as examining the effectiveness of large-scale distribution and utilization of both short and long-lasting forms of NRT, combined. Building on the latter, future research is warranted for investigating the potential utility of personalized treatment regimens or the development of a systematic treatment algorithm to be implemented as part of large-scale free NRT distribution programs, based on evidence-based demographic and smoking history predictors of cessation success. As the vast majority of mailed free NRT programs administered as part of smokers' quitlines had utilized a standardized treatment regimen of a pre-set duration of NRT, a more pragmatic approach of distributing modifiable quantities of NRT with variable dosage strengths based on the assessed level of nicotine dependence, comorbidities, and/or prior NRT use history may improve quit outcomes beyond those seen with the 'one size fits all' standardized approach. Consistent with this notion, more research is needed on elucidating how additional individual-selected services (i.e., behavioural counselling, text-messaging, etc.) influence smokers' odds of quitting and with program satisfaction.

Moreover, it would be prudent to evaluate the effectiveness of alternative NRT distribution models. For example, paradigms in which the provision of free NRT is contingent on primary care physician or pharmacist interaction may experience greater treatment regimen compliance, well-informed treatment tailoring based on patients' complete medical history, as well as superior continuity of care. As previously discussed, there is preliminary evidence to support the adoption of a pharmacy-based free NRT distribution model, of which a version has been recently adopted by the Ontario government. In it, the province is funding 'smart-cards' to be distributed to up to 7,500 people when discharged from more than 80 participating hospitals, to be used to redeem free NRT at community pharmacies across Ontario (Ontario Ministry of Health and Long-Term Care, 2017). To establish the efficacy of the pharmacy-based distribution approach however, a well-designed RCT would be necessary to provide causal evidence of its effectiveness in increasing smoking quit rates when compared to a no-intervention control population.

Finally, additional research is needed to evaluate the long-term effectiveness of mailed free NRT. As evidence on the impact of mailed NRT has been largely restricted to a final follow-up of 6 to 12 months following the start of treatment, and relapse to smoking is known to occur beyond this period, it is important to elucidate whether the net benefit of mailed distribution of free NRT can be maintained long-term. Further research on the long-term effectiveness of mailed free NRT as distributed via smokers' helplines in combination with behavioural support is necessary.

6.2   Conclusions

The present body of research has helped identify some of the individual and treatment-level factors that contribute to the effectiveness of the mailed free distribution of NRT as a population-level smoking cessation intervention. Outlining the intervention's effectiveness in specific patient populations, delineating predictors of treatment utilization and cessation, as well as developing insights on the impact of the approach in harnessing additional smoking cessation support, the research strengthens the knowledge base and support for the inclusion of free NRT provision as part of a comprehensive tobacco control strategy. It is important to recognize however, that with smoking quit rates among nicotine patch recipients in the current research below 10% at 6 months and generally below 25% as part of smokers' quitline-affiliated mailed free NRT distribution efforts, the provision of free NRT even to smokers who are highly motivated to quit does not guarantee that they will quit and remain abstinent. Combined with the extant tobacco control research, the present findings suggest for the mailed distribution free NRT intervention to be implemented as part of a heterogeneous approach to reducing the smoking prevalence, focusing on prevention, education through public health messaging, evidence-based policy making, and treatment. Given the benefits associated with this approach, particularly in increasing access to efficacious and effective tobacco dependence treatment and cost effectiveness associated with helping smokers quit, the free distribution of NRT is a tool that has the potential of helping Canada realize its Tobacco Endgame goals.

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