EXPECTANCY AS A MEDIATOR OF DRUG AND PLACEBO EFFECTS:
METHODOLOGICAL AND CLINICAL CONSIDERATIONS FOR HUMAN
RESEARCH OF NICOTINE AND TOBACCO EFFECTS

by

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ABSTRACT

Drug responses are frequently presumed to arise directly from the pharmacological properties of ingested substances; however, there is growing recognition that non-pharmacological factors likely also make important contributions. Despite this, limited research has assessed the independent and interactive contributions of pharmacological and non-pharmacological factors to drug responses. The present dissertation aimed to assess the relative contribution of pharmacological and non-pharmacological factors to drug responses using nicotine and tobacco as a model. This dissertation included four studies which used the balanced placebo design, a factorial design that allows for the assessment of the independent and combined impact of drug pharmacology and drug expectation (i.e. the belief that an active drug has been consumed; a non-pharmacological factor) on drug responses. This was achieved by crossing actual drug assignment (given active drug vs. inert placebo) with instructions regarding drug assignment (told active drug vs. inert placebo). Findings from the four studies suggest that expectancy makes a substantial contribution to the acute effects of nicotine replacement therapy (NRT) and tobacco administration on subjective craving. A number of additional non-pharmacological factors also impacted craving and cigarette self-administration following NRT and tobacco use. Taken together, these findings highlight that non-pharmacological factors make an important contribution to subjective and behavioural drug responses. Targeting non-pharmacological factors in interventions may therefore be effective in improving treatment outcomes, particularly within the context of smoking cessation.

Keywords: expectancy; balanced placebo design; nicotine; tobacco

LIST OF ABBREVIATIONS USED

ANOVA   Analysis of variance
BOLD   Blood oxygen level dependent
CO   Carbon monoxide
EEG   Electroencephalography
fMRI   Functional magnetic resonance imaging
FTCD   Fagerström Test for Cigarette Dependence
FTND   Fagerström Test for Nicotine Dependence
h   Hour
F   F-test from ANOVA or linear mixed models
M   Mean
mg   Milligram
min   Minute
ml   Milliliter
N   Population sample size
n   Sample size
NFI   Nicotine-free inhaler
NI   Nicotine inhaler
nl   Nanoliter
NRT   Nicotine replacement therapy
p   P-value for testing significance
PET   Positron emission tomography
PPM   Parts per million
PR   Progressive ratio
QSU-B   Questionnaire of Smoking Urges-Brief
s   Second
SD   Standard deviation
SE   Standard error
SPSS   Statistical Package for Social Sciences
T1   Time 1
T2   Time 2
T3   Time 3
T4   Time 4
VAS   Visual analogue scale

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CHAPTER 1. INTRODUCTION

1.1 Placebo and antiplacebo effects

Placebo effects are defined as effects that arise from the administration of a substance or procedure, yet are not a result of the inherent powers of the substance or procedure. Rather, the effects are a product of individual beliefs or learning regarding the effects of the placebo (Stewart-Williams & Podd, 2004). One common example of the placebo effect is when individuals experience subjective, physiological, and/or behavioural drug effects after being administered a sugar pill under the guise that it is an active medication; however, placebo effects have also been documented to interact with pharmacological effects to produce drug responses when active substances are administered (Kirsch & Sapirstein, 1998). While there has been debate about the magnitude and clinical relevance of placebo effects (e.g., Hróbjartsson & Gøtzsche, 2001, 2010) and whether placebo effects are merely a form of response bias (Price, Finniss, & Benedetti, 2008), a number of studies report genuine placebo effects on both acute and longer-term subjective and objective measures (Finniss, Kaptchuk, Miller, & Benedetti, 2010; Price et al., 2008; Stewart-Williams & Podd, 2004). For example, placebos have been demonstrated as effective in reducing subjective pain resulting from chronic headaches (de Craen, Tijssen, de Gans, & Kleijnen, 2000) and in reducing pain and associated changes in heart rate following experimental pain inductions (Aslaksen & Flaten, 2008). Further, placebo-induced reductions in self-reported pain are associated with reduced neural activity in brain areas associated with pain processing (e.g., the thalamus, insula, and anterior cingualte corex; Wager et al., 2004). While the majority of research examining placebo effects has been conducted within the pain literature, placebo

effects have also been documented in other diverse fields of research including the treatment of Parkinson's disease, Alzheimer's disease, depression, anxiety, addiction, asthma, and cardiovascular problems (see Finniss et al., 2010 for a review). Taken together, the current body of evidence suggests that placebo effects have neurobiological underpinnings and exert genuine effects on subjective experience, the brain and the body.

Additional evidence for the placebo effect has been found using open-hidden paradigms, in which an identical active substance is administered to two groups of patients. While one group of patients receives the substance in an "open" condition, where it is provided by a clinician in full view of the patient consistent with standard clinical practice, the other group receives the substance in a "hidden" condition, where it is administered in the absence of the clinician, and without the client's awareness (Levine & Gordon, 1984). Analgesia studies using this paradigm have demonstrated that pain reduction is greater when substance are administered in the "open" condition than in the "hidden" condition (Amanzio, Pollo, Maggi, & Benedetti, 2001; Benedetti et al., 2003; Colloca, Lopiano, Lanotte, & Benedetti, 2004; Levine & Gordon, 1984), particularly when clinicians provide verbal information about the effectiveness of the substance in relieving pain in the "open" condition (Amanzio et al., 2001). These studies provide evidence that placebo effects interact with the pharmacological effects of administered substances to generate maximal drug responses. The blunting of drug responses when substances are administered in hidden conditions has been termed the antiplacebo effect, which is defined as the observed drug response associated with the belief that one has consumed no drug, despite the administration of an active substance (Perkins, Sayette, Conklin, & Caggiula, 2003).

In summary, both placebo and antiplacebo effects suggest that non-pharmacological factors mediate drug responses. Indeed, non-pharmacological factors appear to be sufficient to generate drug responses in the absence of pharmacological effects (placebo effect), to interact with pharmacological effects to maximize drug responses (placebo x pharmacology effect), and to blunt drug responses in the presence of pharmacological effects (antiplacebo effect). Despite widespread consensus on the existence and importance of placebo and antiplacebo effects, the mechanisms that underlie these effects are subject to ongoing debate.

1.1.1 Mechanisms underlying placebo effects

Expectancy theory and classical conditioning are the two main approaches that account for placebo effects (Stewart-Williams & Podd, 2004). The classical conditioning approach views active medications as unconditioned stimuli which, when taken, produce a variety of drug effects (unconditioned responses). Environmentally salient cues associated with drug administration (e.g., capsules, pills, dose instructions) are conditioned stimuli which come to elicit conditioned responses (i.e., drug effects) through repeated pairing with drug administration. In other words, after repeated drug administration, drug-related cues come to elicit drug effects, even in the absence of actual drug administration. Therefore, placebo effects are considered to be conditioned responses (Kirsch, 1997; Montgomery & Kirsch, 1997; Stewart-Williams & Podd, 2004). While conditioning trials have been demonstrated to enhance placebo effects (e.g., Montgomery & Kirsch, 1997), conditioning theories are not sufficient to explain all placebo effects, as placebo effects that do not correspond with pharmacological effects have been documented. For example, Hull and Bond (1986) demonstrated that the belief

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that alcohol had been consumed (i.e., a placebo effect) was associated with an increase in sexual arousal in response to erotic stimuli, yet actual alcohol consumption did not significantly impact sexual arousal. Given that increased sexual arousal is not an unconditioned response associated with alcohol consumption, the presence of increased sexual arousal in the placebo condition cannot be accounted for by classical conditioning.

Expectancy theory states that placebo effects are a product of the anticipation of particular responses to situational cues. In other words, placebos activate the expectation that subjective, behavioural, or physiological changes will occur, which then produce consistent drug responses. Therefore, expectations are considered to mediate placebo effects (Kirsch, 1997; Stewart-Williams & Podd, 2004). Expectations are believed to be learned through classical conditioning processes (as described above), verbal information (e.g., overhearing descriptions of drug effects), and observational learning (e.g., observing drug effects experienced by others; Kirsch, 1997; Stewart-Williams & Podd, 2004).

Expectancy theories of placebo effects posit that a number of factors may impact the magnitude of placebo effects. Specifically, environmental stimuli accompanying product administration are thought to have a significant impact on expectancies. Relevant stimuli include verbal instructions regarding active drug content, dose or anticipated effects of the product, and non-verbal cues about the product being administered (e.g., the packaging containing the product). These stimuli then activate stimulus expectancies, which are defined as beliefs about the active drug content of a product (e.g., the belief that an administered substance will exert pharmacological effects), which in turn activate response expectancies. Response expectancies are beliefs about the subjective, cognitive,

physiological and/or behavioural effects of a particular substance. The activation of response expectancies then influences responses to the administered product, whether it be a placebo effect, placebo by pharmacology interaction, or antiplacebo effect (Kirsch, 1997; Perkins et al., 2003). Such a theory of placebo effects can therefore account for drug responses that are consistent with and contrary to pharmacological effects, as expectancies may conceivably diverge from same.

A number of neuroimaging studies have sought to elucidate the neurophysiological mechanisms associated with placebo responses. Wager et al. (2004) used functional magnetic resonance imaging (fMRI) to evaluate placebo-induced changes in neural activity in brain regions associated with pain processing. Findings demonstrated that the anticipation of placebo-induced pain relief was negatively correlated with activity in the dorsolateral prefrontal cortex and orbitofrontal cortex, suggesting that these brain regions may play an important role in the anticipation of placebo effects. Greater placebo-induced pain relief following varied pain induction procedures (the administration of electrical shocks and heat) was also associated with reduced neural activity in pain-responsive brain areas including the rostral anterior cingulate cortex, insula, and thalamus. Overall, these findings demonstrate that the placebo effect is associated with robust neurophysiological processes.

Scott et al. (2008) used positron emission tomography (PET) to evaluate the role of the endogenous opioid and dopaminergic systems in the development of placebo responses following an experimental pain induction procedure (saline injections into the left masseter muscle) in 20 healthy subjects. Results demonstrated that placebo administration was associated with increased endogenous opioid neurotransmission in the

anterior cingulate cortex, orbitofrontal cortex, insular cortex, nucleus accumbens, right amygdala and periaqueductal gray matter. In addition, placebo administration was associated with increased dopamine neurotransmission in the nucleus accumbens, ventral putamen, and right ventral caudate nucleus. Finally, analyses demonstrated that increased dopaminergic neurotransmission in the right nucleus accumbens was the strongest predictor of the magnitude of placebo-induced analgesia. Findings suggest that both the mesolimbic dopaminergic system and the endogenous opioid receptor system play an important role in the generation of placebo responses.

Volkow and colleagues have assessed the relative influence of expectation and actual administration of intravenous methylphenidate on regional brain glucose metabolism using PET in 16 healthy male subjects with limited previous use of illicit substances (Volkow et al., 2006) and in 25 cocaine abusers (Volkow et al., 2003). Results demonstrated that the expectation that methylphenidate was administered exerted independent effects (i.e., placebo effects) and interacted with actual methylphenidate administration (i.e., placebo x pharmacology interaction) to produce changes in subjective responding and brain glucose metabolism.

More specifically, Volkow et al. (2006) demonstrated that, in participants with a limited history of previous illicit substance use, expected methylphenidate administration (i.e., a placebo x pharmacology effect) was associated with a greater reduction in striatal activity relative to unexpected methylphenidate administration, but no differences in subjective drug effects were noted, suggesting that expectancy may interact with drug pharmacology to potentiate drug-induced changes in neural activity. The expectation of amphetamine, in the absence of actual administration (i.e., a placebo effect), was also

associated with increased activity in the ventral cingulate gyrus and nucleus accumbens, suggesting that these regions may also play an important role in the expectation of drug effects. Alternatively, Volkow et al. (2003) found that expected methylphenidate administration (i.e. placebo x pharmacology effect) was associated with a 50% increase in whole brain glucose metabolism, particularly within the cerebellum and thalamus, and with greater subjective reports of feeling "high", relative to unexpected methylphenidate administration in cocaine abusing participants. Taken together, findings suggest that placebo-induced subjective and neural changes may vary according to prior experience with substance use, where greater placebo-induced effects are associated with a more extensive history of substance use.

Finally, Gu et al. (2016) recently conducted an fMRI study to assess the relative impact of nicotine content instructions (i.e., told nicotine containing cigarette vs. no nicotine cigarette) and actual nicotine administration (i.e., smoke nicotine containing cigarette vs. no nicotine cigarette) on subjective craving and neural activity following acute cigarette smoking in 24 chronic cigarette smokers. Results demonstrated significantly reduced subjective craving and significantly reduced activity in the insular cortex when nicotine was both expected and administered (i.e., a placebo x pharmacology interaction) than when nicotine was administered yet unexpected. These findings are consistent with those of Volkow et al (2003), and suggest that placebo and drug pharmacology may interact to produce subjective and neural changes in experienced drug users.

1.1.2 Importance of assessing the placebo effect

Given that placebo effects have been demonstrated to produce independent drug responses and to interact with pharmacological effects to maximize drug responses, it is likely that such effects make an important contribution to the therapeutic benefits of a wide array of medications. Because expectancies regarding drug content and drug effects are believed to mediate placebo effects, assessing participant expectancies in studies exploring treatment effects and efficacy is critical. Double-blind placebo-controlled designs, in which participants are informed that they have an equal chance of receiving placebo or active medication, are frequently deemed the gold standard in assessing drug effects and therapeutic efficacy (Sutton, 1991). In such designs, participants typically make guesses about whether they have been assigned to the placebo or active medication condition (Sutton, 1991; Thomas et al., 2008). These participant perceptions about drug assignment may activate divergent stimulus and response expectancies, which may in turn impact participant behaviour and/or study outcome measures (Correa et al., 2014; Stewart-Williams & Podd, 2004; Thomas et al., 2008).

Indeed, if participants guess that they have received the active drug, this may activate an expectation of benefit from treatment, which may lead to improvements in outcome measures regardless of whether or not an active drug was actually administered (i.e., a placebo effect or placebo by pharmacology interaction). Alternatively, if participants guess that they have received the placebo, expectancies that they will not benefit from treatment may be activated, which may then blunt treatment reactivity even if a pharmacological agent has been administered to the participant (i.e., an antiplacebo effect). Varying participant perceptions about drug assignment pose a substantial threat to the internal validity of placebo-controlled trials. In effect, one cannot be certain whether

study findings are attributable to pharmacological effects, expectancy effects, or some combination of these (Benedetti, 2008; Correa et al., 2014; Stewart-Williams & Podd, 2004; Thomas et al., 2008).

If the blind of a placebo-controlled design is not adequately maintained, participants may be able to accurately guess to which study condition they have been assigned. This is particularly likely when participants experience medication side effects, which may lead them to guess that they have received the active treatment. If this is the case, findings may overestimate the contribution of drug pharmacology to treatment effects while disregarding expectancy effects, as results in the active drug condition may be enhanced by interactions among placebo and pharmacology effects, while findings in the placebo condition may be diminished due to antiplacebo effects (Benedetti, 2008; Correa et al., 2014; Stewart-Williams & Podd, 2004; Thomas et al., 2008). Given that evidence suggests that study blinding is frequently unsuccessful (Fergusson, Glass, Waring, & Shapiro, 2004; Fisher & Greenberg, 1993; Greenberg, Bornstein, Greenberg, & Fisher, 1992; Margraf et al., 1991), findings from double-bind placebo controlled trials are vulnerable to systematic bias.

Assessing participant perceptions regarding drug assignment in double-blind placebo-controlled trials is essential to better gauge whether findings are a result of the independent or combined contribution of drug pharmacology and/or expectancy; however, perceptions regarding treatment assignment are rarely directly assessed. For example, Mooney, White and Hatsukami (2004) conducted a meta-analysis to assess fidelity of the blind in double-blind placebo-controlled studies of nicotine replacement therapy (NRT). Of the 73 studies included in the analysis, only 17 assessed blind

integrity. Of these studies, 12 uncovered blinding failure, suggesting that participants can frequently correctly guess their administration condition.

Schnoll and colleagues (2008) assessed blind integrity, and the link between blind integrity and study findings in a placebo-controlled buproprion smoking cessation trial. Results demonstrated that 55% of participants were able to accurately identify whether they had received buproprion or placebo. Further, treatment guess was significantly associated with quit rates, such that the association between actual treatment assignment and smoking cessation was no longer significant when treatment guess was entered into models. Dar, Stronguin, and Etter (2005) reported a similar pattern of findings when data from a placebo controlled study of the effectiveness of NRT in curbing smoking behaviour was re-analysed. They demonstrated that the belief that nicotine was received was associated with reduced smoking behaviour at 6 month follow-up, regardless of whether or not nicotine was actually consumed. Further, the association between NRT and curbed smoking behaviour was no longer found to be significant when beliefs regarding drug assignment were controlled for. Patient beliefs regarding drug assignment have also been demonstrated to significantly impact clinical outcomes in trials assessing treatments for depression (Chen et al., 2011), asthma (Luparello, Leist, Lourie, & Sweet, 1970), hypertension (Agras, Horne, & Taylor, 1982), gastrointestinal motility (Sternbach, 1964), post-operative pain (Bausell, Lao, Bergman, Lee, & Berman, 2005), and hypoglycemia (Pohl, Frohnau, Kerner, & Fehm-Wolfsdorf, 1997). Taken together, these findings suggest that fidelity of the blind may be frequently compromised in placebo-controlled trials, which has important implications for the findings of such trials. This is particularly concerning, as findings from double-blind, placebo-controlled trials are

instrumental in establishing drug efficacy and approval for clinical use (Lipsky & Sharp, 2001).

1.2 The balanced placebo design

Given that expectancy has been demonstrated to significantly influence the findings of placebo-controlled trials, an improved understanding of how expectancy and pharmacology interact to influence drug responses is warranted. Indeed, if expectancy has an important impact on drug responses, and thus potentially clinical efficacy, then targeting expectancy in future interventions may lead to improved outcomes. The balanced placebo design is a powerful alternative to the placebo-controlled design, as it allows for the direct evaluation of the independent and combined contributions of expectancy and pharmacology to drug responses (Rohsenow & Marlatt, 1981; Sutton, 1991). In the balanced placebo design, instructions (told drug vs. told placebo) are crossed with actual drug administration (administered drug vs. administered placebo), such that four experimental groups result: (a) a told drug, administered drug condition, (b) a told drug, administered placebo condition, (c) a told placebo, administered drug condition, and (d) a told placebo, administered placebo condition. Expectancy effects can be assessed by comparing results of conditions where participants were told drug relative to told placebo, while pharmacology effects can be evaluated by comparing the administered drug versus administered placebo conditions. Finally, the combined effect of expectancy and pharmacology can be assessed by comparing the told drug and administered drug condition to the remaining three conditions.

1.2.1 The balanced placebo design in nicotine and tobacco research

Tobacco smoking is a leading cause of preventable death, as approximately half of long term smokers die as a result of tobacco-related illness (Royal College of Physicians, 2007). Tobacco addiction is generally considered to be a result of nicotine dependence, as nicotine is the primary psychoactive substance in tobacco (Benowitz, 2010). Indeed, nicotine replacement therapies (NRTs) are considered to be the first line treatment for smoking cessation, and placebo-controlled trials have demonstrated that NRT increases the odds of successful cessation by 50-70% relative to unaided attempts (Stead et al., 2012). Given the widespread perception that tobacco addiction is driven by nicotine dependence (U.S.DHSS, 2010), it is likely that smokers have strong beliefs that nicotine administration (via smoked tobacco or NRT) is effective in curbing craving to smoke (Dar & Barrett, 2014). As a result, expectations regarding nicotine administration and effects may contribute to responses to both tobacco smoking and NRT administration. This assertion is supported by findings that the belief that one received NRT relative to placebo is significantly associated with improved cessation outcomes, regardless of actual drug assignment, in placebo-controlled smoking cessation trials (Dar et al., 2005; Mooney, Leventhal, & Hatsukami, 2006). Given these findings, nicotine and tobacco may be ideal models with which to assess the relative contribution of expectancy and pharmacology to drug responses. To date, several studies have assessed the relative contribution of nicotine expectancy and pharmacology to responses to tobacco smoking and NRT administration.

1.2.2 Balanced placebo designs and tobacco smoking

1.2.2.1 Laboratory based studies

Juliano and Brandon (2002) assessed the relative impact of nicotine expectancy and administration components of smoked tobacco on self-reported anxiety, craving and withdrawal in 132 dependent smokers. Participants were assigned to one of the four conditions of the balanced placebo design, in which nicotine content instructions (told normal cigarette with normal nicotine content vs. nicotine-free cigarette) were crossed with the actual nicotine content (1.1 milligrams (mg) vs. 0.06mg nicotine) of a study cigarette. Prior to smoking the cigarette, all participants completed an anxiety-induction procedure. A manipulation check demonstrated that 88% of participants reported believing nicotine content instructions and 74% provided estimates of the nicotine content of the cigarette that were consistent with nicotine content instructions. Findings were consistent regardless of belief of instruction or estimate of nicotine content. Regardless of nicotine content instructions, nicotine administration was associated with reduced urge to smoke, while nicotine content instructions were only associated with significantly reduced urge to smoke when participants received the denicotinized (i.e., 0.06 mg) cigarette. Nicotine-containing cigarettes were rated to smell and taste better, and to be more acceptable than denicotinized cigarettes, suggesting that some of the findings regarding nicotine content may be attributable to increased palatability rather than to a genuine pharmacological effect.

A 2004 study by Perkins et al. used a modified balanced placebo design to assess the relative contribution of nicotine expectancy (told regular nicotine vs. low nicotine cigarette) and administration (given a 0.9mg vs. <0.05mg nicotine cigarette) to the subjective and reinforcing effects of cigarette smoking. Ninety six dependent smokers were randomly assigned to one of the four conditions of the balanced placebo design,

during which they self-administered two puffs of a study cigarette. A manipulation check revealed that 72% of participants provided ratings of nicotine content that were consistent with nicotine content instructions. Participant ratings of craving and withdrawal were not impacted by nicotine content instructions nor administration; however, both nicotine content instructions and administration were associated with increased ratings of cigarette liking, satisfaction, and cigarette strength. One hour after taking puffs on the study cigarette, participants were offered an opportunity to self-administer up to seven additional puffs on a study cigarette. Self-administration data revealed nicotine content instructions were associated with increased self-administration of denicotinized cigarettes, yet were not found to impact self-administration of nicotine-containing cigarettes; however, it is possible that this may be due to the limited amount of smoking behaviour in which participants were permitted to engage. The majority of findings were consistent when analyses were performed with all participants versus only those who believed nicotine content instructions; however, the significant association between nicotine administration and ratings of cigarette liking and satisfaction found in all participants was present at only a trend level when analyses were restricted to participants who believed nicotine content instructions.

Kelemen and Kaighobadi (2007) assigned 120 dependent smokers to one of the four conditions of the balanced placebo design, in order to assess the relative impact of nicotine expectancy (told nicotine vs. no nicotine) and administration (given a 0.60mg vs. 0.05mg nicotine cigarette) on subjective craving and memory performance. A manipulation check revealed that the majority (92.5%) of participants reported believing nicotine content instructions. Findings revealed that both nicotine content instructions

and administration were associated with increased subjective satisfaction and calming. Nicotine content instructions were associated with reduced urge to smoke and hunger, and increased self-reported wakefulness and concentration, while nicotine administration was associated with reduced ratings of cigarette craving and irritability, and increased ratings of good taste of the cigarette, cigarette strength, dizziness and nausea. Memory was not found to be impacted by nicotine content instructions or administration. In addition, findings remained identical when analyses were conducted with all participants and with only those that were found to believe nicotine content instructions.

In a Perkins et al. (2008) study, the relative contribution of nicotine expectancy (told nicotine vs. no nicotine) and administration (given a 0.6mg vs. <0.05mg nicotine cigarette) to acute responses to smoking were assessed following a mood induction procedure. Two hundred smokers were assigned to one of the four conditions of the balanced placebo design, and an additional no-smoking group was included as a control. The study consisted of two sessions, where nicotine content instructions and administration remained identical, yet mood induction procedures (positive vs. negative) varied between sessions. Participants in the balanced placebo conditions took four puffs on a study cigarette, and then were subsequently offered an opportunity to smoke a maximum of four additional study cigarettes over the course of 14 minutes. A manipulation check revealed that 60.6% (n=97) reported believing nicotine content instructions during both sessions, and all analyses were restricted to this group of 'believers'. Nicotine content instructions were associated with a shorter latency to subsequent cigarette self-administration, while smoking behaviour was not impacted by nicotine administration. Nicotine content instructions and administration were both

associated with increased self-reported cigarette liking, while only nicotine content instructions were associated with increased self-reported satisfaction. Finally, in the positive mood condition, nicotine content instructions were associated with reduced craving following subsequent smoking; however, this same pattern of findings was not observed after the negative mood induction.

Juliano, Fucito, and Harrell (2011) evaluated the independent and combined impact of nicotine expectancy (told nicotine vs. placebo) and administration (0.6mg vs. 0.05mg nicotine) components of cigarette smoking on a sustained attention task, and subjective measures of craving, mood, and rewarding effects of smoking. One hundred and forty eight dependent smokers were assigned to one of the four conditions of the balanced placebo design. A manipulation check revealed that 82% of participants believed nicotine content instructions. Findings demonstrated that both nicotine content instructions and administration were associated with improved performance on the sustained attention task, increased ratings of satisfaction and good taste, and reduced ratings of cigarette craving and irritability. Nicotine content instruction and administration interactions were also observed, such that participants who expected nicotine yet received placebo reported a greater reduction in urge to smoke and tension relative to other participants, while participants who expected nicotine and received placebo smoked their cigarette in fewer puffs than participants who both expected and received nicotine. Findings did not differ when analyses were performed using all participants or only those participants who believed nicotine content instructions

Darredeau, Stewart, and Barrett (2013) assessed the relative impact of nicotine expectancy (told nicotine-containing vs. nicotine-free cigarette) and administration (given

a 0.6mg vs. 0.05mg nicotine cigarette) on cigarette self-administration and subjective responses in 60 smokers. Participants completed two of the four sessions of the balanced placebo design, such that they received the same cigarette across both sessions, but instructions regarding nicotine content varied between sessions. After sampling three puffs of the study cigarette, participants completed subjective ratings, then were offered an opportunity to self-administer additional cigarette puffs over the course of 90 minutes. The final 50 participants completed a manipulation check, which revealed that every participant believed nicotine content instructions across both study sessions. Findings demonstrated that nicotine content instructions were associated with increased cigarette self-administration; however, nicotine administration was associated with increased self-reported stimulation and satisfaction after taking the sample puffs.

A 2016 study conducted by Robinson et al. assessed the relative impact of nicotine expectancy (told nicotine-containing vs. told denicotinized) and administration (give a 0.6mg vs. 0.05mg nicotine cigarette) on the subjective effects of smoking. Fifty one smokers completed four laboratory sessions in accordance with the four conditions of the balanced placebo design. A manipulation check was not conducted in order to avoid raising suspicion about the deception regarding nicotine content instructions. Nicotine content instructions and administration were associated with increased ratings of satisfaction and craving reduction, while nicotine administration was uniquely associated with increased psychological reward, aversion, and enjoyment of upper respiratory tract sensations. Nicotine content instructions and administration were also associated with increased ratings of nicotine content and similarity to participants' usual brand of

cigarettes, and nicotine administration was found to be associated with diminished ratings of harshness.

In summary, the available body of balanced placebo research assessing the relative contribution of nicotine expectancy and administration to the subjective and behavioural effects of cigarette smoking suggests that both expectancy and nicotine administration make important contributions to cigarette responses. Indeed, effects of both nicotine expectancy and administration were observed in all studies. While the observed effects of nicotine administration may be interpreted as indicative of nicotine-specific effects on responses to cigarette smoking, it is also possible that interactions of nicotine with other psychoactive tobacco constituents may have contributed to these findings. Indeed, non-nicotine pharmacologically active tobacco constituents such as anabasine, nornicotine, and acetaldehyde may contribute to the reinforcing effects of tobacco either independently or in combination with nicotine (Caine et al., 2014; Clemens, Caillé, Stinus, & Cador, 2009; Hoffman & Evans, 2013), which may in turn impact the subjective and behavioural effects specific to nicotine-containing cigarettes observed in balanced placebo research. Given this limitation, balanced placebo research assessing the contribution of nicotine expectancy and administration to the subjective and behavioural effects of NRT may be better suited to delineate the relative contribution of expectancy and pharmacology to subjective and behavioural drug effects.

1.2.3 Balanced placebo designs and nicotine replacement therapy administration

1.2.3.1 Naturalistic studies

Two early studies examined the relative contribution of nicotine expectancy and administration to the effectiveness of NRT in facilitating smoking cessation (Gottlieb,

Killen, Marlatt, & Taylor, 1987; Hughes, Gulliver, Amori, Mireault, & Fenwick, 1989).

In the Gottlieb et al. (1987) study, 109 smokers engaged in a two-week quit attempt, during which they were provided with placebo or nicotine (2mg) gum and assigned to one of the four conditions of the balanced placebo design. Participants were required to abstain from cigarette smoking, and were permitted to self-administer as many as 30 pieces of the study gum per day, depending on the extent of their craving to smoke. During the first week of the cessation attempt, nicotine content instructions were associated with decreased smoking behaviour, increased smoking abstinence, and reduced subjective withdrawal symptoms, while nicotine administration did not impact the outcome measures. Following the second week of the cessation trial, neither nicotine content instructions nor administration were found to be associated with subjective or behavioural outcome measures. At the end of the trial, participants were asked what kind of gum they thought they had received. Drug identification was observed to be similar regardless of the actual nicotine content of the administered gum.

Hughes et al. (1989) conducted a similar between subjects balanced placebo design, in which 72 smokers were instructed to use gum (placebo or 2mg nicotine) to help cope with cravings over the course of a two week cessation attempt; however the study also included two conditions consistent with a traditional placebo-controlled design (i.e., participants did not receive explicit instructions regarding the nicotine content of the study gum). Overall, findings demonstrated that nicotine content instructions were associated with reduced cigarette smoking, while both nicotine content instructions and administration were associated with increased abstinence during the cessation attempt; however, when analyses were restricted to include only the four conditions of the

balanced placebo design, only effects of nicotine content instructions were observed. At the end of the trial a manipulation check revealed that 8% of participants believed they were deceived, and 63% of participants were unsure whether they had been deceived regarding the nicotine content of the study gum; however, beliefs regarding deception were consistent across all study groups. Taken together, the Gottlieb et al. (1987) and Hughes et al. (1989) studies suggest that nicotine expectancy makes an important contribution to the clinical effectiveness of NRT.

A 2007 study by Fucito and Juliano assessed the impact of nicotine expectancy on responses to placebo transdermal patches in 72 dependent smokers engaged in a practice two-day cessation attempt. Participants were assigned to one of three possible instruction conditions: (a) told nicotine patch and provided information that maximized the patch's benefits, (b) told nicotine patch and provided routine information about the patch (e.g., information regarding its side effects), or (c) told placebo patch. Nicotine content instructions were associated with reduced cigarette smoking and increased ratings of patch helpfulness during the practice cessation attempt. In addition, instructions maximizing patch benefits were associated with increased self-reported positive patch effects relative to standard instructions.

1.2.3.2 Laboratory based studies

Darredeau and Barrett (2010) assessed the relative contribution of nicotine expectancy and administration (4mg nicotine vs. placebo) to the acute effects of inhalers on subjective craving to smoke using a modified balanced placebo design. Twenty four dependent smokers were assigned to one of two possible conditions in which they self-administered a nicotine or placebo inhaler over 20 minutes across two sessions, yet were

instructed that they had received nicotine during one session and placebo during the other. Participants received differently flavored inhalers (mint vs. citrus) across sessions to increase believability of nicotine content instructions. Instructions regarding nicotine content and flavoring were counterbalanced across the sessions, and actual nicotine content was randomized across participants. Following inhaler self-administration, participants reported reduced intentions to smoke when they were instructed the inhaler contained nicotine relative to placebo, regardless of actual nicotine administration. Nicotine administration was not observed to impact self-reported intentions to smoke. In addition, neither nicotine content instructions nor administration were found to impact subjective withdrawal relief.

Perkins et al. (2009) also used a modified balanced placebo design to assess the relative contribution of nicotine expectancy and administration to the acute effects of nicotine (1mg) and placebo nasal spray on self-reported cigarette craving. Ninety seven dependent smokers were assigned to one of the four conditions of the balanced placebo design, or to a control condition in which nasal spray was not used. The study involved two sessions, during which participants received identical nicotine content instructions and were administered the same product, yet one session commenced with a positive mood induction, and the other with a negative mood induction. The effects of nicotine content instructions and administration on craving were only analysed in participants who reported believing the instructions (n=48, 57.8%). Results demonstrated that nicotine content instructions and administration were independently associated with reduced craving; however, findings are difficult to interpret due to the inclusion of mood manipulations.

In summary, findings from the aforementioned studies suggest that nicotine expectancy makes a critical contribution to the subjective and behavioural effects of NRT. Indeed, effects of nicotine content information were consistently demonstrated across all studies, while effects of nicotine pharmacology were relatively scant in comparison.

1.2.4 Sex differences in balanced placebo research

While the majority of balanced placebo studies have not assessed sex differences in the influence of nicotine expectancy and administration on NRT and cigarette responses, a small body of research suggests that female smokers may be more sensitive to non-pharmacological manipulations than male smokers (Caggiula, Donny, & Chaudhri, 2002; Darredeau et al., 2013; Perkins et al., 2001; Perkins, Doyle, et al., 2006; Perkins, Jacobs, Ciccocioppo, et al., 2004). A secondary aim of the Perkins et al. (2004) balanced placebo study was to examine sex differences in the influence of nicotine expectancy and administration in 56 male and 40 female dependent smokers. Results suggested that under accurate nicotine content instruction conditions (i.e. told and administered nicotine) smoking was associated with greater reward in female than male participants; however, sex differences in smoking reinforcement (as measured by a computerized progressive ratio task where cigarette puffs could be earned by completing increasing response requirements) were not observed. These findings suggest that females may be more sensitive to the rewarding effects of smoking when nicotine content instructions are consistent with nicotine administration.

Perkins et al (2006) sought to directly assess sex differences in the subjective and reinforcing effects of nicotine expectancy and administration components of cigarette

smoking. Sixty male and 60 female dependent smokers were assigned to one of four possible conditions. Half of the study participants received a nicotine-containing (0.6mg) cigarette, while the other half received a low nicotine (0.05mg) cigarette. Within each group, half the participants were instructed that they had received a normal nicotine or nicotine-free cigarette, while the remaining half of the participants did not receive any instructions regarding nicotine content. Participants were permitted to take two puffs of their assigned cigarette, then completed subjective ratings of cigarette craving, and finally were allotted 30 minutes to self-administer study cigarettes ad libitum. Results suggested that female smokers experienced increased smoking reward and self-administered more cigarette puffs when nicotine administration was accompanied with consistent nicotine content instructions, while nicotine content instructions were not observed to impact smoking reward and self-administration in male smokers.

In the Darredeau, Stewart and Barrett (2013) balanced placebo design study, nicotine content instructions, nicotine administration and sex were observed to interact such that, in male dependent smokers, increased cigarette self-administration associated with nicotine content instructions was only observed when nicotine-containing cigarettes were self-administered, while in female dependent smokers, increased self-administration associated with nicotine content instructions was only observed when denicotinized cigarettes were self-administered. The finding that nicotine expectancy and administration interacted to impact smoking behaviour more in male than female smokers appears inconsistent with the findings of Perkins et al (2004) and (2006), where nicotine content instructions and administration were found to interact to increase smoking reward and reinforcement in female smokers only; however, a number of methodological

variations (e.g., differences in abstinence requirements prior to commencing study sessions, cigarette self-administration tasks, and study design) across studies may account for these differences.

Taken together, findings suggest that smoking reinforcement and reward may be more influenced by expectancy in female relative to male smokers, indicating that females' smoking behaviour may be more influenced by non-pharmacological factors than males' smoking behaviour. However, given the currently limited body of research assessing sex differences in sensitivity to pharmacological and non-pharmacological manipulations, replication is required before firm conclusions can be drawn. However, if the effects are observed to be genuine, they may have important implications for smoking cessation interventions, such that the development of interventions targeting non-pharmacological factors may be of greater benefit to female smokers.

1.2.5 Summary and implications of the balanced placebo design in nicotine and tobacco research

Despite variation in modes of nicotine administration (various cigarettes, gum, lozenge, nasal spray, patch), participant characteristics (treatment seeking, non-treatment seeking), design (between subjects, within subjects), outcome measures (behavioural, subjective, cognitive), setting (laboratory, field), assessment of sex differences, and the use of additional manipulations (mood inductions) findings of the above balanced placebo designs suggest that nicotine expectancies account for a major proportion of both tobacco and NRT effects. Effects of nicotine pharmacology were less consistent. While findings of nicotine administration on subjective effects were demonstrated in studies using nicotine-containing cigarettes, the presence of additional psychoactive constituents in smoked tobacco (Caine et al., 2014; Clemens et al., 2009; Hoffman & Evans, 2013),

makes it difficult to attribute these findings exclusively to the unique impact of nicotine administration. Alternatively, only one balanced placebo study using NRT found effects of nicotine administration (Perkins, Grottenthaler, et al., 2009); however, this study included additional mood manipulations, rendering the results difficult to interpret.

Given that findings from balanced placebo designs using NRT and tobacco demonstrate that expectancy plays an important role in laboratory studies and trials, future research assessing drug effects and efficacy would likely benefit from directly assessing and/or manipulating participant beliefs regarding drug assignment. Unfortunately, this is not standard practice at present (e.g., Mooney et al., 2006). Direct assessment and/or manipulation of beliefs regarding drug assignment would not only help to clarify the pharmacological and non-pharmacological factors that contribute to drug responses, it would also contribute to an improved understanding of the potential therapeutic benefits of non-pharmacological factors, which could then be targeted in future interventions in order to maximize desired outcomes. Laboratory studies, such as a number of the balanced placebo studies described in the paragraphs above, represent an important first step in exploring and documenting the contributions of non-pharmacological factors to drug responses, as laboratory studies frequently inform clinical trials, which provide important evidence regarding drug efficacy, which then guide decisions regarding the approval of drugs for clinical use (Lipsky & Sharp, 2001). Therefore, incorporating the direct assessment and/or manipulation of participants beliefs regarding drug assignment into laboratory based studies may be an important first step towards improving the methodology of clinical trials, the conclusions following from such trials, and decisions regarding drug effectiveness, efficacy and clinical use.

1.3 Purpose and contents of the present dissertation

Given that assessing expectancy effects in laboratory based research is an important step towards incorporating same into clinical trials, the primary purpose of the current work was to add to the currently small body of research assessing the relative contribution of expectancy and pharmacology to drug responses using nicotine and tobacco as a model. While previous research has consistently demonstrated important contributions of expectancy to behavioural and subjective tobacco and NRT responses, varied study designs, products, participant characteristics, outcome measures, settings, and the use of additional manipulations render findings difficult to compare across studies. Therefore, further examination of the relative contribution of expectancy and pharmacology to NRT and tobacco responses is warranted; particularly, as an improved understanding of the mechanisms underlying such responses may have important implications for the development of future interventions with improved treatment outcomes.

This dissertation is comprised of four individual experiments and a general discussion. The first paper was based on a laboratory experiment that used a balanced placebo design to evaluate the relative impact of nicotine expectancy and administration on subjective craving reduction associated with acute NRT use in 70 dependent smokers. The study also assessed the relative effectiveness of nicotine expectancy and administration components of NRT administration in preventing episodic peaks in craving triggered by exposure to smoking-associated cues (i.e., cue-induced craving), as such peaks in craving are closely associated with relapse into smoking (Ferguson & Shiffman, 2009). The second paper details a laboratory study that assessed the

independent and combined impact of nicotine expectancy and administration components of tobacco smoking on acute subjective craving and cue-induced craving using a modified balanced placebo design in 35 dependent smokers. The study also assessed potential sex differences in the impact of nicotine expectancy and administration on craving, as previous research suggests that female smokers may be more reactive to non-pharmacological manipulations, including manipulations of expectancy and cue-reactivity (Barrett, 2010; Field & Duka, 2004; Perkins, Donny, & Caggiula, 1999; Rose, 2006).

The third paper is based on a balanced placebo laboratory study of 154 dependent smokers that assessed the relative contribution of nicotine expectancy and administration to acute NRT effects on subjective craving and cigarette self-administration when smoking opportunities were unanticipated versus anticipated. Beliefs regarding the availability of a future smoking opportunity were manipulated as research using animal models suggests that unpredictable drug availability is associated with increased drug-related responding (Lagorio & Winger, 2014), indicating that unanticipated opportunities to smoke may be associated with increased smoking behaviour and thus potentially increased risk for relapse. The final study was a laboratory based study which used a modified balanced placebo design in order to evaluate the relative contribution of nicotine expectancy and administration to acute NRT effects on craving, heart rate and cigarette self-administration in 21 quitting motivated and 26 quitting unmotivated dependent smokers, as these two groups of dependent smokers have been demonstrated to respond differently to smoking-related manipulations (Donohue, Harris, Heinze, Woldorff, & Schoenfeld, 2016; Wilson, Sayette, & Fiez, 2012). In addition, quitting

motivated dependent smokers appear to show increased sensitivity to smoking cessation aids (e.g., NRT, varenicline and buproprion) during short-term smoking cessation trials than quitting unmotivated dependent smokers (Perkins, Lerman, et al., 2008, 2009; Perkins & Lerman, 2014; Perkins, Stitzer, & Lerman, 2006). Taken together, these findings suggest that quitting motivated and unmotivated dependent smokers may also show unique patterns of acute responses to nicotine expectancy and administration manipulations. The last chapter of the dissertation consists of a general discussion of the aggregated results and implications of the four individual investigations.

1.4. Main measures used in the present dissertation

All four studies in this dissertation assessed subjective craving using the Questionnaire of Smoking Urges-Brief (QSU-B; Cox, Tiffany, & Christen, 2001; Toll, Katulak, & McKee, 2006). The QSU-B is a two-factor self-report questionnaire which assesses urges and craving to smoke with 10 items (5 items per factor). Factor 1 craving measures intention to smoke (e.g., "I have a desire for a cigarette right now"), and is reflective of the positively reinforcing aspects of smoking behaviour, while factor 2 measures withdrawal-related craving (e.g., "I could control things better right now if I could smoke"), and is reflective of the negatively reinforcing aspects of smoking. Participants provide responses to items on a seven point Likert-type scale with response options ranging from 1 (*strongly disagree*) to 7 (*strongly agree*). Scores on each factor can range from 5 to 35, with higher scores reflecting greater craving. There is strong support for the two factor structure of the QSU-B, and each factor has been demonstrated to measure distinct constructs (Toll et al., 2006). There is also strong support for the reliability and validity of the QSU-B, and the measure has been demonstrated to be

sensitive to nicotine and tobacco-related craving, and abstinence effects (Cox et al., 2001;

Toll et al., 2006).

In addition to assessing subjective craving with the QSU-B, studies 3 and 4 also

assessed cigarette self-administration using a computerized progressive ratio (PR) task

(Barrett, 2010; Willner, Hardman, & Eaton, 1995). Participants are seated in front of a

computer with a lit cigarette of their preferred brand for the duration of the 60-minute

task. Participants are instructed that they can smoke a little or as much as desired over the

course of the task, and all cigarettes are provided to participants by a researcher. Cigarette

puffs must be earned by repeatedly pressing a keyboard key a predetermined number of

times. The first puff requires 10 key presses, and the required key presses to earn each

subsequent puff increase on a ratio of 1.3 (e.g., 13, 17, 22, etc.). Following each cigarette

puff, participants can resume the task at their own pace. A researcher is present for the

duration of the task in order to verify compliance. Three measures of cigarette self-

administration can be collected using the PR task. These include (a) latency to self-

administration, which is operationalized as the duration in seconds to initiate the first

puff, (b) total self-administered cigarette puffs during the task, and (c) breakpoint, which

is operationalized as the total number of key presses required to earn the final cigarette

puff during the PR task. Latency is considered to be a measure of drug-seeking behaviour

(Carter & Tiffany, 2001) or incentive salience (Berridge, 2007; Perkins, Ciccocioppo, et

al., 2008), total self-administered cigarette puffs is a measure of overall drug

consumption (Perkins, Ciccocioppo, et al., 2008), and breakpoint is an estimate of the

reinforcing value of smoking (e.g., the amount of effort (number of key presses) one is

willing to expend to earn cigarette puffs; Barrett, 2010; Perkins, Jacobs, Ciccocioppo, et

al., 2004). PR tasks have been demonstrated as sensitive to changes in mood and

abstinence-based craving (Willner et al., 1995; Willner & Jones, 1996) and to

pharmacological and non-pharmacological manipulations (Barrett, 2010; Barrett &

Darredeau, 2012).

CHAPTER 2. EXPERIMENT 1: THE IMPACT OF NICOTINE LOZENGES AND STIMULUS EXPECTANCIES ON CIGARETTE CRAVING

Sections of this chapter were taken from the following: Schlagintweit, H. E., Good, K. P., & Barrett, S. P. (2014). The impact of nicotine lozenges and stimulus expectancies on cigarette craving. *Journal of Psychopharmacology*, *28*(8), 773–779. doi:10.1177/0269881113519508

Hera Schlagintweit served as first author of the manuscript included in this chapter. She took the lead role in reviewing the relevant literature, designing and conducting the research, writing original manuscript drafts, and making revisions based on suggestions from co-authors, editors, and peer-reviewers.

2.1 Abstract

Reduced craving associated with nicotine replacement therapy use is frequently attributed to the effects of nicotine pharmacology, however non-pharmacological factors may also play a role. This study examined the impact of nicotine pharmacology and non-pharmacological components of an acute nicotine lozenge (4 mg) on cigarette craving, mood and heart rate in 70 daily smokers (36 male). Smoking-related stimuli were used to assess cue-induced craving. Participants were randomly assigned to one of four conditions in a balanced placebo design where half the participants were provided deceptive information regarding the nicotine content of a lozenge. Subjective ratings of craving and mood were collected and heart rate was assessed before and after neutral and smoking cues. Nicotine expectancy reduced withdrawal-related craving ($p=0.006$) regardless of actual nicotine administration while combined nicotine expectancy and administration reduced intentions to smoke ($p=0.046$) relative to each of the other conditions. Exposure to smoking-related stimuli increased cigarette craving ($p \leq 0.001$) and negative affect ($p \leq 0.001$) regardless of expectancy or pharmacology. Following the smoking cue, women reported a greater increase in withdrawal-related craving than men ($p=0.027$). Findings suggest that both pharmacological and non-pharmacological components of nicotine lozenge administration contribute to its acute effects on craving, yet neither appears effective in preventing craving triggered by exposure to environmental smoking stimuli.

2.2 Introduction

Nicotine replacement therapies (NRTs) provide an alternate source of nicotine in order to aid smoking abstinence during smoking cessation attempts. NRTs are effective in reducing background cigarette craving, thus mitigating smokers' risk for relapse (Stead et al., 2012). This reduction in craving is frequently attributed to dependence on the pharmacological effects of nicotine (Benowitz, 2008; U.S.DHSS, 1988, 2010). However, accumulating evidence indicates that non-pharmacological factors also contribute to reductions in craving associated with NRT use, and thus to the therapeutic benefits of NRTs (Barrett, 2010). As such, both nicotine pharmacology and non-pharmacological factors associated with NRTs may contribute toward reduced craving and thus improved cessation outcomes; however, the relative impact of nicotine pharmacology and non-pharmacological factors on craving remains poorly understood.

The importance of non-pharmacological factors in craving reduction and relief from withdrawal symptoms has been demonstrated, for example, in research using balanced placebo designs, where information about the nicotine content (told nicotine vs told no nicotine) of a product is crossed with the actual nicotine content of the product administered (receive nicotine vs receive no nicotine). As a result, beliefs about nicotine content (stimulus expectancies) are manipulated independently of nicotine pharmacology, enabling direct examination of each factor's impact on craving and/or other outcome measures of interest (Perkins et al., 2003; Sutton, 1991).

Balanced placebo designs have been used to examine the impact of stimulus expectancies and nicotine pharmacology on various aspects of tobacco-related craving using numerous NRTs. For example, Gottlieb et al. (1987) found that participants who

were told they had received nicotine gum, relative to those who were told they had received placebo, reported suppressed withdrawal symptoms during the first week of a cessation attempt. Hughes et al. (1989) demonstrated that participants who were told they had received nicotine gum reported slightly reduced tobacco-related craving but not withdrawal relative to those who were told they had received placebo gum during a two-week cessation attempt. Darredeau and Barrett (2010) reported that in non-treatment-seeking smokers who received a placebo or nicotine inhaler, the belief that nicotine was consumed reduced self-reported intention to smoke, but not withdrawal-related craving. In none of these studies, did the actual nicotine content of the administered products impact on craving, withdrawal symptoms or intention to smoke.

In a 2007 study, Fucito and Juliano used a partially balanced placebo design where participants wore a placebo patch over the course of a three-day quit attempt. Instructions regarding the nicotine content of the patch were manipulated. Participants who were told they had received a nicotine patch reported reduced cigarette intake and more helpful effects of the patch (including reduced craving) relative to those who were told they had received a placebo. Withdrawal and urge to smoke were not affected by nicotine content instructions. Finally, in a balanced placebo study where non-treatment-seeking smokers were administered placebo or nicotine nasal spray across two sessions, Perkins et al. (2009) reported that both the expectancy that nicotine was consumed and actually consuming nicotine reduced cigarette craving, but not withdrawal symptoms. However, because this study included mood manipulations prior to the administration of nasal spray and collection of outcome measures, it is difficult to directly compare its findings to other balanced placebo research using NRTs.

In sum, research indicates that stimulus expectancies have an important influence on various outcome measures including craving, withdrawal, and/or urge to smoke, suggesting that non-pharmacological factors make a substantial contribution to the therapeutic benefits of NRTs. The impact of nicotine pharmacology on various aspects of tobacco-related craving appears less straight forward, given the conflicting results described above. These divergent findings may, in part, be related to differences in study methodology (e.g. the inclusion of a mood manipulation), population (e.g. treatment-seeking versus non-treatment-seeking participants), outcome measures (e.g. craving, withdrawal, cigarette intake), and the currently limited available literature on the subject (only five studies have been identified to date). Additional balanced placebo research may help in clarifying the relative contributions of nicotine pharmacology and non-pharmacological factors of NRTs in suppressing different aspects of tobacco-related craving.

Despite the effectiveness of NRTs in reducing background craving, NRTs are ineffective in preventing relapse in the majority of cases (Hughes, Grass, & Pillitteri, 2000). NRTs' ineffectiveness in relapse prevention may be explained, in part, by their relative inability to prevent sudden peaks in craving triggered by exposure to smoking-related environmental stimuli (cue-induced craving; Ferguson & Shiffman, 2009). Indeed, research suggests that NRTs are not effective in prospectively preventing peaks in cue-induced craving (Ferguson & Shiffman, 2009). Further, cue-induced craving is closely associated with relapse (Cox et al., 2001; Ferguson & Shiffman, 2009). As such, NRTs' inability to prevent cue-induced craving may explain, in part, elevated rates of relapse into smoking.

Other evidence indicates that there may be sex differences in reactivity to smoking cues. Indeed, exposure to smoking cues may have a more pronounced impact on motivation to smoke and smoking behavior in female smokers relative to male smokers (Field & Duka, 2004; Perkins et al., 1999). Cue reactivity research, in which various aspects of tobacco-related craving and withdrawal are assessed before and after exposure to smoking and neutral cues, has demonstrated that women show a greater increase in craving following smoking cue exposure relative to men (Field & Duka, 2004). As such, women may be more vulnerable to relapse associated with smoking cue exposure, even if cessation attempts are aided with NRTs. However, the body of research examining sex differences in cue-reactivity is limited. To our knowledge, no study to date has directly examined whether there are sex differences in the effectiveness of NRTs in combating cue-induced craving.

The first aim of the current study was to clarify the relative impact of nicotine pharmacology and expectancy on craving reduction associated with NRT use. Therefore, the study used a balanced placebo design, in which participant expectations about the nicotine content of non-nicotine and nicotine lozenges (a NRT) were manipulated. A second aim of the study was to examine potential sex differences in the effectiveness of the nicotine lozenge in combating cue-induced craving. These aims were accomplished through having male and female participants provide ratings of tobacco-related craving before and after lozenge consumption, as well as prior and subsequent to exposure to smoking-related and neutral video cues.

2.3 Methods and materials

2.3.1 Participants

Seventy daily smokers (36 male) were recruited through advertisements placed on community and online bulletin boards within Halifax, Nova Scotia. An initial telephone-screening interview was used to confirm that participants conformed to selection criteria. Specifically, participants reported that they were medically healthy, medication-free (with the exception of birth control in women), and free from past or present mental illness including substance use disorders (excluding nicotine dependence). Participants were informed that they would be required to abstain from illicit and prescription drugs on the day of the study session. Abstinence was confirmed with self-report. All participants were dependent smokers (Fagerström Test for Nicotine Dependence (FTND)$\geq$3; Heatherton, Kozlowski, Frecker, & Fagerström, 1991) with no intention to quit smoking within a month of participation. Treatment-seeking smokers were excluded to avoid the possible confounding effects of differences in participants' intentions to stop smoking. None used NRTs at the time of participation or had prior experience with oral NRTs (the gum or lozenge). Participants ranged in age from 19–57 years (mean=27, standard deviation (SD)=9.2), smoked an average of 14 (SD=6.0) cigarettes per day, and received mean scores of 5.0 (SD=1.7) on the FTND. Table 2.1 presents the characteristics of participants included in this study. All participants provided voluntary, written consent to participate and were compensated with $10/hour for their participation in the study. The study received ethical approval from the Capital District Health Authority Research Ethics Board.

Table 2.1 Mean (SD) values across the four study groups. No significant group differences were observed for age in years, age of first tobacco use, cigarettes per day, total years as a daily smoker, FTND or baseline expired carbon monoxide (CO; p values>0.05).

	Told nicotine, receive nicotine (N=19) 10 Male	Told nicotine, receive no nicotine (N=17) 9 Male	Told no nicotine, receive nicotine (N=16) 8 Male	Told no nicotine, receive no nicotine (N=18) 9 Male
Age in years	25.1 (8.2)	27.2 (10.5)	30.1 (11.4)	25.3 (5.9)
Age of first tobacco use	14.2 (3.2)	15.7 (2.6)	14.0 (2.9)	14.3 (2.3)
Cigarettes per day	14.5 (5.8)	14.2 (7.1)	13.9 (5.1)	14.7 (6.1)
Total years as a daily smoker	8.3 (8.5)	9.2 (10.2)	13.1 (12.2)	8.67 (6.8)
FTND	4.8 (1.6)	4.4 (1.4)	5.8 (1.9)	5.4 (1.7)
Baseline expired CO (ppm)	6.21 (3.57)	6.06 (3.54)	6.25 (4.16)	5.33 (2.81)

2.3.2 Materials

Products. Nicotine lozenges (NiQuitin minis 4 mg: GlaxoSmithKline, Marly-le-Roi, France) contained 4 mg of nicotine and were mint flavored. Research on the pharmacokinetic properties of a 4 mg nicotine lozenge indicates that mean blood nicotine levels of approximately 6.0 ng/ml occur at 25–30 min after administration (McEwen, West, & Gaiger, 2008; Shiffman, Fant, Buchhalter, Gitchell, & Henningfield, 2005). Nicotine lozenges have been found to fully dissolve within 10 min, and the absorbed nicotine has a half-life of approximately two hours (ranging from 1–4 h;

GlaxoSmithKline Consumer Healthcare, Brentford, UK). Non-nicotine lozenges (Ricqles Ricqmint Menthe Sans Sucre, Laboratoire Vie et Santé, France), were similar in shape, size, and taste to nicotine lozenges, but contained no nicotine. Ricqles lozenges were selected due to their similar stimulus properties to the nicotine lozenges and because they were not commercially available in Canada at the time of the study, making it unlikely for participants to have prior experience with them. Lozenges were always provided to participants in packaging that conformed to instructions given (stimulus expectancy) regarding nicotine content. As such, participants in the expect nicotine condition received a lozenge in NiQuitin minis packaging and participants in the expect placebo condition received a lozenge in Ricqles packaging. While dissolution characteristics of the lozenges were not identical, participants were instructed not to chew, swallow or spit out the lozenge and to let it dissolve over the course of 30 min.

Demographic information and smoking patterns. A Demographic and Smoking History Questionnaire was used to collect demographic (e.g. age, sex, marital status, education, occupation) and smoking history information (e.g. age of first use, current smoking frequency).

Mood and cigarette craving. A visual analogue scale (VAS) was used to assess 11 mood descriptors (e.g. 'frustrated', 'relaxed'). Each item consisted of a horizontal line with numbers ranging from 1 ("Not at all") to 10 ("Extremely"). Participants were instructed to circle the number on the horizontal line that corresponded with their current subjective experience. VASs have been demonstrated as valid and reliable measures of subjective experiences (Bond & Lader, 1974). The Questionnaire of Smoking Urges-Brief (QSU-B) is a standard, psychometrically sound measure of cigarette craving and

withdrawal. The QSU-B consists of 10 self-report items that assess craving across two dimensions (factor 1: intention to smoke; factor 2: withdrawal-related craving; Toll, Katulak, & McKee, 2006). The QSU-B has been demonstrated as sensitive to nicotine and tobacco-related abstinence effects (Cox et al., 2001).

Heart rate. A Polaris Heart Rate Monitor (Polar Electro Canada, Inc., Lachine, Quebec, Canada) consisting of a chest strap and wristwatch was used to assess average heart rate over the course of 60 seconds.

2.3.3 Procedure

Following overnight (≥12 h) abstinence from smoking, participants completed one laboratory session. All participants were randomly assigned to one of four conditions, in accordance with the balanced-placebo design of the study. The four conditions differed by instruction regarding nicotine content (told nicotine or told no nicotine) and actual nicotine content (receive nicotine or receive no nicotine) of a lozenge. As such, the groups included a told nicotine/receive nicotine group (n=19, 10 male), a told nicotine/receive no nicotine group (n=17, 9 male), a told no nicotine/ receive nicotine group (n=16, 8 male), and a told no nicotine/ receive no nicotine group (n=18, 9 male). During the screening and consent process, participants were informed that they might receive either a nicotine or non-nicotine lozenge. Researchers informed participants of the type of lozenge they had been randomly selected to receive (their expectancy condition) upon presenting participants with a lozenge canister, from which participants selected one lozenge. Participants in the told nicotine condition received lozenges from nicotine lozenge canisters, and those in the told no nicotine condition received lozenges from canisters for non-nicotine lozenges. Full debriefing was delayed until data collection

was complete, in order to prevent past participants from informing potential participants about the deception involved in the study.

At the onset of the laboratory session, overnight abstinence from smoking was confirmed with a breath carbon monoxide (CO) sample (Vitalograph, UK) reading of ≤ 15 ppm. Next, participants smoked one cigarette of their preferred brand in order to avoid ceiling effects on measures of cigarette craving (Erblich, Lerman, Self, Diaz, & Bovbjerg, 2005; Kelly, Barrett, Pihl, & Dagher, 2004; Tong, Bovbjerg, & Erblich, 2007). Subsequently, demographic and smoking history information was collected. Participants were required to wait until one hour from the time they smoked prior to completing any additional study measures to enable craving to increase to above satiated levels (see Tiffany & Drobes, 1991). At this time, participants completed a craving and mood questionnaire and heart rate was assessed (Time 1 (T1)). Participants were then provided with a lozenge and allotted 30 min for consumption. Participants then completed another craving and mood questionnaire and heart rate was reassessed (Time 2 (T2)). Next, participants were comfortably seated at a desk, in front of a computer monitor, and were instructed to view two 2 min video clips that depicted neutral and smoking cues (McBride, Barrett, Kelly, Aw, & Dagher, 2006). The first clip, a neutral cue, depicted various individuals getting haircuts. The second video was a smoking cue, consisting of various individuals smoking cigarettes. Pencil and paper assessments of mood, craving and heart rate were conducted between viewings of the video clips (Time 3 (T3)) and after the second clip had been viewed (Time 4 (T4)). The end of the neutral cue and beginning of the smoking cue were separated by approximately 5 min. The neutral cue was always shown before the smoking cue to reduce the likelihood of carryover effects

impacting ratings of craving, mood and measures of heart rate (see Sayette, Griffin, &

Sayers, 2010).

2.3.4 Statistical analyses

Data were analyzed using mixed models in SPSS version 20 for Macintosh (SPSS

Inc., Chicago, Illinois, USA). In contrast to the general linear model ANOVA method,

which determines F statistics using the least sums of squares, the mixed models method

calculates F using a restricted maximum likelihood approach. This enables deviations

from compound symmetry as well as the inclusion of cases with missing values

(Gueorguieva & Krystal, 2004; Maxwell & Delaney, 2004). Model simplicity and

likelihood ratio tests were used to select appropriate covariance structures. The main

measures were subjective ratings of mood and cigarette craving, and measures of average

heart rate. Data for the main measures were analyzed using Time point (baseline (T1), 30

minutes post lozenge consumption (T2), post exposure to the neutral cue (T3), and post

exposure to the smoking cue (T4)) as a fixed and repeated factor, and Sex, Receive

(nicotine versus no nicotine), and Told (nicotine versus no nicotine) as fixed factors, and

Subject as a random factor, with baseline scores (T1) entered as a time-varying covariate.

The outcomes of interest for these analyses were any main effects of Time, Receive, or

Told, and any interactions between Time, Receive, Told and/or Sex. Tests of simple main

effects were performed on the linearly independent pairwise comparisons between the

estimated marginal means for all analyses. When interactions were observed, the simple

effects of variables within each level combination of the other variable(s) were tested.

Mean values included in the results section are estimated marginal means, and thus may

not reflect the true mean values of relevant conditions.

2.4 Results

2.4.1 Craving

A significant main effect of Told was observed for factor 2 craving [$F(1,61.92)=8.22$, $p=0.006$], with lower withdrawal-related craving when participants were told they received a nicotine lozenge (M=14.09, SE=0.84) then when they were told they received a non-nicotine lozenge (M=17.51, SE=0.85). A Time by Told interaction was found for factor 1 craving ($F(2,60.69)=5.75$, $p=0.005$). Lower ratings of intention to smoke were found after lozenge consumption (told nicotine lozenge: M=20.60, SE=0.92; told non-nicotine lozenge: M=26.85, SE=0.94; $p=0.001$) and after the neutral cue (told nicotine lozenge: M=22.05, SE=1.05; told non-nicotine lozenge: M=27.02, SE=1.06; $p=0.001$) but not after the smoking cue (told nicotine lozenge: M=26.50, SE=0.91; told non-nicotine lozenge: M=28.18, SE=0.92; $p>0.05$) when participants were told they received a nicotine lozenge relative to a non-nicotine lozenge. A Told by Receive interaction was also observed for factor 1 craving ($F(1,60.04)=4.17$, $p=0.046$), see Figure 2.1. Lower intention to smoke was found when participants were both told and received a nicotine lozenge (M=20.92, SE=1.18) compared to when they were told they had received a non-nicotine lozenge but received nicotine (M=27.66, SE=1.22, $p<0.001$) and when they were told they had received a nicotine lozenge but received no nicotine (M=25.18, SE=1.20, $p=0.015$).
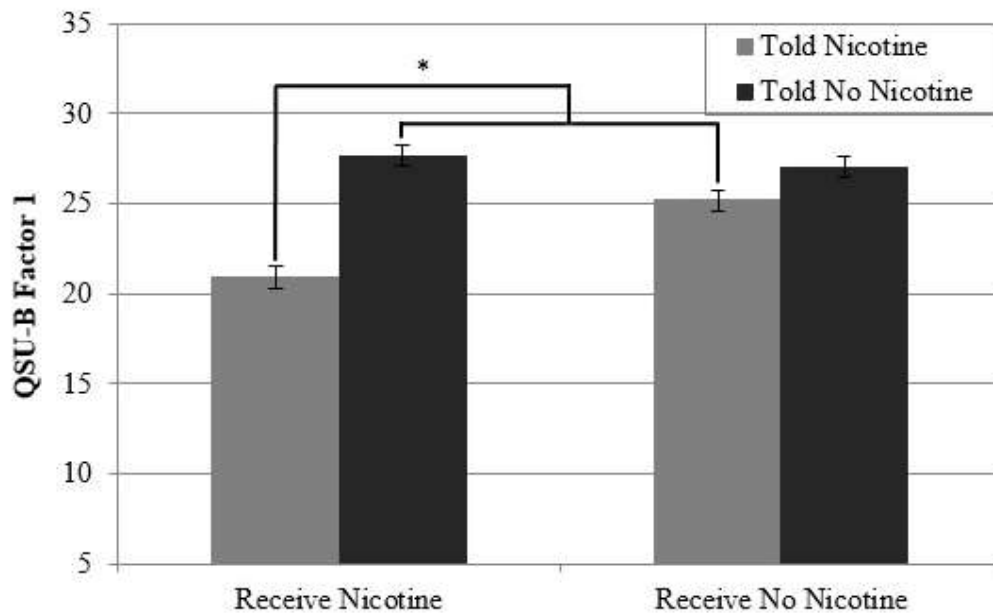
Figure 2.1 Estimated marginal mean scores (±standard error (SE)) for Questionnaire of Smoking Urges-Brief (QSU-B) factor 1 (intention to smoke). Significantly lower intention to smoke was found when participants were both told and received a nicotine lozenge relative to those who were told nicotine but received a non-nicotine lozenge and those who were told no nicotine but received a nicotine lozenge, as evidenced by a Told by Receive interaction (p=0.046*).

Finally, a Time by Sex interaction was found for factor 2 craving (F(2,119.99)=3.74, p=0.027), see Figure 2.2. In female participants, increased withdrawal-related craving was found after the smoking cue (M=17.70, SE=0.93) compared to after lozenge consumption (M=15.39, SE=0.93, p=0.003) and after the neutral cue (M=14.96, SE=0.93, p<0.001). No significant changes in withdrawal-related craving were observed in men.
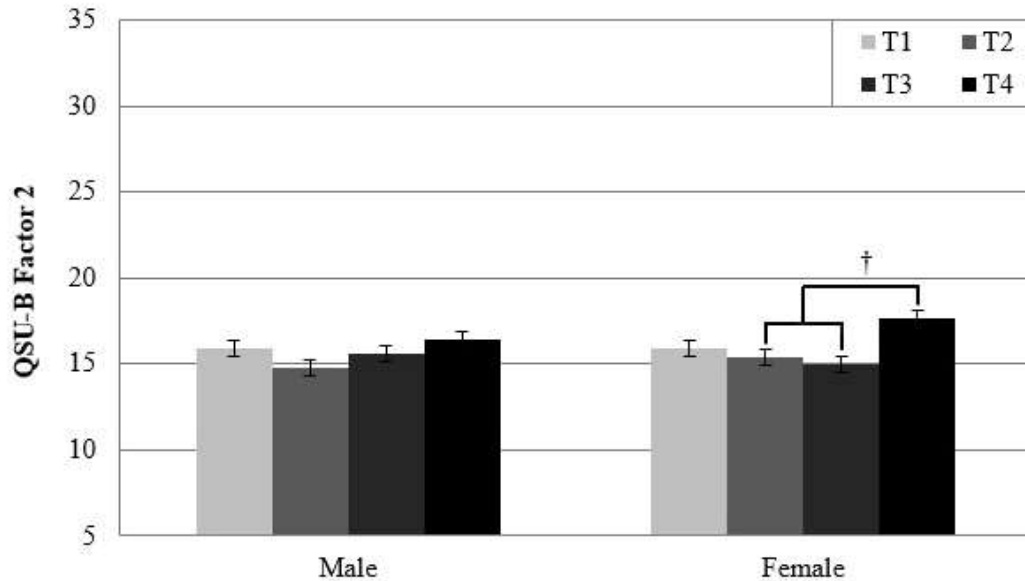
Figure 2.2 Estimated marginal mean scores (±standard error (SE)) for Questionnaire of Smoking Urges-Brief (QSU-B) factor 2 (withdrawal-related craving) at baseline (T1), after lozenge consumption (T2), after exposure to the neutral cue (T3) and after exposure to the smoking cue (T4). Baseline values were fixed as time-varying covariates in the analyses. A Time by Sex interaction revealed significantly increased ratings of withdrawal-related craving at T4 compared to T2 and T3 in female participants. No significant changes over time were found in male participants (p=0.027†).

2.4.2 Heart rate

A main effect of Receive was found for average heart rate ($F(1,30.10)=6.72$, $p=0.015$), see Figure 2.3. Increased average heart rate was observed when participants received a nicotine lozenge (M=71.48, SE=1.06) relative to a non-nicotine lozenge (M=67.56, SE=1.08). A main effect of Time was also observed for average heart rate ($F(2,35.80)=8.01$, $p=0.001$), see Figure 3, where average heart rate decreased after the neutral cue (M=67.75, SE=0.73) and after the smoking cue (M=68.75, SE=0.63) relative to after lozenge consumption (M=72.06, SE=1.30; $p=0.001$, $p=0.005$ respectively).
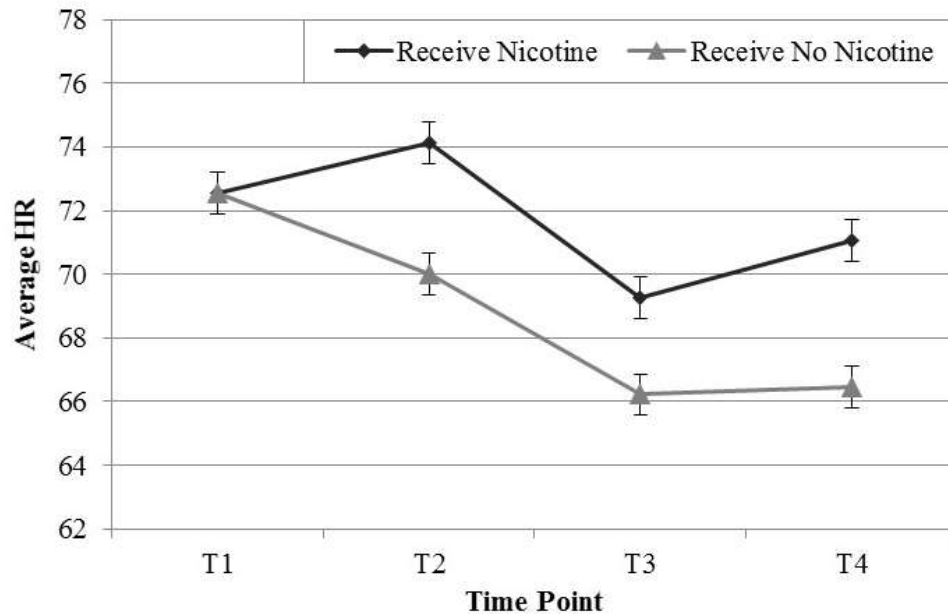
Figure 2.3 Estimated marginal means (±standard error (SE)) for average heart rate (HR) at baseline (T1), after lozenge consumption (T2), after exposure to the neutral cue (T3) and after exposure to the smoking cue (T4). Baseline values were fixed as time-varying covariates in the analyses. A main effect of Receive revealed increased average HR, regardless of time point, in participants who received a nicotine lozenge as opposed to a non- nicotine lozenge. A main effect of Time evidenced decreased heart rate at T3 and T4 relative to T2 across both Receive conditions.

2.4.3 Mood

Subjective state was assessed using the 11 mood items from the VAS. There was a significant main effect of Time for ratings of 'relaxed' $(F(2,60.60)=13.45, p<0.001)$, 'pleasant' $(F(2,60.67)=9.61, p<0.001)$, 'anxious' $(F(2,60.68)=7.94, p=0.001)$, 'irritable' $(F(2,60.69)=7.84, p=0.001)$, 'frustrated' $(F(2,121.29)=8.58, p<0.001)$, and 'dizzy' $(F(2,117.63)=3.99, p=0.021)$. Participants reported feeling less 'relaxed' and 'pleasant', and more 'anxious', 'irritable', and 'frustrated' after the smoking cue compared to after lozenge consumption and after the neutral cue (p values<0.03, see Table 2.2 for M and

SE values). Participants also reported feeling more 'dizzy' at T2 relative to T3 (p=0.008, see Table 2.2 for M and SE values).

Table 2.2 Estimated marginal mean ratings (SE) for VAS mood ratings which had significant main effects of Time after lozenge consumption (T2), after exposure to the neutral cue (T3) and after exposure to the smoking cue (T4). Baseline values (T1) were fixed as time-varying covariates in the analyses.

VAS Mood Ratings	T2	T3	T4
Relaxed	6.30 (0.22)	6.36 (0.22)	5.59 (0.22)
Pleasant	6.42 (0.18)	6.51 (0.16)	5.96 (0.22)
Anxious	3.48 (0.22)	3.49 (0.25)	4.34 (0.31)
Irritable	2.92 (0.17)	2.88 (0.21)	3.63 (0.26)
Frustrated	2.40 (0.20)	2.24 (0.21)	3.09 (0.20)
Dizzy	1.71 (0.14)	1.39 (0.14)	1.54 (0.14)

A Told by Time by Receive interaction was observed for ratings of 'relaxed' $(F_{(2, 60.60)}=7.84, p=0.001)$, where lower ratings of 'relaxed' were found after the smoking cue (M=5.00, SE=0.43) relative to after lozenge consumption (M=6.42, SE=0.42, p=0.002) and after the neutral cue (M=6.79, SE=0.44, p<0.001) when participants were both told and received a nicotine lozenge. Similarly, lower ratings of 'relaxed' were found after the smoking cue (M=5.30, SE=0.43) compared to after lozenge consumption (M=6.19, SE=0.42, p=0.048) and after the neutral cue (M=6.30, SE=0.43, p=0.002) when participants were both told and received a non-nicotine lozenge. Finally, a Told by Time by Sex interaction was observed for ratings of 'irritable'

(F(2,60.69)=3.30, p=0.044). Higher ratings of 'irritable' were found after the smoking cue (M=3.89, SE=0.53) relative to after lozenge consumption (M=2.85, SE=0.35, p=0.021) when male participants were told they received a non-nicotine lozenge, and after the smoking cue (M=3.67, SE=0.50) relative to after the neutral cue (M=2.84, SE=0.41, p=0.026) when male participants were told they had received a nicotine lozenge. Higher ratings of 'irritable' were also found after the smoking cue (M=3.72, SE=0.55) relative to after lozenge consumption (M=2.45, SE=0.36, p=0.008) and after the neutral cue (M=2.78, SE=0.44, p=0.020) when female participants were told they had received a nicotine lozenge.

2.5 Discussion

The current study used a balanced-placebo design to examine the relative impact of pharmacological and non-pharmacological factors of nicotine lozenge administration on tobacco-related craving, subjective mood state and heart rate in male and female non-treatment-seeking smokers. Smoking-related stimuli were used to assess the effectiveness of the nicotine lozenge in mitigating cue-induced craving, and potential sex differences in cue reactivity. The expectancy that nicotine was administered, regardless of whether nicotine was actually consumed, was effective in reducing withdrawal-related craving. Nicotine administration was observed to reduce self-reported intentions to smoke; however, this effect was dependent on the expectation that nicotine had been administered. These findings demonstrate the importance of non-pharmacological factors in craving reduction associated with NRT use and suggest that non-pharmacological factors make a substantial contribution to the therapeutic benefits of NRTs.

Nicotine pharmacology has been shown to independently reduce subjective craving in past research using NRTs (Perkins, Grottenthaler, et al., 2009). The limited impact of nicotine pharmacology in the current study may be related to blood nicotine levels associated with the nicotine lozenges administered. It has been demonstrated that the pharmacokinetic properties of the 4 mg quick-release nicotine lozenge result in mean blood nicotine levels of ~6.0 ng/ml at 25–30 min post consumption (McEwen et al., 2008; McGrath, Dorbeck, & Barrett, 2013; Shiffman et al., 2005). These expected concentrations are believed to fall at the lower end of steady state plasma levels generally associated with therapeutic administration, which are within the range of 5–15 ng/ml (Benowitz, Hukkanen, & Jacob III, 2009; McGrath et al., 2013). As such, it is possible that this dose was insufficient to produce a significant reduction in craving independent of dose expectation. Additionally, participants smoked a cigarette one hour prior to lozenge consumption, which may have resulted in diminished craving reduction associated with the nicotine pharmacology of the lozenges. However, average heart rate was elevated following nicotine lozenge administration, regardless of expectancy, indicating that the dose of nicotine was sufficient to produce at least some pharmacological effect. Additionally, previous balanced-placebo research using nicotine and placebo gum and inhalers have also failed to find an effect of nicotine pharmacology on measures of tobacco-related craving (Darredeau & Barrett, 2010; Gottlieb et al., 1987; Hughes et al., 1989). Continued balanced-placebo research using a variety of NRTs and dose ranges will be important in establishing a more comprehensive understanding of the relative impact of nicotine pharmacology and expectancy on withdrawal symptoms and cigarette craving more broadly. Balanced-placebo designs manipulating the nicotine

content of cigarettes, rather than NRTs, have more consistently found effects of nicotine pharmacology independent of expectancy effects (e.g. Juliano & Brandon, 2002; Juliano, Fucito, & Harrell, 2011; Kelemen & Kaighobadi, 2007). However, cigarettes contain a variety of other non-nicotine pharmacological constituents which may interact with nicotine pharmacology to produce the observed findings (Rabinoff, Caskey, Rissling, & Park, 2007). Additionally, research indicates that smokers hold differing expectancies regarding cigarette smoking versus nicotine (Hendricks & Brandon, 2008), which may contribute to differing impacts of expectancy and nicotine pharmacology on craving reduction in cigarettes versus NRTs.

Consistent with previous findings (see Ferguson & Shiffman, 2009), exposure to smoking cues significantly increased tobacco cravings and indices of negative affect (diminished ratings of 'relaxed' and 'pleasant' and increased ratings of 'irritable', 'anxious', and 'frustrated'). The increase in cue-induced craving occurred regardless of nicotine expectancy and/or administration. This attests to the strong association between smoking-related stimuli and craving, and also may shed light on the significant relapse rates associated with smoking cessation attempts, even when aided by NRTs (Benowitz, 2008; Ferguson & Shiffman, 2009; Hughes et al., 2000). NRTs, including the nicotine lozenge, have been demonstrated as helpful aids in smoking cessation attempts (Stead et al., 2012). However, the current findings indicate that NRTs may be limited in their ability to prevent environmentally triggered craving. It has been suggested that using NRTs, such as the nicotine lozenge, after exposure to smoking-related stimuli may help to diminish cue-induced craving and thus serve as a 'rescue medication' (Ferguson & Shiffman, 2009). As such, nicotine lozenges and other fast-acting NRTs may be more

effective in reducing acute craving than in prospectively preventing the onset of craving. Since smoking cues were presented near the study's conclusion, when future smoking opportunities were approaching, it is possible the observed increase in self-reported craving and negative affect following exposure to smoking-related cues may also relate to participant expectations about the availability of future smoking opportunities (see Dar, Rosen-Korakin, Shapira, Gottlieb, & Frenk, 2010; McBride et al., 2006). However previous research that has varied the expectations about future smoking following one hour of abstinence has failed to find an effect on cue-induced craving (Field & Duka, 2004).

Exposure to the smoking cues resulted in increased withdrawal-related craving in female compared to male participants, indicating female smokers may be more sensitive to smoking-related stimuli than male smokers. These findings are consistent with previous research demonstrating a greater relative increase in craving following exposure to smoking cues (Field & Duka, 2004) as well as other drug cues (Robbins, Ehrman, Childress, & O'Brien, 1999) in women compared to men. As such, it appears that women may display heightened sensitivity to cues associated with a variety of substances of abuse, including tobacco. These results may have important implications for cessation, where sex-specific interventions, such as aiding women in developing strategies to cope with cue-induced craving may be helpful in promoting successful cessation.

The findings of this study should be considered in light of several limitations. First, the study involved the direct manipulation of information regarding nicotine content. To avoid the possibility of suspicion about the nature of deception, debriefing was postponed until data collection had been completed. Thus the believability of the

instructions regarding nicotine content was not directly assessed. It is possible that participants may not have been successfully deceived, and thus results may underestimate the effects of expectancy (see Kelemen & Kaighobadi, 2007). However, participants did not have prior experience with oral NRTs, and participants were only exposed to one type of lozenge (either nicotine or non-nicotine lozenge) in an effort to minimize the possibility of unsuccessful deception. Reliance on subjective, self-report measures of craving and mood within the current study renders findings vulnerable to demand characteristics. However, the fact that distinct effects of expectancy were observed for factor 1 and factor 2 craving lessens this concern. Assessment of the effects of nicotine expectancy and administration using other objective measures of smoking motivation and mood represents an important area for future research. Additionally, the absence of counterbalancing of video cues represents a methodological drawback, although the decision to present the neutral cue prior to the smoking cue was made in an effort to minimize the impact of carryover effects on subjective measures of craving and mood (Sayette et al., 2010). Finally, because this study only involved one session of a between-subjects design, it was not possible to assess within-participant differences in response to nicotine expectancy or administration. A design that permitted for the examination of within-subject differences would have increased statistical power, which could allow for the detection of additional effects.

In conclusion, our findings demonstrate that non-pharmacological components have an important impact on the effects of nicotine lozenges on tobacco-related craving. Nicotine pharmacology was only effective in reducing craving when paired with the expectation that nicotine had been consumed. Neither expectancy nor pharmacology was

effective in preventing increased craving associated with exposure to smoking stimuli. This increase in craving was most pronounced in women, indicating that women may show heightened sensitivity to smoking cues compared to men. The importance of expectancy effects, nicotine pharmacology, cue-induced cigarette craving, and sex differences should be considered when examining smoking cessation strategies involving NRTs.

2.6 Linking statement and rationale for experiment 2

The primary aim of experiment 1 was to assess the relative impact of nicotine expectancy and administration components of acute NRT use on background and cue-induced craving. To our knowledge, this is the first report to document the unique impacts of nicotine pharmacology, expectancy and smoking-related stimuli on cigarette craving and withdrawal symptoms using a nicotine lozenge. However, experiment 1 was limited in that it did not include a manipulation check to verify whether participants believed nicotine content instructions. If deception regarding nicotine content instructions was unsuccessful, then findings from the present study may underestimate expectancy effects. Therefore, experiment 2 sought to extend the findings of experiment 1 by evaluating the independent and combined impact of nicotine expectancy and administration components of tobacco smoking on background and cue-induced craving. The decision to use cigarettes instead of lozenges was guided by previous findings that smokers have stronger expectations for craving reduction following smoking relative to NRT use (Juliano & Brandon, 2004), suggesting that nicotine expectancy may be more effective in curbing background and cue-induced craving following acute tobacco relative to NRT use. Unlike experiment 1, experiment 2 used a manipulation check in order to

verify participant belief of nicotine content instructions. Findings of main effects of and/or interactions of expectancy with nicotine content instructions are therefore more likely to reflect genuine effects of nicotine expectancy on subjective craving.

CHAPTER 3. EXPERIMENT 2: DOES ACUTE TOBACCO SMOKING PREVENT CUE-INDUCED CRAVING?

Sections of this chapter were taken from the following: Schlagintweit, H.E. and Barrett, S.P. (2016) Does acute tobacco consumption prevent cue-induced craving? *Journal of Psychopharmacology, 30*(5), 468-473.

Hera Schlagintweit served as first author of the manuscript included in this chapter. She took the lead role in reviewing the relevant literature, designing and conducting the research, writing original manuscript drafts, and making revisions based on suggestions from co-authors, editors, and peer-reviewers.

3.1 Abstract

Background: Smoking cessation aids appear to be limited in their ability to prevent craving triggered by exposure to smoking-associated stimuli; however, the extent to which cue-induced cravings persist following denicotinized or nicotine-containing tobacco smoking is not known. Methods: Thirty (17 male) $\geqslant$12-hour abstinent dependent smokers completed two sessions during which they smoked a nicotine-containing or denicotinized cigarette. Instructions regarding the nicotine content of the cigarette varied across sessions, and all participants were exposed to a neutral cue followed by a smoking cue after cigarette consumption. Craving was assessed before and after cigarette consumption and cue exposure. Results: Reduced intentions to smoke were associated with both nicotine expectancy ($p<0.05$) and nicotine administration ($p<0.01$), while reduced withdrawal-related craving was uniquely associated with nicotine administration ($p<0.05$). Smoking-associated stimuli increased craving regardless of nicotine expectancy or administration (p-values<0.001). Conclusions: While both nicotine pharmacology and expectancy appear to contribute to craving reduction associated with acute tobacco smoking, neither smoking-related nicotine administration nor expectation prevents increases in craving following exposure to smoking-associated stimuli. These findings suggest that cue-induced craving may be resistant to various pharmacological and psychological interventions.

3.2 Introduction

Nicotine replacement therapy (NRT) administration and expectancy (the belief that nicotine has been consumed) are generally ineffective in preventing episodic peaks in cigarette craving triggered through exposure to smoking-associated stimuli (i.e. cue-induced craving; Ferguson & Shiffman, 2009).We recently reported that neither the independent nor combined effects of nicotine administration, via acute NRT use, or nicotine expectancy prevented craving following exposure to smoking-associated stimuli (Schlagintweit, Good, & Barrett, 2014). Research examining the impact of varenicline, an α4β2 nicotinic receptor partial agonist, on cue-induced craving have produced more ambiguous findings. For example, Franklin et al. (2011) reported diminished ventral striatum and medial orbitofrontal cortex responses to smoking cues following varenicline treatment, but this study failed to observe significant medication by time interactions involving cue-induced craving. In a second study, Brandon et al. (2011) reported relatively diminished cue-induced craving following varenicline treatment, but because the effect was moderated by perceived drug condition, it is unclear to what extent these findings are due to drug effects or expectancy effects. The persistence of cue-induced craving following smoking cessation aid use may represent an important factor contributing to cessation failure, as cue-induced craving has been found to play an important role in relapse into smoking (Ferguson & Shiffman, 2009).

To our knowledge, the extent to which cue-induced cravings persist following actual smoking behavior has not been directly examined. Assessing the effectiveness of denicotinized cigarettes, which contain much less nicotine than conventional cigarettes, in preventing cue-induced craving may be of particular interest, as switching from

conventional to denicotinized tobacco smoking has been found to facilitate smoking

cessation (Dermody & Donny, 2014; Hatsukami et al., 2010; Walker et al., 2012). In

double-blind, placebo-controlled, laboratory-based studies, denicotinized tobacco has

been found to be more effective than NRT in delaying subsequent smoking behavior

(Barrett, 2010), as well as to curb craving and withdrawal in a manner comparable to

conventional cigarettes (Dallery, Houtsmuller, Pickworth, & Stitzer, 2003; Donny,

Houtsmuller, & Stitzer, 2007). Denicotinized and conventional tobacco smoking have

similar sensori-motor characteristics (i.e. similar appearance, smell, taste and

administration rituals; Rose, Behm, Westman, & Johnson, 2000). It is possible that the

replacement of such conditioned stimuli might reduce the salience of other environmental

smoking associated stimuli. In addition, tobacco smoke contains a number of non-

nicotine psychoactive components, such as anabasine and acetaldehyde (Caine et al.,

2014; Hoffman & Evans, 2013) as well as the monoamine oxidase inhibitors harman and

norharman (e.g. Herraiz, 2004). These constituents might also provide adequate satiation

in the presence of smoking-associated cues. Moreover, smokers have also been found to

have much greater expectations that cigarettes will help ameliorate negative affect and

craving relative to NRT (Juliano & Brandon, 2004), and it is possible that such findings

translate to denicotinized tobacco. On the other hand, nicotine consumed through

conventional tobacco smoking might be more effective in preventing cue-induced craving

than denicotinized tobacco due to a rapid delivery of nicotine (Hukkanen, Jacob III, &

Benowitz, 2005), to interactions of nicotine with various non-nicotine tobacco entities

(Clemens et al., 2009; Harris, Mattson, LeSage, Keyler, & Pentel, 2010), to interactions

of sensorimotor aspects of smoking with nicotine (Rose et al., 2000) or to psychological processes such as the belief that nicotine had been consumed (see Dar & Barrett, 2014).

An increasing body of research documents sex differences in cue-induced craving and reactivity to nicotine and non-nicotine aspects of tobacco smoking (Barrett, 2010; Field & Duka, 2004; Perkins et al., 1999; Rose, 2006; Schlagintweit et al., 2014). Females appear to demonstrate greater reactivity to smoking-related stimuli than males, even when exposed to smoking cues following acute NRT consumption (Field & Duka, 2004; Schlagintweit et al., 2014). Perhaps females may also show greater cue reactivity than males following denicotinized and nicotine-containing tobacco consumption. Alternatively, Barrett (2010) reported that denicotinized tobacco is more effective in suppressing tonic subjective craving in females than males. Thus, one may also expect that denicotinized tobacco may be more effective in suppressing cue-induced craving in females relative to males. To our knowledge, sex differences in cue reactivity following nicotine-containing and denicotinized tobacco consumption have not been assessed.

The present study aimed to (a) evaluate the independent and combined impact of acute nicotine administration and expectancy components of tobacco smoking on cue-induced craving and (b) identify potential sex differences in cue reactivity following nicotine-containing and denicotinized tobacco smoking. The study used a balanced placebo design, which manipulated participant expectancies about the nicotine content of nicotine-containing and denicotinized cigarettes. Following cigarette smoking, participants were exposed to smoking-associated stimuli, and subjective craving was assessed prior to and after cigarette consumption and stimulus exposure. Heart rate was also assessed prior to and after cigarette consumption and cue exposure, in order to verify

differences in the physiological effects of nicotine-containing and denicotinized tobacco consumption, as nicotine-containing tobacco smoking has been found to lead to greater increases in heart rate than denicotinized tobacco smoking (Benowitz, 1986). It is hoped that findings from this study will help to identify pharmacological or psychological factors that might help prevent increases in craving that result from the exposure to smoking-related stimuli, as well as to clarify the mechanisms underlying the therapeutic benefits of denicotinized tobacco.

3.3 Material and methods

3.3.1 Participants

Thirty-five (18 male) healthy, medication-free dependent smokers (Fagerström Test for Cigarette Dependence (FTCD) $\geqslant$ 3; Fagerström, 2012) participated in the current study; however, five of these participants (one male) failed to complete both study sessions. Thus, the final study sample consisted of 30 (17 male) participants with mean FTCD scores of 5.10 (standard deviation (SD)=1.60). Participants self-reported an absence of a lifetime history of psychiatric illness, smoked an average of 12.75 (SD=5.98) cigarettes per day, ranged in age from 20 to 58 years (mean=26.37, SD=7.28) and had been daily smokers for at least one year. Table 3.1 presents additional demographic characteristics of the participants.

Table 3.1 Mean (standard deviation) demographic information for participants who completed both study sessions (n=30). No significant differences in demographic information were observed across study groups (p>0.05).

| | Denicotinized cigarette (n=15) | | Nicotine-containing cigarette (n=15) | |
	Female (n=7)	Male (n=8)	Female (n=6)	Male (n=9)
Age in years	23.57 (3.31)	30.63 (11.56)	23.67 (3.01)	26.56 (5.57)
Age of first cigarette	12.71 (0.95)	14.75 (3.20)	15.67 (2.50)	13.67 (4.39)
Cigarettes per day	12.36 (6.41)	14.88 (6.68)	12.33 (6.61)	11.44 (5.06)
Years as a daily smoker	6.79 (4.28)	13.13 (13.16)	6.33 (3.61)	7.01 (5.96)
FTCD	5.00 (1.41)	5.25 (1.58)	5.33 (2.07)	4.89 (1.69)

3.3.2 Materials

Cigarettes. Nicotine-containing and denicotinized cigarettes (Quest 1 and Quest 3, respectively – Vector Tobacco, Mebane, North Carolina, USA) were aesthetically identical and contained similar tar yields (10 mg); however, maximum nicotine yields were 0.6 mg and 0.05 mg, respectively.

Cigarette craving. Intention to smoke (factor 1 craving) and withdrawal-related craving (factor 2 craving) were assessed with the Questionnaire of Smoking Urges-Brief (QSU-B), a reliable and sensitive measure of nicotine and tobacco-related craving and abstinence effects (Cox et al., 2001; Toll et al., 2006).

Like cigarette. A single-item visual analogue scale was used to assess the degree to which participants liked the cigarette consumed during the study (i.e. "like product"). The item consisted of a horizontal line with numbers ranging from 1 (not at all) to 10

(extremely). Visual analogue scales have been found to be valid and reliable measures of subjective experiences (Bond & Lader, 1974).

Heart rate. Average heart rate was assessed over 60 seconds using a Polaris heart rate monitor (Polar Electro Canada Inc., Lachine, Quebec, Canada).

Smoking and neutral cues. Two 2-minute video clips depicting individuals getting haircuts (neutral cue) and smoking cigarettes (smoking cue) were used to assess cue-induced cigarette craving. The videos were similar with respect to facial exposure, movement and physical characteristics of the actors, and have been shown to reliably induce subjective craving in previous investigations (Balter, Good, & Barrett, 2015; McBride et al., 2006; Schlagintweit et al., 2014).

3.3.3 Procedure

Participants attended two sessions and were randomly assigned to smoke either a nicotine-containing (n=15, nine male) or denicotinized cigarette (n=15, eight male) during both sessions, but were informed that the nicotine content of the cigarettes differed between sessions. The order of the nicotine content instructions was counterbalanced.

After consent was ascertained, overnight ($\geqslant$12 hour) abstinence from smoking was confirmed with a breath carbon monoxide sample reading of $\leqslant$15 ppm (Vitalograph, UK). Craving and heart rate were then assessed (Time 1 (T1)). Next, participants were given a cigarette and instructions regarding its nicotine content (i.e. a researcher told participants they would be smoking a nicotine-free or nicotine-containing cigarette during the session). All cigarettes were provided to participants in packaging consistent with instructions regarding nicotine content. After the smoking of the cigarette, craving and heart rate were assessed (Time 2 (T2)), as were ratings of cigarette liking. Participants

then viewed the neutral and smoking video clips. Craving and heart rate were measured between (Time 3 (T3)) and after (Time 4 (T4)) the video clips. The neutral cue was presented prior to the smoking cue to prevent carryover effects (Sayette et al., 2010), and video clips were presented within five minutes of one another in order to minimize the possibility of changes in craving resulting from the passage of time. At the end of each session, as a manipulation check, a researcher inquired about the nicotine content of the cigarette participants had smoked.

3.3.4 Statistical analyses

Data were analyzed using linear mixed models. Model simplicity and likelihood ratio tests were used to select appropriate covariance structures. The main measures included subjective ratings of cigarette craving, cigarette liking and average heart rate. Changes in cigarette craving and heart rate associated with tobacco consumption were analyzed using Time (baseline (T1) and post cigarette consumption (T2)) and Instruction (told nicotine-containing vs. told denicotinized cigarette) as fixed and repeated factors, Receive (nicotine-containing vs. denicotinized cigarette) and Sex (male vs. female) as fixed factors and Subjects as a random factor. Cue reactivity was examined using the same analytic strategy; however, the time points included in the analyses (post neutral cue (T3) and post smoking cue (T4)) differed. The outcomes of interest were the main effects of Time or the interactions between Time and Instruction, Sex and/or Receive. For cigarette liking, a similar analytic strategy was employed, but since it was measured only at one time point, Time was not included as a factor. Across analyses, when interactions were observed, the simple effects of variables within each level combination of the other variable(s) were tested. The mean values reported below are estimated marginal means.

3.4 Results

3.4.1 Study completion

Thirty of the 35 participants completed both experimental sessions, while the remaining five completed only one session. No significant differences in cigarettes per day or FTCD scores were found between participants who did and did not complete both study sessions. The findings reported below are from participants who completed both sessions.

3.4.2 Manipulation check

Five of the 30 participants were found not to believe instructions regarding the nicotine content of the cigarette during one session (five of 60 sessions). No significant differences in cigarettes per day or FTCD scores were found when believers were compared with non-believers. However, because previous research has revealed different findings in believers versus all participants (Kelemen & Kaighobadi, 2007; Schlagintweit, Greer, Good, & Barrett, 2015) results from both groups are reported below.

3.4.3 Findings from all participants who completed both sessions

3.4.3.1 Cigarette craving

Tobacco consumption. The main effects of Time were observed for both factor 1 (intention to smoke; $F(1,27.80)=58.76$, $p \leqslant 0.001$) and factor 2 (withdrawal-relief; $F(1,30.69)=25.35$, $p \leqslant 0.001$) craving. Craving was found to be reduced following tobacco consumption (factor 1: Mean (M)=20.01, standard error (SE)=1.21; factor 2: M=13.80, SE=1.31) compared to baseline (factor 1: M=29.50, SE=1.21; factor 2: M=19.31, SE=1.31). Receive by Time interactions were also observed for factor 1

(F(1,27.80)=11.65, p=0.002) and factor 2 (F(1,30.69)=4.44, p<0.05) craving. Following

tobacco consumption, craving was reduced in the receive nicotine-containing cigarette

condition (factor 1: M=14.28, SE=1.73; factor 2: M=10.96, SE=1.87) relative to the

receive denicotinized cigarette condition (factor 1: M=25.74, SE=1.70, p⩽0.001; factor

2: M=16.63, SE=1.84, p<0.05). Craving was also reduced after tobacco consumption

relative to baseline in the receive nicotine-containing cigarette (factor 1, T1: M=28.00,

SE=1.73, p⩽0.001; factor 2, T1: M=18.78, SE=1.87, p⩽0.001) and receive denicotinized

cigarette conditions (factor 1, T1: M=31.00, SE=1.70, p=0.005; factor 2, T1: M=19.84,

SE=1.84, p<0.05). Finally, a significant Instruction by Time interaction was observed for

factor 1 craving (F(1,33.83)=4.69, p<0.05). Following tobacco consumption, craving was

reduced in the told nicotine-containing cigarette condition (M=18.44, SE=1.32) relative

to the told denicotinized cigarette condition (M=21.58, SE=1.32, p⩽0.001). Craving was

also reduced after tobacco consumption relative to baseline in the told nicotine-

containing cigarette (T1: M=29.21, SE=1.32, p⩽0.001) and told denicotinized cigarette

conditions (T1: M=29.80, SE=1.32, p⩽0.001).

   Cue reactivity. The main effects of Time were observed for both factor 1

(F(1,26.00)=28.08, p⩽0.001) and factor 2 (F(1,26.00)=15.72, p=0.001) craving. Craving

was greater after the smoking cue (factor 1: M=24.93, SE=1.12; factor 2: M=15.60,

SE=1.24) relative to the neutral cue (factor 1: M=21.24, SE=1.28; factor 2: M=13.61,

SE=1.16). A near significant Sex by Instruction by Time interaction was also observed

for factor 1 craving (F(1,26.00)=4.16, p=0.052, see Figure 3.1). Craving was elevated

following the smoking cue relative to the neutral cue in females in the told nicotine-

containing cigarette condition (T3: M=20.18, SE=2.07; T4: M=26.10, SE=1.98,

p⩽0.001), as well as in males in the told nicotine-containing cigarette (T3: M=20.26, SE=1.80; T4: M=23.13, SE=1.73, p<0.05) and told denicotinized cigarette (T3: M=21.32, SE=1.85; T4: M=25.10, SE=1.64, p<0.01) conditions. Craving did not differ between the smoking and neutral cues in females who were told that they had received a denicotinized cigarette (p>0.05).
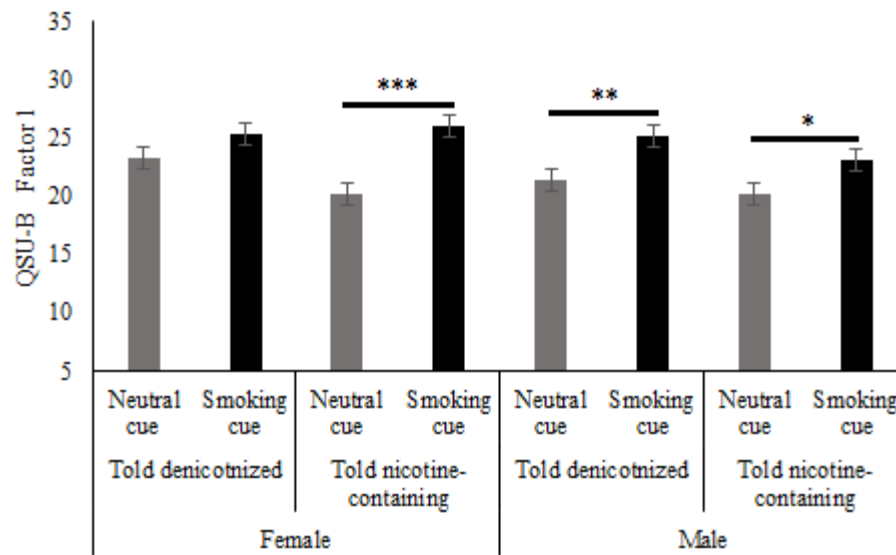
Figure 3.1 Estimated marginal mean values (+/- standard error) for QSU-B factor 1 craving. Craving was elevated following the smoking cue relative to the neutral cue in females and males who were told that they had received a nicotine-containing cigarette and males who were told that they had received a denicotinized cigarette, but not females who were told the same (*p<0.05, **p<0.01, ***p≤0.001).

3.4.3.2 Heart rate

Tobacco consumption. A main effect of Time was observed for average heart rate (F(1,76.42)=38.28, p⩽0.001), where heart rate was elevated after cigarette smoking (M=82.14, SE=2.07) relative to baseline (M=72.10, SE=2.07). A Receive by Time interaction (F(1,76.42)=25.71, p⩽0.001) also revealed that, following tobacco

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consumption, heart rate was increased in the receive nicotine-containing cigarette

condition (M=87.97, SE=2.94) relative to the receive denicotinized tobacco condition

(M=76.31, SE=2.90, p<0.01). In the receive nicotine-containing cigarette condition, heart

rate was elevated following tobacco consumption relative to baseline (M=69.69,

SE=2.97, p⩽0.001). This was not observed in the receive denicotinized tobacco condition

(p>0.05).

Cue reactivity. No significant findings were observed.

3.4.3.3 Like cigarette

The main effects of Receive (F(1,25.68)=8.43, p<0.01) and Instruction

(F(1,25.18)=14.30, p=0.001) were observed for ratings of like cigarette. Increased ratings

of like cigarette were found when participants were told (M=5.08, SE=0.41) and received

(M=5.31, SE=0.50) a nicotine-containing cigarette compared to a denicotinized cigarette

(Instruction: M=3.48, SE=0.42; Receive: M=3.25, SE=0.50).

3.4.4 Findings from only those participants who believed nicotine content instructions

Findings remained largely similar when analyses were restricted to only those

who believed nicotine content instructions. However, there were two exceptions. While

the cue reactivity Sex by Instruction by Time interaction for factor 1 craving was no

longer evident (p=0.2), the tobacco consumption Instruction by Time interaction for

factor 1 craving remained present at a trend level (F(1,21.00)=2.81, p=0.11). The

observed group differences for the Instruction by Time interaction remained consistent.

After tobacco consumption, craving was reduced in the told nicotine-containing cigarette

condition (M=18.56, SE=1.81) relative to the told denicotinized cigarette condition

(M=21.83, SE=1.63, p<0.05). Craving was also reduced after tobacco consumption

relative to baseline in the told nicotine-containing cigarette (T1: M=30.05, SE=0.94, p⩽0.001) and told denicotinized cigarette conditions (T1: M=31.05, SE=0.97, p⩽0.001).

3.5 Discussion

While cigarette consumption was found to reduce acute cigarette craving, exposure to smoking-associated stimuli increased craving regardless of expectancy and/or nicotine effects of recent smoking. The current findings are consistent with prior observations that smoking cues increase cigarette craving following as few as 30 minutes of abstinence (McBride et al., 2006), and suggest that smoking-associated stimuli may play a critical role in the maintenance of smoking behavior regardless of recency of smoking, nicotine administration or expectancy. The important role of cue-induced craving in maintaining smoking behavior has also been demonstrated in naturalistic studies, where exposure to smoking-associated stimuli leads to a greater likelihood of smoking (Shiffman et al., 2014; Shiffman, Paty, Gwaltney, & Dang, 2004). While there is some debate regarding the association between smoking cue exposure in the laboratory versus the natural environment (see Shiffman et al., 2015), findings attest to the critical role of cue-induced craving in maintained smoking behavior.

The persistence of cue-induced craving following denicotinized tobacco consumption suggests that denicotinized tobacco's effectiveness as a smoking cessation aid is likely not a result of curbed cue-induced craving. In fact, nicotine-containing tobacco was also relatively ineffective in preventing cue-induced craving. These findings, along with those of previous studies examining cue-induced craving following acute NRT use (e.g. Schlagintweit et al., 2014) and prolonged varenicline use (Brandon et al., 2011; Franklin et al., 2011), suggest that smoking salient stimuli may continue to pose a

risk for relapse despite the use of varied psychological and pharmacological interventions. Given that cue-induced cravings have been found to persist for several months following cessation, despite reduced background craving and withdrawal (Balter et al., 2015; Bedi et al., 2011), and that individuals who respond less strongly to smoking cues are more likely to successfully quit (Ferguson & Shiffman, 2009), identifying an effective means to combat cue-induced craving may contribute to a substantial increase in cessation success. At present, however, smoking cessation strategies may benefit from advising individuals attempting cessation to avoid smoking-related cues.

While no robust sex differences were observed in the current study, there was a trend toward blunted cue reactivity in females who were told that they had received a denicotinized cigarette. These findings are consistent with previous work suggesting that females may be more reactive to non-pharmacological manipulations, including expectancy and cue exposure, than males (Barrett, 2010; Field & Duka, 2004; Perkins et al., 1999; Rose, 2006; Schlagintweit et al., 2014); however, the present findings should be interpreted with caution due to the relatively small sample size and marginal statistical significance.

Nicotine administration and expectancy components of acute tobacco smoking were independently associated with an immediate reduction in intention to smoke and an increase in ratings of subjective liking of the cigarettes, while nicotine administration alone was associated with reduced withdrawal-related craving. Consistent with these findings, Darredeau and Barrett (2010) demonstrated that nicotine content instructions associated with inhaler use led to reduced intention to smoke but not withdrawal-related craving, while Darredeau, Stewart, and Barrett (2013) found that nicotine-containing, but

not denicotinized, cigarette smoking was associated with reduced withdrawal-related craving, while expectancy manipulations had no impact. Taken together, these findings suggest that both psychological and pharmacological manipulations may impact the rewarding aspects of smoking behavior, yet pharmacological manipulations may be necessary to impact withdrawal and negative reinforcement.

Whether these effects are nicotine-specific or a result of interactions between non-nicotine tobacco constituents and nicotine remains unknown. Intravenously administered nicotine has been found to reduce withdrawal symptoms (Rose et al., 2000), yet the extent to which these effects were due to expectancy versus nicotine pharmacology remains unclear, as expectancy was not manipulated independently of nicotine pharmacology. Other research suggests that nicotine-containing tobacco may be more effective than nicotine administered via NRT in reducing withdrawal-related craving (Barrett, 2010), which is consistent with the possibility that non-nicotine tobacco constituents may contribute to withdrawal-relieving properties of smoking (Harris et al., 2010; Hoffman & Evans, 2013). Additional research is needed to clarify the various pharmacological and non-pharmacological mechanisms that underlie craving and withdrawal reduction associated with nicotine-containing and denicotinized tobacco use.

The findings of this study should be considered in light of the following limitations. The nicotine content of the nicotine-containing cigarettes used in the study was lower than that of most marketed brands, which may have limited findings of nicotine effects. However, the observed nicotine effects and increased heart rate following nicotine-containing cigarette administration suggest a pharmacologically active dose. In addition, the same brand of nicotine-containing cigarettes have been previously

shown to reduce withdrawal-related craving and increase subjective satisfaction and stimulation compared to denicotinized cigarettes, suggesting that they have sufficient nicotine to yield prototypical smoking effects (Barrett, 2010; Darredeau et al., 2013). It is possible, however, that consumption of participants' preferred brand of cigarettes may have been more effective in preventing cue-induced craving. Second, the design of this study allowed for the examination of the effects of nicotine as well as of nicotine content information, but not for a direct comparison between these, since this would have required a comparison of within-subject and between-subject effects. While the present study had greater power to detect expectancy effects than pharmacology effects, it is noteworthy that several nicotine-specific effects were observed. In addition, previous balanced placebo studies using similar designs and sample sizes have identified significant effects of both within and between subject factors (Darredeau & Barrett, 2010; Hughes et al., 1989), suggesting that the current study is adequately powered. Finally, the presentation of the neutral cue prior to the smoking cue raises the possibility of order effects. The decision not to counterbalance the cues was made in an effort to avoid carryover effects (Sayette et al., 2010) and because the cues were presented in close proximity to each other (within 5 minutes) it is unlikely that any differences observed can be attributed to the mere passage of time.

3.5.1 Conclusions

In conclusion, findings demonstrate that while both nicotine content and expectancy contribute to the liking of cigarettes and reduced intention to smoke, nicotine content appears to have a unique influence on relief from withdrawal-related craving. Neither nicotine content nor expectancy were observed to prevent craving following

exposure to smoking-associated stimuli, suggesting that cue-induced craving is resistant to acute pharmacological and psychological manipulations. Overall, findings suggest that cue-induced craving persists regardless of acute nicotine-containing or denicotinized tobacco smoking, suggesting that another mechanism is responsible for the therapeutic benefits ascribed to denicotinized tobacco use.

3.6 Linking statement and rationale for experiment 3

The main aim of experiment 2 was to evaluate the independent and combined impact of nicotine expectancy and administration components of acute tobacco smoking on background and cue-induced craving. To our knowledge, this was the first report to empirically evaluate the impact of acute nicotine-containing and denicotinized tobacco smoking on cue-induced craving; however because the study involved relatively short experimental sessions, it is possible that participant knowledge that the session was nearing an end may have resulted in elevations in craving unrelated to the cue manipulations. Indeed, the perception that an opportunity to smoke is imminent has been associated with increased self-reported background and cue-induced craving regardless of duration of smoking abstinence (Bailey, Goedeker, & Tiffany, 2009; Dar et al., 2010; Dols, van den Hout, Kindt, & Willems, 2002; Juliano & Brandon, 1998; Sayette et al., 2003; Wertz & Sayette, 2001). Therefore, it is possible that findings of increased craving following smoking cue exposure may have been contaminated by participant beliefs that they would be able to smoke imminently after the end of the session. In addition, both experiment 1 and experiment 2 exclusively employed measures of subjective craving. As a result, the extent to which nicotine expectancy and administration components of tobacco and/or NRT administration impacts subsequent smoking behaviour remains

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uncertain. Therefore, experiment 3 was designed to account for these limitations. The aims of experiment 3 were to (a) examine the impact of varying beliefs about the temporal proximity of a future smoking opportunity on subsequent smoking behaviour, and to (b) assess the impact of the nicotine expectancy and administration components of acute NRT use on subjective craving and smoking behaviour when smoking opportunities are anticipated versus unanticipated.

CHAPTER 4. EXPERIMENT 3: THE IMPACT OF ANTICIPATED AND UNANTICIPATED SMOKING OPPORTUNITIES ON CIGARETTE SMOKING AND NICOTINE LOZENGE RESPONSES

Sections of this chapter were taken from the following: Schlagintweit, H. E., Greer, H., Good, K. P., & Barrett, S. P. (2015). The impact of anticipated and unanticipated smoking opportunities on cigarette smoking and nicotine lozenge responses. *Drug and Alcohol Dependence*, *147*, 97–102.

Hera Schlagintweit served as first author of the manuscript included in this chapter. She took the lead role in reviewing the relevant literature, designing and conducting the research, writing original manuscript drafts, and making revisions based on suggestions from co-authors, editors, and peer-reviewers.

4.1 Abstract

Background: Perceptions regarding the availability of smoking opportunities are known to affect cigarette craving; however, whether they impact actual smoking or how smokers respond to acute nicotine replacement therapy (NRT) administration is not known. This study examined the impact of pharmacological and expectancy components of NRT administration on craving and smoking in smokers anticipating or not anticipating an imminent smoking opportunity. Methods: In total, 154 smokers (84 male) completed an experimental session in which instructions regarding the nicotine content of a lozenge (4 mg vs. no nicotine) and regarding the availability of a future smoking opportunity were manipulated. Cigarette craving was assessed before and after manipulations and lozenge administration. All participants were then allotted 1 h to self-administer as many cigarette puffs as they wished. Results: Unanticipated smoking opportunities reduced latency to self-administration ($p < 0.001$), regardless of nicotine expectancy or pharmacology. When analyses included all participants, nicotine reduced intentions to smoke ($p = 0.016$) and withdrawal-related craving ($p = 0.043$) regardless of expectancy. Conversely, analyses using only "believers" of the nicotine content instructions revealed that nicotine expectancy reduced intentions to smoke ($p = 0.034$) and withdrawal-related craving ($p = 0.047$) regardless of actual nicotine administration. "Believers" also reported increased withdrawal-related craving when a smoking opportunity was perceived to be imminent ($p = 0.041$). These effects were not significant when analyses included all participants. Conclusions: Findings suggest that unexpected smoking opportunities may be more appealing than expected ones regardless of perceived or actual acute NRT use. They also

highlight the importance of reporting balanced placebo findings using all participants as well as "believers" only.

4.2 Introduction

Perceptions regarding the availability of a future smoking opportunity (i.e., believing one will or will not have an imminent opportunity to smoke) have been shown to have a substantial impact on cigarette craving. In a naturalistic study using cigarette-dependent flight attendants, Dar, Rosen-Korakin, Shapira, Gottlieb, and Frenk (2010) demonstrated that cigarette craving increases gradually during flights, when smoking is not permitted, and peaks at the conclusion of a flight, when a smoking opportunity becomes imminent. Similar elevations in craving associated with increasing availability of a smoking opportunity have been demonstrated in laboratory based studies (Bailey et al., 2009; Dols et al., 2002; Juliano & Brandon, 1998; Sayette et al., 2003; Wertz & Sayette, 2001). To the best of our knowledge, no study to date has examined the impact of anticipating a smoking opportunity on actual smoking behaviour. However, given that craving has been found to increase with the proximity of a smoking opportunity, one might expect increased smoking behaviour during expected relative to unexpected smoking opportunities. On the other hand, recent findings suggest that laboratory animals display increased responding to obtain reinforcing substances when substances are delivered on a random as opposed to fixed schedule (Lagorio & Winger, 2014). Such findings suggest that unpredictable drug availability is associated with increased drug-related responding and thus it is possible that smokers may be more likely to engage in smoking related behaviours when unexpected opportunities to smoke occur.

Little is also known about how nicotine replacement therapies (NRTs) impact responses to anticipated and unanticipated smoking opportunities. However, because NRTs appear to be more effective in suppressing tonic or background craving as opposed

to phasic or peaks in craving (Ferguson & Shiffman, 2009; Schlagintweit et al., 2014), one might expect that NRTs would be most effective when smoking opportunities are not perceived to be imminently available. NRT effects are generally attributed to the pharmacological properties of nicotine (e.g., Benowitz, 2008; Stead et al., 2012); however, there is growing evidence that suggests that non-pharmacological factors make a substantial contribution (Caggiula et al., 2001; Dar & Barrett, 2014). Balanced placebo research, which crosses instructions regarding nicotine content (told nicotine-containing vs. told nicotine-free) with actual nicotine content (contains nicotine vs. no nicotine) suggests that the belief that nicotine has been consumed reduces cigarette craving and withdrawal regardless of whether or not nicotine was actually consumed (Dar & Barrett, 2014; Darredeau & Barrett, 2010; Gottlieb et al., 1987; Schlagintweit et al., 2014).

This study aimed to (a) examine the impact of varying beliefs about the temporal proximity of a future smoking opportunity on subsequent smoking behaviour, and to (b) assess the impact of the psychological and pharmacological components of NRT administration when smoking opportunities are anticipated versus unanticipated. The study used a balanced placebo design, which manipulated participant expectancies about the nicotine content of nicotine and non-nicotine lozenges. Beliefs regarding the occurrence of a future smoking opportunity were manipulated such that some of the study participants were instructed that they could smoke during the study, while the others were told that they could not smoke until after completing the study. Subjective craving was assessed prior to and following lozenge consumption, and all participants were provided an opportunity to self-administer their preferred brand of cigarette during the final hour of the study.

4.3 Materials and methods

4.3.1 Participants

Participants were 154 daily smokers (84 male) recruited through online and community advertisements within Halifax, Nova Scotia, Canada. A telephone interview was used to verify that participants conformed to selection criteria. Specifically, participants reported that they were medication- and NRT-free, medically healthy, had been daily smokers for at least 1 year, had no intention to quit smoking within a month of participation, and had no prior experience using oral NRTs (the gum or lozenge). All participants were dependent smokers (Fagerström Test for Nicotine Dependence (FTND) ≥ 3; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), with mean FTND scores of 5.2 (standard deviation (SD) = 1.6). Participants ranged in age from 19 to 57 (mean = 27.5, SD = 8.74) and smoked an average of 13.3 (SD = 6.0) cigarettes per day. Please refer to Table 4.1 for additional participant characteristics. All participants provided informed written consent to participate in the study and received compensation of $10 per hour of participation in the study. The study received ethical approval from the Capital District Health Authority Research Ethics Board.

Table 4.1. Mean (standard deviation) values for all variables except sex (% male) across the eight study conditions. No significant group differences were observed for age, age of first tobacco use, total years as a daily smoker, or Fagerström Test for Nicotine Dependence (FTND) scores (p values>0.05). A significant sex difference was observed for cigarettes per day, with males consuming more cigarettes than females (p=0.003).

	Expect nicotine, Receive nicotine (n=39)		Expect nicotine, receive no nicotine (n=38)		Expect no nicotine, receive nicotine (n=37)		Expect no nicotine, receive no nicotine (n=40)	
	Unantic-ipated (n=17)	Anticip-ated (n=22)	Unantic-ipated (n=17)	Anticip-ated (n=21)	Unantic-ipated (n=15)	Anticip-ated (n=22)	Unantic-ipated (n=17)	Anticip-ated (n=23)
Age in years	26.82 (6.36)	28.95 (8.89)	29.35 (11.97)	26.10 (7.54)	26.40 (9.49)	27.59 (8.46)	30.12 (10.64)	25.04 (6.54)
Sex (% male)	10 (59%)	11 (50%)	11 (65%)	10 (48%)	9 (60%)	11 (50%)	10 (59%)	12 (52%)
Age of first tobacco use	15.15 (2.72)	14.95 (3.59)	15.47 (7.64)	13.14 (3.00)	13.27 (2.68)	13.86 (3.11)	13.82 (3.67)	14.65 (2.87)
Cigarettes per day	14.32 (7.10)	13.36 (5.98)	12.97 (6.34)	12.19 (5.94)	13.33 (6.31)	12.86 (4.90)	13.35 (5.74)	14.13 (6.76)
Total years as a daily smoker	9.46 (6.23)	11.52 (9.73)	11.16 (11.44)	9.40 (8.33)	9.63 (9.89)	11.25 (10.72)	11.71 (10.65)	8.80 (7.13)
FTND score	5.24 (1.82)	5.36 (1.76)	5.18 (1.55)	4.81 (1.89)	4.93 (1.71)	5.68 (1.52)	5.53 (1.55)	5.04 (1.46)

4.3.2 Materials

Lozenges. Nicotine lozenges (NiQuitin minis 4 mg: GlaxoSmithKline, Marly-le-Roy, France) and non-nicotine lozenges (Ricqles Ricqmint Menthe Sans Sucre, Laboratoire Vie et Santé, France) were similar in size, appearance and mint flavouring; however, nicotine lozenges contained 4 mg of nicotine, while the non-nicotine lozenges were nicotine free. Participants were instructed to keep the lozenges in their mouths until they fully dissolved and not to spit out, chew or swallow them. Nicotine lozenges take approximately 10 min to dissolve, have an average half-life of 2 h (ranging from 1 to 4 h; GlaxoSmithKline Consumer Healthcare, Brentford, UK), and mean blood nicotine levels of ~6.0 ng/ml occur 25–30 min following nicotine lozenge consumption (McEwen et al.,

2008; Shiffman et al., 2005). The non-nicotine lozenges were selected because they were not commercially available in Canada, and therefore participants were unlikely to have prior experience consuming them. All lozenges were provided to participants in packaging consistent with instructions regarding nicotine content, such that participants who were informed they received a nicotine lozenge were provided with a lozenge in a NiQuitin minis package, while those who were informed they received a non-nicotine lozenge were given a lozenge in a Ricqles package.

Demographic information and smoking patterns. Demographic (e.g., age, sex) and smoking history (e.g., age of first cigarette use, current smoking frequency) information was assessed using a Demographic and Smoking History Questionnaire.

Subjective cigarette craving. The Questionnaire of Smoking Urges-Brief (QSU-B) consists of 10 items used to assess subjective cigarette craving across two dimensions (factor 1: intention to smoke; factor 2: withdrawal-related craving; Toll, Katulak, & McKee, 2006). The QSU-B has been demonstrated to be a reliable and sensitive measure of nicotine and tobacco-related craving and other abstinence-related effects (Cox et al., 2001; Toll et al., 2006).

Heart rate. Average heart rate was assessed over the course of 60 s using a Polaris Heart Rate Monitor chest strap and wristwatch (Polar Electro Canada Inc., Lachine, Quebec, Canada).

Cigarette self-administration. Cigarette self-administration was assessed using a computerised progressive ratio (PR) task, where participants were allotted 60 min to earn puffs of their preferred brand of cigarettes by repeatedly pressing a keyboard a predetermined number of times. The first puff required 10 presses, and the number of

presses required to earn each subsequent puff increased by a ratio of 1.3. Following the administration of each puff, participants could resume the task at their own pace to earn an additional puff. Participants could earn as many or a few puffs as they wished, but were required to remain seated in front of a cigarette and the PR computer until the session ended. Measures of latency (duration in seconds to initiate the first puff) and total number of self-administered puffs were collected. Similar PR tasks have been demonstrated to be sensitive to changes in subjective cigarette craving (Willner et al., 1995; Willner & Jones, 1996) and to pharmacological manipulations (Barrett, 2010; Barrett & Darredeau, 2012).

4.3.3 Procedure

Participants attended one experimental session, during which they were randomly assigned to one of the four conditions of the balanced-placebo design. Conditions differed by instructions regarding nicotine content (told nicotine vs. told no nicotine) and nicotine administration (receive nicotine vs. receive no nicotine). Within each condition, participants were also assigned to one of two groups that differed by instructions regarding the temporal proximity of a future smoking opportunity. One group was informed that they could smoke their preferred brand of cigarettes during the study (anticipated smoking opportunity), and the other group was informed that they could not smoke during the study, which lasted for approximately 2 h (unanticipated smoking opportunity). Thus, participants could be assigned to one of eight possible conditions, as outlined in Table 4.1.

After participants provided written consent to participate, overnight abstinence from smoking (≥12 h) was verified with a breath carbon monoxide sample (Vitalograph,

UK) reading of ≤15 ppm. Next, participants were informed whether they could (anticipated smoking opportunity) or could not smoke (unanticipated smoking opportunity) during the study session. Participants then completed a craving questionnaire and their heart rate was assessed (Time 1 [T1]), and they were provided with a lozenge and allotted 30 min for absorption. Following lozenge absorption, participants completed another craving questionnaire, and their heart rate was reassessed (Time 2 [T2]). At this time, participants in the unanticipated smoking opportunity group were informed that the researcher had made an error and that they would have an opportunity to smoke during the study session after all. Next, participants were seated in front of a computer and provided a pack of their preferred brand of cigarettes. Participants were instructed that they could smoke as little or as much as they desired for the subsequent 60 min using a PR task. The experimenter remained with participants during the entire self-administration period to ensure compliance with the PR task. Upon completing the PR task, the researcher asked participants what type of lozenge they believed they had consumed during the session, with possible response options including "nicotine", "no nicotine", or "don't know". This question was included as a manipulation check in order to determine whether participants believed the instructions they were given regarding the nicotine content of the lozenge. Full debriefing was delayed until data collection was complete, in order to ensure that past participants did not inform potential participants of the deceptive nature of the study.

4.3.4 Statistical analyses

Data were analysed using mixed models in SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). The main measures were subjective ratings of cigarette craving following

lozenge consumption (T2), average heart rate following lozenge consumption (T2), and

cigarette self-administration data (latency, number of puffs self-administered). To satisfy

the assumption of normalcy, a logarithmic transformation was applied to latency, as this

measure was found to violate assumptions of skewness and kurtosis. Data for the main

measures were analysed using Receive (nicotine versus no nicotine), Instruction (nicotine

versus no nicotine), and Smoking Opportunity (anticipated versus unanticipated) as fixed

factors and subjects as a random factor. Baseline scores (T1) were entered as a time

varying covariate for subjective ratings of cigarette craving and measures of average

heart rate. The effects of interest were any main effects or interactions of Receive,

Instruction, or Smoking Opportunity. Tests of simple main effects were performed on the

linearly independent pairwise comparisons between the estimated marginal means for all

analyses. Mean values reported are estimated marginal means.

4.4 Results

4.4.1 Manipulation check

　　Twenty-six of the 154 participants (17%) were found to either not believe or be

uncertain of their expectancy condition. The vast majority of participants in the told no

nicotine, receive no nicotine group (90%, n = 36, 20 males) and in the told nicotine,

receive nicotine group (100%, n = 39, 21 males) believed nicotine content instructions,

while a somewhat smaller proportion of participants in the told nicotine, receive no

nicotine group (71%, n = 27, 15 males) and in the told no nicotine, receive nicotine group

(70%, n = 26, 14 males) believed same. No significant differences in cigarettes per day

($F(1, 280) = 1.47$, $p = 0.226$), FTND score ($F(1, 281) = 0.20$, $p = 0.652$), or number of

years as a smoker ($F(1, 281) = 0.25$, $p = 0.620$) were found when believers were

compared with non-believers. While this lack of systematic differences is encouraging, findings from all participants, as well as from only the participants that believed the manipulation are reported below.

4.4.2 Analyses using all study participants

4.4.2.1 Cigarette self-administration

A main effect of Smoking Opportunity was observed for latency ($F(1, 144) = 25.10$, $p < 0.001$, see Figure 4.1), where latency to self-administration was significantly shorter in participants in the unanticipated smoking opportunity condition (M = 0.82, SE = 0.08) than in the anticipated smoking opportunity condition (M = 1.32, SE = 0.07). No significant main effects or interactions of Instruction, Receive or Smoking Opportunity were found for number of self-administered puffs (p-values > 0.10).
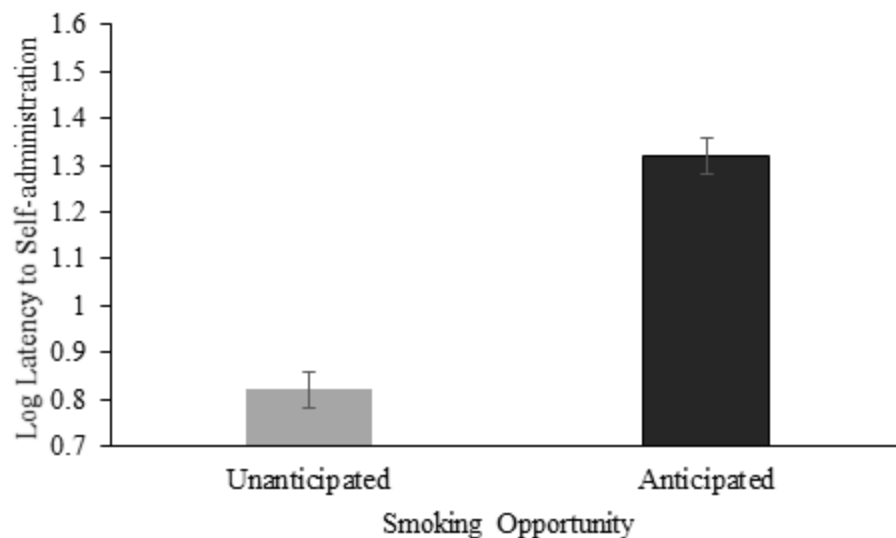
Figure 4.1 Estimated marginal mean scores (+/-SE) for the logarithmic transformation of latency to cigarette self-administration during the progressive ratio (PR) task. Latency to self-administration was significantly shorter when participants were presented with an unanticipated smoking opportunity relative to an anticipated smoking opportunity (p<0.001).

4.4.2.2 Subjective cigarette craving

Main effects of Receive were found for both factor 1 ($F_{(1, 144)} = 5.92$, $p = 0.016$, see Figure 4.2) and factor 2 craving ($F_{(1, 144)} = 4.17$, $p = 0.043$). Lower intention to smoke and withdrawal-related craving were observed when participants received nicotine (factor 1: M = 25.64, SE = 0.66; factor 2: M = 16.94, SE = 0.58) relative to no nicotine (factor 1: M = 27.88, SE = 0.64; factor 2: M = 18.58, SE = 0.56).
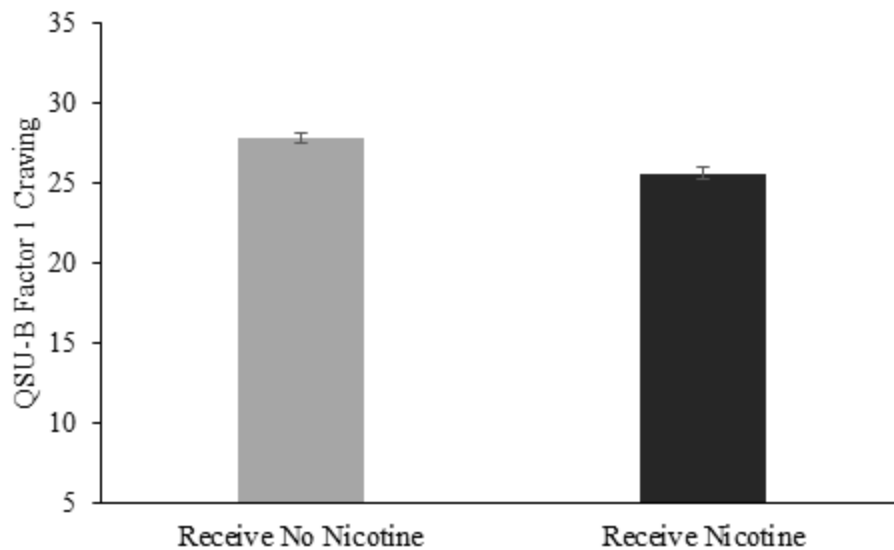
Figure 4.2 Estimated marginal mean scores (+/-SE) for QSU-B factor 1 craving. In analyses using all participants, intention to smoke was reduced when participants received nicotine relative to no nicotine (p=0.016).

4.4.2.3 Heart rate

A main effect of Receive was observed for average heart rate ($F_{(1, 133)} = 24.85$, $p < 0.001$), where average heart rate was significantly elevated in participants who received nicotine (M = 74.43, SE = 0.86) relative to those who received no nicotine (M = 68.40, SE = 0.85).

4.4.3 Analyses using only participants who believed nicotine content instructions

When analyses were restricted to only participants who believed nicotine content instructions (i.e., "believers"), the main effects of Smoking Opportunity on latency to self-administration and of Receive on average heart rate remained identical; however, the main effects of Receive on factor 1 ($F(1, 118) = 3.36$, $p = 0.070$) and factor 2 craving ($F(1, 118) = 3.07$, $p = 0.083$) were no longer found to be significant. Instead, main effects of Instruction were observed for both factor 1 ($F(1, 118) = 4.58$, $p = 0.034$) and factor 2 craving ($F(1, 118) = 4.02$, $p = 0.047$), where lower intention to smoke and withdrawal-related craving were observed when participants expected nicotine (factor 1: M = 26.31, SE = 0.66; factor 2: M = 17.45, SE = 0.59) relative to no nicotine (factor 1: M = 28.30, SE = 0.66; factor 2: M = 19.15, SE = 0.60). Additionally, a main effect of Smoking Opportunity was observed for factor 2 craving ($F(1, 118) = 4.25$, $p = 0.041$, see Figure 4.3), where increased withdrawal related-craving was found in the anticipated (M = 19.17, SE = 0.55) relative to the unanticipated smoking opportunity condition (M = 17.43, SE = 0.64).
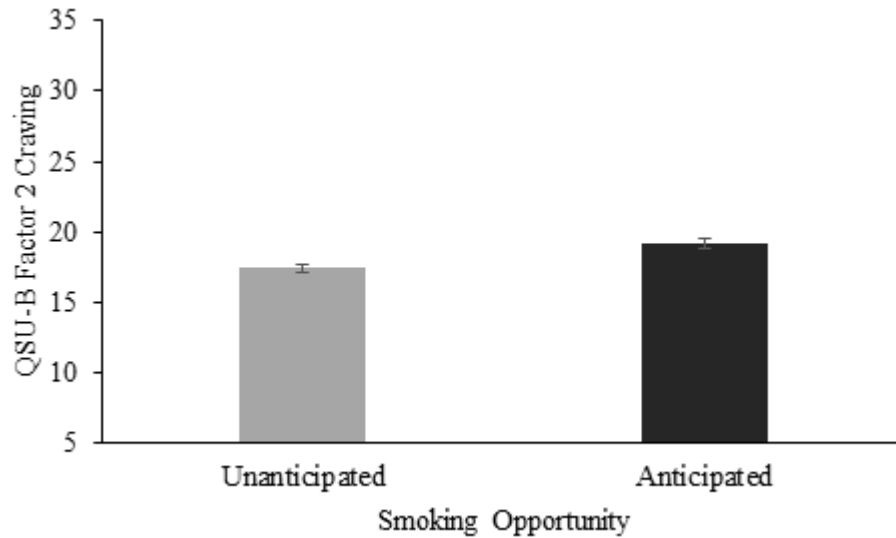
Figure 4.3 Estimated marginal mean scores (+/- SE) for QSU-B factor 2 craving. Increased withdrawal-related craving was found in the anticipated smoking opportunity condition relative to the unanticipated smoking opportunity condition (p=0.041).

4.5 Discussion

In this study, being presented with an unexpected smoking opportunity resulted in a significantly shorter latency to self-administer cigarettes relative to being presented with an expected smoking opportunity, regardless of nicotine expectancy or administration. This finding suggests that tobacco smoking may be especially appealing when an opportunity to smoke is unanticipated. While this is, to the best of our knowledge, the first finding of its kind in human smokers, Lagorio and Winger (2014) recently reported an increased response rate in laboratory animals when reinforcing substances were delivered on a random, and thus unanticipated, schedule relative to a fixed schedule of delivery. Given the wide spread availability of cigarettes, and smokers' tendency to cluster within social networks (Christakis & Fowler, 2008), it is likely that smokers frequently encounter unexpected opportunities to smoke, which may be more

difficult to resist. In contrast to latency, total number of puffs consumed did not systematically differ between smoking opportunity conditions, suggesting that the impact of an unanticipated smoking opportunity on smoking may be specific to a more rapid initiation of the behaviour. Past findings suggest that psychological manipulations may have a greater impact on measures of latency to smoke than on measures of amounts self-administered (Copp, Collins, Dar, & Barrett, 2015; Perkins, Ciccocioppo, et al., 2008) and it is possible participants may engage in their preferred pattern of smoking once the behaviour has been initiated. The fact that nicotine administration failed to impact either latency to smoke or total amount self-administered, raises the possibility that acute NRT administration may not be effective for suppressing tobacco use once a smoking opportunity becomes available. However, because the current study did not include smokers who intended to quit, it is unclear to what extent these findings would apply to those using NRT as part of a cessation attempt.

Acute nicotine administration was found to suppress subjective intentions to smoke when data were analysed using all study participants; however, this effect was present only at a trend level when analyses were restricted to only those participants who believed nicotine content instructions. It is possible that analyses using all participants favoured the detection of effects of pharmacology, while analyses using only "believers" favoured the detection of expectancy effects. The majority of "non-believers" in this study were from conditions in which nicotine content instructions and administration were mismatched. It is possible that participants did not believe the instructions due to either the unexpected presence or the unexpected absence of nicotine effects. Previous balanced placebo studies using NRT have frequently either omitted manipulation checks

(e.g. Darredeau & Barrett, 2010; Hughes, Gulliver, Amori, Mireault, & Fenwick, 1989; Schlagintweit et al., 2014) or reported findings from the "believers" only (e.g. Perkins et al., 2008, 2009). Our findings suggest that it may be important for balanced placebo research to report any discrepancies between the findings of analyses using all participants and "believers" only.

When data were analysed using "believers" only, nicotine expectation was found to be associated with reduced intention to smoke and withdrawal-related craving. Effects of nicotine expectancy on subjective craving have been observed consistently in previous balanced placebo research using NRT (see Dar & Barrett, (2014) for a review). As such, the current findings build upon a growing literature documenting the important contribution of non-pharmacological components to NRT effects. The observation that among 'believers' withdrawal-related craving was increased when a smoking opportunity was perceived to be imminently available, regardless of NRT administration or expectancy, is consistent with previous research demonstrating that anticipatory craving increases with the temporal proximity of a future smoking opportunity (Bailey et al., 2009; Dar et al., 2010; Dols et al., 2002; Juliano & Brandon, 1998; Sayette et al., 2003; Wertz & Sayette, 2001) and that nicotine replacement is more effective in curbing background or tonic craving relative to episodic or phasic craving (Ferguson & Shiffman, 2009; Schlagintweit et al., 2014). To the best of our knowledge, the impact of perceived smoking opportunity availability has not been systematically controlled for in previous investigations of NRT effects. The present findings suggest that the psychological and pharmacological components of NRT administration may have a limited impact on craving in circumstances when there are known opportunities to smoke.

The findings of this study should be considered in light of the following limitations. First, because subjective craving was not assessed immediately after informing participants in the unanticipated smoking opportunity condition that they would be able to smoke during the PR task, the impact of an unexpected smoking opportunity on subjective craving could not be assessed. Given that the unexpected smoking opportunity had a significant impact on smoking behaviour, it is possible that it may have also had a substantial impact on subjective craving. Next, nicotine was administered in a 4 mg dose and it is possible that this dose was insufficient to produce an optimal pharmacological effect. Indeed, the 4 mg nicotine lozenges have been found to produce mean blood nicotine levels of ~6.0 ng/ml at 25–30 min post-consumption (McEwen et al., 2008; Shiffman et al., 2005). These concentrations fall at the lower end of steady state plasma levels generally associated with therapeutic nicotine administration, in the range of 5–15 ng/ml (Benowitz et al., 2009). However, the acute administration of similar nicotine doses have reliably produced expected physiological and subjective changes in past research (e.g. McGrath, Dorbeck, & Barrett, 2013; Schlagintweit et al., 2014), and in the present study, measures of heart rate were significantly elevated following nicotine lozenge administration, regardless of expectancy, suggesting a pharmacologically active dose of nicotine. Finally, sex differences were not examined in the present study, due to an insufficient sample size. Previous research has revealed that females may be more sensitive to non-pharmacological factors involved in NRT administration and smoking behaviour (Caggiula et al., 2002; Perkins et al., 2001; Perkins, Doyle, et al., 2006) and it is

recommended that future research examine the extent to which this is also true for varying perceptions regarding a future smoking opportunity.

The present findings are, to the best of our knowledge, the first to show that an unanticipated smoking opportunity is associated with a reduced latency to smoke, an effect that was unaltered by an acutely administered NRT. Additionally, results highlight the importance of reporting findings from all study participants as well as from those who believed experimental manipulations in balanced placebo research, as findings may systematically differ between these two participant groups. The importance of nicotine pharmacology, smoking opportunity, and non-pharmacological factors such as expectancy effects should all be considered when examining smoking cessation strategies using NRT.

4.6 Linking statement and rationale for experiment 4

The aim of experiment 3 was to (a) examine the impact of varying beliefs about the temporal proximity of a future smoking opportunity on subsequent smoking behaviour, and to (b) assess the impact of the nicotine expectancy and administration components of NRT use on subjective craving and smoking behaviour when smoking opportunities are anticipated versus unanticipated. To our knowledge, this was the first report to document the impact of varying perceptions about the availability of a smoking opportunity on smoking behaviour and acute NRT effects. A potential limitation of experiments 1, 2, and 3 is that all three studies used samples of dependent smokers with no imminent intention to quit smoking at the time of participation; however, the extent to which findings from these experiments generalize to smokers who are motivated to cease smoking has been called into question. Indeed, Perkins and colleagues (2008)

demonstrated that quitting motivated dependent smokers show a greater number of days of abstinence from smoking during a week-long nicotine patch-assisted cessation attempt relative to quitting unmotivated smokers. Additionally, research using electroencephalography (EEG; Donohue et al., 2016) and functional magnetic resonance imaging (fMRI; Wilson et al., 2012) have demonstrated that quitting motivated and unmotivated smokers show differing patterns of craving-associated neural activity. To our knowledge, no previous research has directly assessed differences between quitting motivated and unmotivated participants using a balanced placebo design. Therefore, experiment 4 addressed this limitation by recruiting both quitting motivated and unmotivated smokers. The aim of this experiment was to assess the impact of nicotine expectancy and administration components of acute NRT use on subjective craving, heart rate and subsequent smoking behaviour in smokers with varying intentions to quit smoking.

CHAPTER FIVE. EXPERIMENT 4: QUIT INTENTIONS MODERATE SUBJECTIVE AND PHYSIOLOGICAL RESPONSES TO ACUTE NICOTINE REPLACEMENT THERAPY ADMINISTRATION IN DEPENDENT SMOKERS

Sections of this chapter were taken from the following: Hera E. Schlagintweit, Niamh K. Campbell, and Sean P. Barrett (2016). Quit intentions moderate subjective and physiological responses to acute nicotine replacement therapy administration in dependent smokers. *Nicotine & Tobacco Research*, doi: 10.1093/ntr/ntw307.

Hera Schlagintweit served as first author of the manuscript included in this chapter. She took the lead role in reviewing the relevant literature, designing and conducting the research, writing original manuscript drafts, and making revisions based on suggestions from co-authors, editors, and peer-reviewers.

5.1 Abstract

Introduction: This study assessed the impact of expectancy and administration components of acute nicotine inhaler use on craving, heart rate and smoking behaviour in smokers with varying intentions to quit. Methods: 47 dependent smokers that differed in self-reported intention to quit (no intention to quit during the next month N=26 vs. intention to initiate a quit attempt within two weeks N=21) were randomly administered a 4mg nicotine or nicotine free inhaler across two sessions. Instructions regarding the inhaler's nicotine content (expect nicotine vs. expect nicotine free; nicotine expectancy) and flavour (mint vs. citrus) varied across sessions. Craving and heart rate were assessed before and after inhaler administration (two second inhalations every 10 seconds over 20 minutes). Next, participants were offered an opportunity to self-administer puffs of their preferred tobacco brand during an hour-long progressive ratio task. Results: Across participants, nicotine expectancy independently reduced withdrawal related craving (p=0.018), but no comparable effects of nicotine administration were evident. In quitting motivated smokers, nicotine expectancy and administration interacted to reduce intention to smoke (p=0.040), while nicotine expectancy (p=0.047) and administration (p=0.025) independently reduced intention to smoke in quitting unmotivated smokers. Blunted heart rate reactivity to nicotine administration was observed in quitting motivated relative to unmotivated smokers (p=0.042); however, neither expectancy nor administration impacted smoking behaviour in either group (p values>0.25). Conclusions: Findings indicate that participant quitting intentions moderate acute nicotine replacement therapy (NRT) responses. In quitting motivated smokers, a combination of pharmacological and psychological factors may be necessary for NRT to impact craving. Implications:

Findings from this study demonstrate that motivations to quit smoking moderate subjective and physiological responses to acute nicotine administration and expectancy in dependent cigarette smokers. Quitting motivated smokers showed blunted heart rate reactivity to nicotine administration, suggesting that they may be less sensitive to the rewarding aspects of nicotine consumption. Nicotine administration and expectancy were found to interact to reduce craving in quitting motivated but not in unmotivated smokers, suggesting that pharmacological and psychological factors may be necessary for nicotine replacement therapy to impact craving in smokers who plan to quit.

5.2 Introduction

Nicotine replacement therapies (NRTs) are effective smoking cessation aids, and their use has been shown to increase quit rates by 50 to 70% relative to unaided attempts (Stead et al., 2012). NRTs are believed to produce their therapeutic benefits by curbing cigarette craving and withdrawal. These effects are frequently attributed to the pharmacological properties of nicotine (Benowitz, 2008; U.S.DHSS, 2010). However, to date the majority of research examining the therapeutic benefits of NRT have used double blind placebo controlled designs, which have failed to account for the impact that non-pharmacological factors, such as beliefs about drug assignment (i.e. stimulus expectancy), have on outcome measures (Dar & Barrett, 2014; Perkins, 2004). This is an important consideration as there is evidence to suggest that perceived drug assignment may have a greater impact than actual drug assignment on smoking cessation outcomes (Dar et al., 2005).

Balanced placebo research, which crosses drug administration (given drug vs. given placebo) with instructions regarding drug content (told drug vs. told placebo; Sutton, 1991), assessing acute NRT effects has consistently shown that the mere belief that nicotine has been received is sufficient to reduce craving and/or withdrawal regardless of whether or not nicotine had been received (Darredeau & Barrett, 2010; Perkins, Jacobs, Clark, et al., 2004; Schlagintweit et al., 2014, 2015). However, an important limitation of the available balanced placebo literature is that studies have exclusively recruited dependent smokers with no immediate intention of quitting at the time of participation. The extent to which their findings can generalize to smokers who are motivated to quit remains unclear. Additionally, the perception that smoking

cessation aids are effective is associated with the intention to initiate a cessation attempt (Hammond, McDonald, Fong, & Borland, 2004). Quitting motivated smokers may therefore have greater expectations of benefit from treatment (i.e. NRT-induced craving reduction) than quitting unmotivated smokers, which may in turn lead to greater expectancy effects on responses to NRT in quitting motivated relative to unmotivated smokers.

In the current study, we used a modified balanced placebo design, where participants were administered the same product (administered a nicotine or nicotine-free inhaler) across two study sessions but differing instructions regarding the product's nicotine content (expect nicotine-containing or nicotine-free) to assess the degree to which nicotine expectancy and administration effects are comparable across smokers with varying intentions to quit. It was predicted that quitting motivation and expectancy would interact so that (a) quitting motivated smokers who expected nicotine-containing inhalers would report a greater reduction in subjective craving following NRT administration than quitting unmotivated smokers in the same expectancy condition, and (b) quitting motivated smokers who expected a nicotine-containing inhaler would self-administer fewer cigarette puffs and be less motivated to smoke following NRT administration than quitting unmotivated smokers in the same expectancy condition. Heart rate was also assessed before and after inhaler consumption in order to assess any potential differences in physiological reactivity to inhaler administration between quitting motivated and unmotivated smokers; however, no a-priori predictions regarding these were made.

5.3 Method

5.3.1 Participants

Forty-seven (31 male) daily, dependent (Fagerström Test for Cigarette Dependence (FTCD) ≥ 3; Fagerström, 2012) smokers were included in the study. During a telephone pre-screening interview, all participants reported that they were medically healthy, free of psychiatric illness, medication-free (with the exception of birth control in females), had been daily smokers for at least the past year, and had no prior experience using nicotine inhalers. Quitting motivation was also assessed during the telephone pre-screening interview using dichotomous questions: (a) do you intend to quit within the next 30 days and (b) do you intend to quit within the next two weeks. Twenty-six participants (18 male) reported no intention to quit smoking within 30 days of enrolment in the study (quitting unmotivated smokers) while 21 participants (13 male) reported an intention to quit smoking within two weeks of study participation but had not initiated their cessation attempt prior to participation (i.e., had made no systemic changes to their smoking behaviour; quitting motivated smokers). Participants ranged in age from 19 to 56 years (M=29, SD=10), smoked an average of 14.6 (SD=12.6) cigarettes per day, and received mean scores of 4.7 (SD=1.5) on the FTCD. Table 5.1 presents additional characteristics of participants included in this study. All participants provided written consent to participate and received compensation of $10 CAD per hour of study participation, which lasted approximately four hours (2 hours/session). The study received ethical approval from the Capital District Health Authority Research Ethics Board in Halifax, Nova Scotia (protocol number: 1017191, protocol title: The impact of

the nicotine inhaler and varying intentions to quit smoking on cigarette craving and self-administration in dependent smokers).

Table 5.1 Mean (standard deviation) values for all variables except sex (% male) across the four study conditions. No significant group differences were observed for age, sex, age of first tobacco use, cigarettes per day, or total years as a daily smoker during either session (p values>0.05). A significant Administered (Admin.) difference was observed for Fagerström Test for Cigarette Dependence (FTCD) scores, with increased FTCD scores in participants who were administered a nicotine inhaler (M=5.27, SD=1.40) relative to those who were administered a nicotine free inhaler (M=4.25, SD=1.54, p=0.037).

	Quitting unmotivated (n=26)		Quitting motivated (n=21)	
	Admin. nicotine inhaler (n=12)	Admin. nicotine free inhaler (n=14)	Admin. nicotine inhaler (n=11)	Admin. nicotine free inhaler (n=10)
Age in years	27.42 (11.71)	27.64 (9.71)	32.91 (11.37)	27.40 (7.50)
Sex (% male)	9 (75%)	9 (64%)	6 (55%)	7 (70%)
Age of first tobacco use	15.38 (3.80)	14.57 (2.66)	14.64 (4.99)	14.95 (4.22)
Cigarettes per day	13.67 (5.69)	17.36 (20.41)	13.95 (9.92)	12.75 (7.58)
Total years as a daily smoker	7.64 (11.70)	10.82 (9.74)	15.55 (11.42)	7.65 (5.58)
FTCD score	4.92 (1.08)	4.43 (1.74)	5.45 (1.69)	4.00 (1.25)

5.3.2 Materials

5.3.2.1 Products

Nicotine inhalers (NI; 10mg; 4mg deliverable, Pharmacia, Mississauga, Ontario, Canada) and nicotine-free inhalers (NFI) were identical in appearance; however, NFIs contained pharmacologically inert cellulose filters. All inhalers were flavoured with 2ml of citrus or mint solution containing menthol, thymol, and eucalyptol (Johnson & Johnson Inc., Markham, Ontario, Canada). Participants received differently flavoured inhalers across sessions in order to increase the believability of the different nicotine

content instructions (Darredeau & Barrett, 2010). An independent blinder prepared inhalers so that study researchers were unaware of their true nicotine content.

5.3.2.2 Cigarette craving

The Questionnaire of Smoking Urges-Brief (QSU-B) consists of 10 self-report items that assess craving across two factors (factor 1: intention to smoke, factor 2: withdrawal related craving; Toll, Katulak, & McKee, 2006). The QSU-B has been demonstrated to be psychometrically sound and sensitive to nicotine administration and abstinence related effects (Cox et al., 2001; Toll et al., 2006).

5.3.2.3 Cigarette self-administration

Two measures of cigarette self-administration (total self-administered puffs and breakpoint, described below) were collected with the use of a computerized progressive ratio (PR) task (Barrett, 2010; Willner et al., 1995). During the PR task, participants were allotted 60 minutes to earn puffs of their preferred brand of cigarette by repeatedly pressing a keyboard key a predetermined number of times. Ten key presses were required to earn the first puff. The key presses required for each subsequent puff increased by a ratio of 1.3 (i.e. 13, 17, 22 presses). Participants were informed that they could smoke as much or as little as they wanted and that they could earn puffs at their preferred pace, but they were required to sit in front of the PR computer with a lit cigarette for the duration of the task. Measures of the number of key presses required to earn the final cigarette puff (i.e., breakpoint) and the total number of cigarette puffs self-administered were collected. Total number of self-administered puffs is a measure of the amount of smoking behaviour participants engaged in during the task, while breakpoint is an estimate of the reinforcing value of smoking (i.e., the amount of effort (number of key presses) the

smoker is willing to expend to earn cigarette puffs). Measures of self-administered puffs and breakpoint collected with similar PR tasks have been shown to be sensitive to changes in mood and abstinence-based craving (Willner et al., 1995; Willner & Jones, 1996) and to pharmacological and non-pharmacological manipulations (Barrett, 2010; Barrett & Darredeau, 2012; Schlagintweit et al., 2015).

5.3.2.4 Heart rate

A Polaris Heart Rate Monitor (Polar Electro Canada, Inc., Lachine, Quebec, Canada) chest strap and wristwatch were used to measure average heart rate over 60 seconds.

5.3.3 Procedure

Participants completed two sessions of a mixed within (expect NI vs. expect NFI) and between (administered NI vs. administered NFI; quitting motivated vs. quitting unmotivated) subjects modified balanced placebo design. As a result, the study included four groups: quitting motivated/administered NI (n=11, 6 male), quitting motivated/administered NFI (n=10, 7 male), quitting unmotivated/administered NI (n=12, 9 male), and quitting unmotivated/administered NFI (n=14, 9 male). Participants were randomly assigned to administer a NI or NFI and administered the same product during both sessions, while instructions regarding the nicotine content of the product (expect NI vs. expect NFI) and the flavouring of the inhaler (mint vs. citrus) varied across sessions in counterbalanced order.

Written consent was ascertained in person during the first study session. Overnight abstinence from smoking (≥ 12 hours) was then confirmed with a breath carbon monoxide (Vitalograph, UK) reading of ≤15 ppm. Baseline subjective craving and

heart rate were assessed while participants were seated at rest (Time 1), then the researcher provided participants with an inhaler and instructions about its nicotine content (expect NI vs. expect NFI). In order to standardize inhaler consumption across participants, participants were required to take two-second inhalations every ten seconds over the course of 20 minutes (Darredeau & Barrett, 2010). Compliance was verified by a researcher. Craving and heart rate were then assessed again while participants were seated at rest (Time 2), immediately following the 20-minute inhaler self-administration period. Next, participants were comfortably seated in front of a computer and provided with their preferred brand of cigarettes. Participants then completed the hour-long PR task under the supervision of a researcher. Finally, as a manipulation check of believability of nicotine content instructions, participants were asked what type of inhaler they had received during the session, with response options including "nicotine", "nicotine-free" or "don't know". Full debriefing was delayed until data collection was complete, in order to prevent past participants from informing potential participants about the deception involved in the study. Please refer to table 5.2 for a timeline of study procedures.

Table 5.2 Timeline of study procedures

Procedure	Time (min)	Total time (min)
Confirmation of smoking abstinence	10	10
T1. Heart rate and craving assessment	10	20
Nicotine content instructions and inhaler administration	20	40
T2. Heart rate, craving assessment, and like product rating	10	50
Progressive ratio task	60	110
Manipulation check	10	120

5.3.4 Statistical analyses

Data were analyzed using linear mixed models in SPSS version 20 (SPSS Inc., Chicago, Illinois, USA). Main measures were subjective ratings of cigarette craving and heart rate (averaged over 60 seconds) at baseline (Time 1) and post-inhaler administration (Time 2) and cigarette self-administration data (number of self-administered puffs and breakpoint). Data for the main measures were analyzed using Expect (nicotine vs. nicotine-free) as a fixed and repeated factor, Administered (nicotine vs. nicotine-free) and Quitting Intention (quitting motivated vs. quitting unmotivated) as fixed factors, and subjects as a random factor. Fagerström Test for Cigarette Dependence (FTCD) scores were entered as covariates for all main measures and baseline measures (Time 1) were entered as time-varying covariates for ratings of cigarette craving and heart rate. Effects

of interest included any main effects or interactions of Expect, Administered, and/or Quitting Intention. Interactions involving Quitting Intention were decomposed using planned comparisons, where linear mixed models were run separately for quitting motivated and unmotivated smokers. Effects of interest were main effects or interactions of Expect and/or Administered. For interactions that did not involve Quitting Intention, tests of simple main effects were performed on the linearly independent pairwise comparisons between the estimated marginal means. Mean values reported are estimated marginal means.

5.4 Results

5.4.1 Study completion

Forty-three of the 47 participants completed both experimental sessions, while the remaining four participants (two male) completed one session. As a result, session two data was missing from one participant in each of the four study conditions (expect and administered NI, expect and administered NFI, expect NI and administered NFI, and expect NFI and administered NI). In addition, due to a computer malfunction during the PR task, cigarette self-administration data was not available for one session for one participant in the expect and administered NI condition. Participants with and without complete data were not found to differ significantly in cigarettes per day or FTCD score. Because linear mixed models can accommodate for missing data in repeated designs through the simultaneous consideration of individual and group effects (Gueorguieva & Krystal, 2004), analyses were conducted using the entire sample. Therefore, session one data from 47 participants and session two data from 43 participants were included in the analyses.

5.4.2 Manipulation check

Six (five male) of the 47 participants (13%) were found not to believe or to be uncertain of the nicotine content instructions during one session (six of 90 sessions; one participant in the expect NFI and administered NI condition during session one and five participants, including two in the expect and administered NI and one in each of the other three conditions, during session two). No significant differences in cigarettes per day or FTCD scores were found between participants who did and those who did not believe nicotine content instructions; however, results from all participants and from only participants who believed nicotine content instructions are reported below, as findings could vary between analyses that include all participants and analyses restricted to those who believed nicotine content instructions (Kelemen & Kaighobadi, 2007; Schlagintweit et al., 2015, 2016).

5.4.3 Analyses using all participants

5.4.3.1 Craving

Main effects of Expect were observed for both QSU-B factor 1 craving (intention to smoke; $F(1,37.52)=10.82$, $p=0.002$) and factor 2 craving (withdrawal related craving; $F(1,37.06)=6.08$, $p=0.018$). In both cases, lower ratings of craving were observed in the expect NI (factor 1: M=21.52, SE=0.93; factor 2: M=14.42, SE=0.70) relative to the expect NFI condition (factor 1: M=24.94, SE=0.93; factor 2: M=16.54, SE=0.71). A main effect of Administered was also found for QSU-B factor 1 craving ($F(1,37.02)=9.60$, $p=0.004$). Lower ratings of craving were observed in the administered NI (M=20.70, SE=1.12) relative to the administered NFI condition (M=25.75, SE=1.13).

A three-way interaction of Quitting Intention by Expect by Administered was observed for QSU-B factor 1 craving ($F(1,38.12)=4.81$, $p=0.034$, see figure 5.1). Planned comparisons were conducted in quitting motivated and unmotivated smokers separately. In quitting motivated smokers, a main effect of Expect was observed ($F(1,16.13)=8.37$, $p=0.011$), where lower ratings of craving were found in the expect NI ($M=21.26$, $SE=1.44$) relative to the expect NFI condition ($M=25.52$, $SE=1.41$). An Expect by Administered interaction was also observed ($F(1,16.86)=4.97$, $p=0.040$), where lower ratings of craving were found in the expect and administered NI condition ($M=17.56$, $SE=2.04$) relative to the expect NI and administered NFI ($M=24.96$, $SE=2.23$, $p=0.027$) and the expect NFI and administered NI conditions ($M=25.14$, $SE=2.02$, $p=0.002$). In quitting unmotivated smokers, main effects of both Administered ($F(1,22.23)=5.79$, $p=0.025$) and Expect ($F(1,23.68)=4.39$, $p=0.047$) were observed, such that lower ratings of craving were found in the administered NI ($M=20.63$, $SE=1.45$) relative to the administered NFI condition ($M=25.41$, $SE=1.33$) and in the expect NI ($M=21.53$, $SE=1.43$) relative to the expect NFI condition ($M=24.51$, $SE=0.93$).
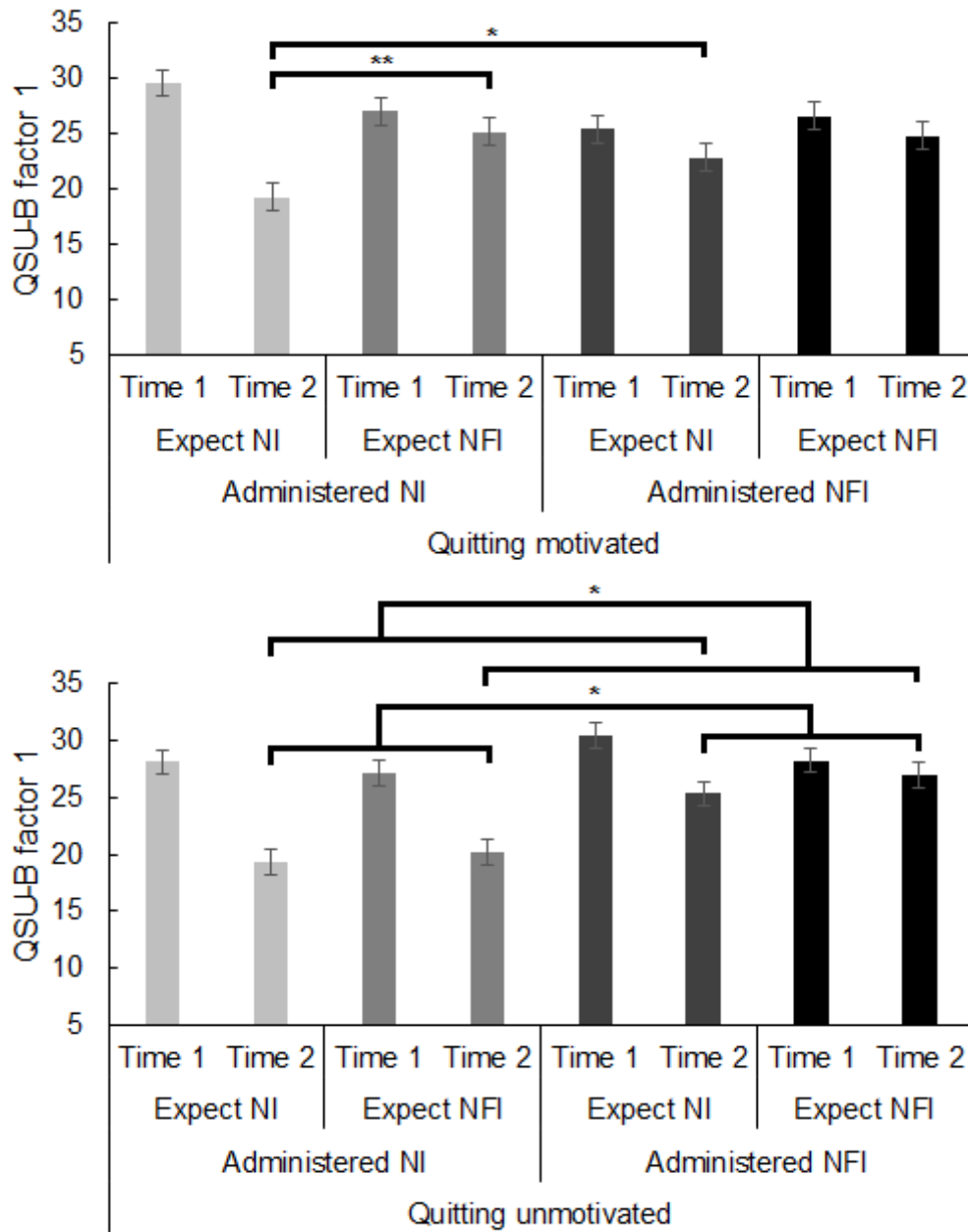
Figure 5.1 Estimated marginal mean (+/- SE) QSU-B factor 1 craving scores for the three-way interaction of Quitting Intention by Expect by Administered (p=0.034) in quitting motivated (top) and unmotivated (bottom) participants. In quitting motivated participants, nicotine content expectancy and administration interacted to curb craving, while in quitting unmotivated participants nicotine content expectancy and nicotine administration independently curbed self-reported craving (* p<0.05, ** p<0.01). While baseline (Time 1) craving is presented in the figure, it was used as a time varying covariate in all analyses.
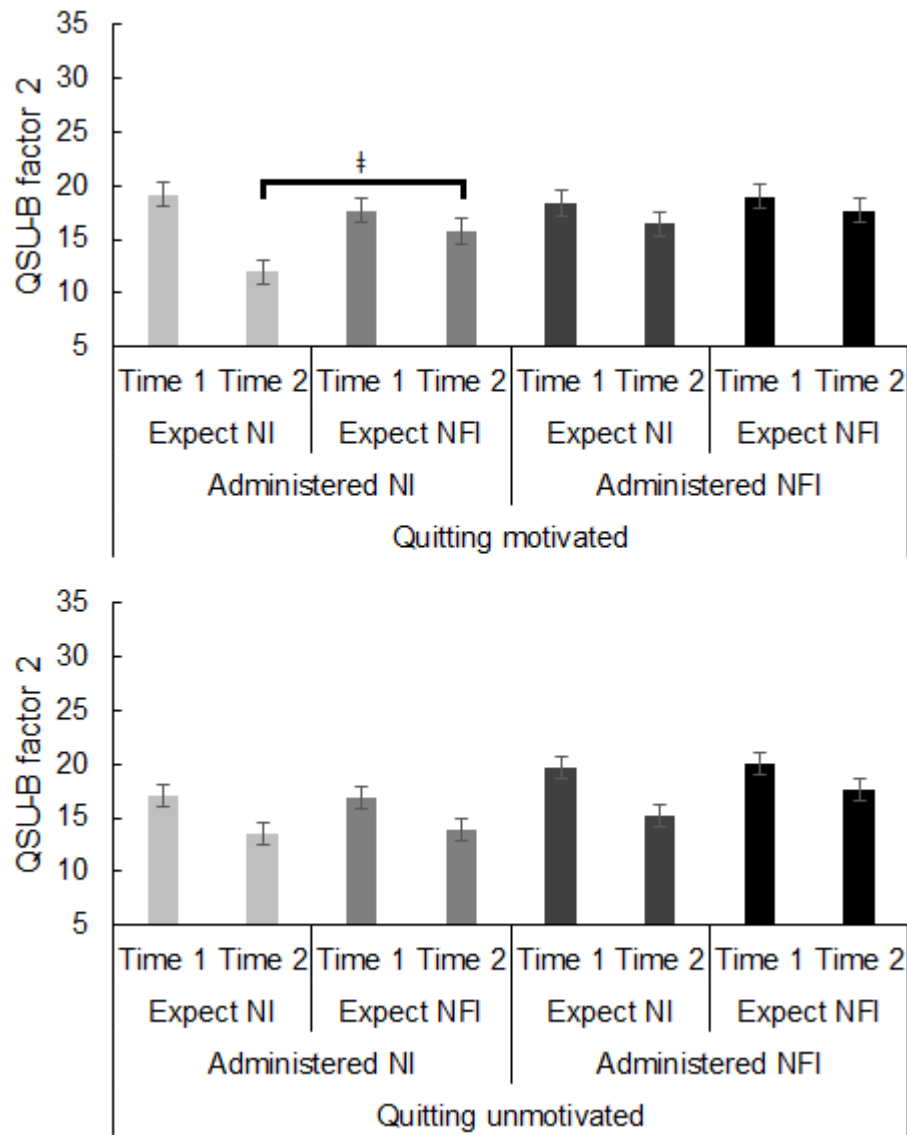
A trend toward a three-way interaction of Quitting Intention by Expect by

Administered was also observed for QSU-B factor 2 craving ($F(1,37.10)=3.13$, $p=0.085$,

see figure 5.2). Planned comparisons did not reveal any significant main effects or

interactions of Expect or Administered for quitting motivated or unmotivated smokers.

Figure 5.2 Estimated marginal mean (+/- SE) QSU-B factor 2 craving scores for the trend toward a three-way interaction of Quitting Intention by Expect by Administered (p=0.085) in quitting motivated (top) and unmotivated (bottom) participants. However, results failed to meet the threshold for statistical significance for main effects of Expect (quitting motivated participants: ‡ p=0.09, quitting unmotivated participants: p=0.14) and Administered (quitting motivated participants: p=0.13, quitting unmotivated participants: p=0.97). While baseline (Time 1) craving is presented in the figure, it was used as a time varying covariate in all analyses.

5.4.3.2 Heart rate

Main effects of Quitting Intention ($F_{(1,31.86)}=5.64$, $p=0.024$), Expect ($F_{(1,36.06)}=5.12$, $p=0.030$) and Administered ($F_{(1,33.34)}=10.37$, $p=0.003$) were observed for average heart rate. Increased heart rate was observed in quitting unmotivated (M=75.57, SE=1.01) relative to quitting motivated smokers (M=71.91, SE=1.16), in the expect NFI (M=75.79, SE=0.82) relative to the expect NI condition (M=71.70, SE=1.46), and in the administered NI (M=76.32, SE=1.06) relative to the administered NFI condition (M=71.17, SE=1.15),

A two-way interaction of Quitting Intention by Administered was also found for average heart rate ($F_{(1,32.25)}=4.49$, $p=0.042$, see figure 5.3). Planned comparisons were conducted in quitting motivated and unmotivated smokers separately. No significant effects were observed in quitting motivated smokers; however, a main effect of Administered was found in quitting unmotivated smokers ($F_{(1,22.16)}=17.35$, $p<0.001$), where increased heart rate was found in the administered NI (M=79.30, SE=1.44) relative to the administered NFI condition (M=71.00, SE=1.33).
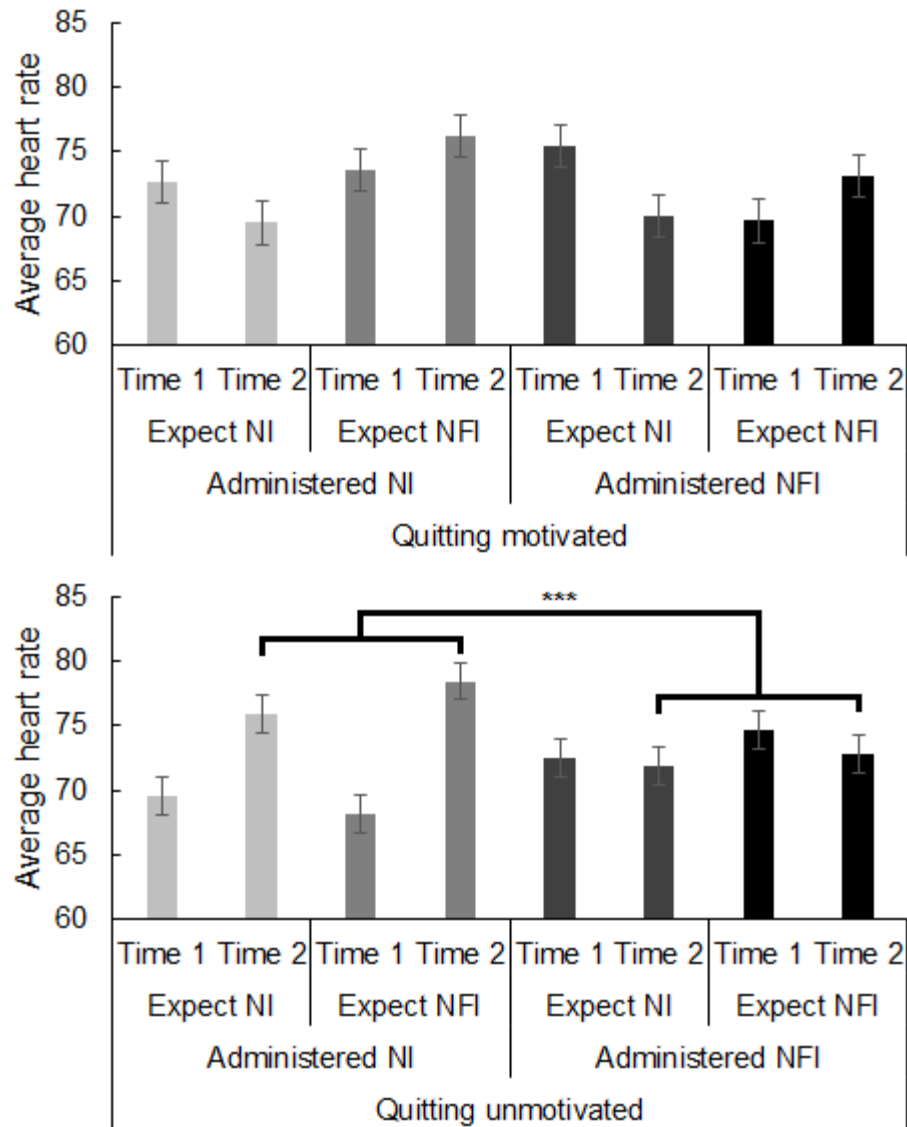
Figure 5.3 Estimated marginal mean (+/- SE) measures of average heart rate for the two-way interaction of Quitting Intention by Administered (p=0.042) in quitting motivated (top) and unmotivated (bottom) participants. In quitting unmotivated participants, average heart rate was associated with nicotine administration (*** p<0.001), while nicotine administration was not observed to impact heart rate in quitting motivated participants (p>0.05). While baseline (Time 1) heart rate is presented in the figure, it was used as a time varying covariate in all analyses.

5.4.3.3 Cigarette self-administration

Neither Quitting Intention, nor Expect, nor Administered were found to impact number of self-administered puffs or breakpoint during the progressive ratio task (p values>0.25; see figure 5.4).
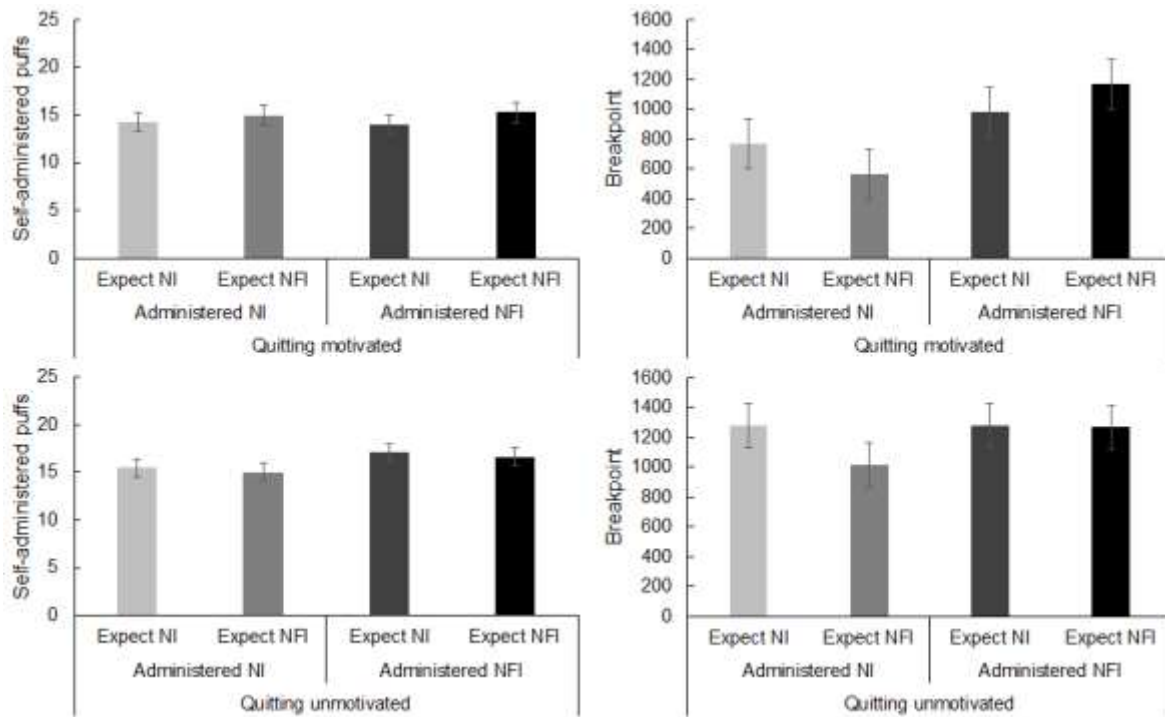
Figure 5.4 Estimated marginal mean (+/- SE) measures of self-administered puffs (left) and breakpoint (right) during the PR task for quitting motivated (top) and unmotivated (bottom) participants. Neither quitting intention, nor nicotine expectancy, nor nicotine administration were observed to impact self-administered puffs or breakpoint (p values>0.25).

5.4.4 Analyses using only participants who believed nicotine content instructions

While the pattern of findings remained consistent between analyses involving all participants and those involving only participants who believed nicotine content instructions, the three-way interaction of Quitting Intention by Expect by Administered for QSU-B factor 1 craving ($F_{(1,33.25)}=3.71$, $p=0.063$) was present only at a trend level when analyses were restricted to 'believers' only, likely owing to reduced power. Similarly, the Quitting Intention by Expect by Administered interaction trend for QSU-B factor 2 craving was no longer present ($F_{(1,31.33)}=1.65$, $p=0.208$).

5.5 Discussion

This study sought to assess the impact of nicotine expectancy and administration components of acute NRT use on cigarette craving and self-administration in dependent smokers who were either quitting motivated or quitting unmotivated. Partially in line with our hypotheses, results suggest that quitting motivated and unmotivated smokers may exhibit different subjective responses to acute NRT administration. While nicotine expectancy and administration were observed to have independent effects on craving reduction in quitting unmotivated smokers, the combined effects of nicotine expectancy and administration were necessary to reduce craving in quitting motivated smokers, suggesting that a combination of pharmacological and psychological processes may be necessary for NRT to yield therapeutic effects in those wishing to quit smoking. However, given that this is, to our knowledge, the first study to assess differences in NRT responses between quitting motivated and unmotivated smokers, and due to the relatively modest sample size, findings require replication before firm conclusions can be drawn.

The bulk of prior research examining differences between quitting motivated and unmotivated smokers has assessed reactivity to smoking cues in populations of treatment-seeking and non-seeking individuals. Findings demonstrate blunted cue reactivity in treatment-seeking smokers, which is theorized to result from different perceptions about future smoking opportunities (i.e., treatment-seeking smokers may be unable or unwilling to smoke while smokers not seeking treatment may plan to smoke imminently; Sayette, 2016; Wertz & Sayette, 2001; Wilson, Sayette, & Fiez, 2004). However, given that all participants were presented with an opportunity to smoke in the current study, the observed differences in craving between quitting motivated and unmotivated smokers are unlikely to be a result of differences in current drug use opportunity.

A relatively unexpected finding of the current study was that nicotine administration led to increased heart rate only in smokers with no intention to quit. Previous balanced placebo research has demonstrated increased heart rate associated with nicotine administration (Schlagintweit et al., 2014, 2015), yet these studies included only quitting unmotivated smokers. It is possible that nicotine may have enhanced incentive motivational properties in smokers with no desire to quit and that this may impact their cardiac reactivity to its acute administration. Increased heart rate has been associated with enhanced reward sensitivity, such that individuals who experience various substances, including alcohol and nicotine, as more rewarding tend to display greater heart rate reactivity to the administration of these substances (Conrod, Peterson, & Pihl, 2001; Sofuoglu, Herman, Nadim, & Jatlow, 2012). Neuroimaging findings of Wilson, Sayette and Fiez (2012) have also demonstrated that, when anticipating an imminent smoking opportunity, quitting unmotivated smokers showed increased smoking cue-induced

neural activity in areas associated with reward related processing (the rostral prefrontal cortex, anterior cingulate cortex and medial orbitofrontal cortex) relative to quitting motivated smokers. Alternatively, it is possible that a blunted cardiac response to nicotine and/or smoking related stimuli may be a marker for an increased probability of contemplating smoking cessation. This is consistent with previous observations of blunted heart rate reactivity associated with smoking cue exposure in quitting motivated dependent smokers who go on to achieve successful cessation relative to those who relapse (Abrams, Monti, Carey, Pinto, & Jacobus, 1988), and in former smokers relative to current smokers (Balter et al., 2015). Longitudinal research assessing heart rate and craving reactivity to tobacco and/or nicotine use over the course of tobacco addiction is needed to clarify whether changes in craving and heart rate reactivity precede or follow from the desire to quit smoking.

Despite the aforementioned differences in subjective craving and heart rate in quitting motivated and unmotivated smokers, quitting motivation was not observed to impact smoking behaviour during the progressive ratio task. This finding is not entirely unexpected given that neither nicotine expectancy nor administration components of acute NRT use have been observed to impact cigarette self-administration in previous research (Barrett, 2010; Schlagintweit et al., 2015) and because quitting motivated participants were still engaging in daily smoking at the time of their participation in the study. While quitting motivated participants in the current study reported an intention to take future action toward smoking cessation, they may not have been ready to implement the required behavioural changes (smoking cessation), consistent with the preparation stage of the Transtheoretical Model of health behaviour change (Prochaska & Velicer,

1997). It is expected that nicotine expectancy and/or administration effects of NRT use on subsequent smoking behaviour may be more pronounced in treatment-seeking smokers or in smokers who have begun to implement systematic changes to their smoking behaviour.

The findings of the current study should be considered in light of the following limitations. First, the cross-sectional, non-interventional nature of the study did not permit the assessment of whether quitting motivated participants went on to attempt cessation following study participation. Given that physiological differences in response to smoking cues have been demonstrated between dependent smokers who do and do not achieve smoking cessation (Abrams et al., 1988), it is recommended that future research examining quitting motivation include follow-ups to assess cessation attempt initiation and outcome. Second, sex differences were not examined in the current study. Sex was excluded from analyses due to an already complex study design and a limited sample size. Research suggests that female smokers display heightened reactivity to non-pharmacological components of smoking and NRT administration (Caggiula et al., 2002; Perkins et al., 2001; Perkins, Doyle, et al., 2006); however, the extent to which these findings generalize to quitting motivated smokers is unknown. Further, sex differences have been demonstrated in resting heart rate (Agelink et al., 2001); however, the extent to which this impacted the present findings is not known. It is recommended that future research consider potential sex differences in quitting motivated smokers. Third, while overnight abstinence from smoking was verified with an exhaled carbon monoxide reading of ≤15ppm, it is possible that some participants may have been able to meet the cut-off without having abstained overnight; however, the majority of CO readings (88%)

were less than 10ppm across both sessions, and CO measurements were not found to be correlated with baseline craving (p values>0.2). Because sessions were run on mornings following overnight abstinence, and the half-life of CO is greater during sleeping than during waking hours (Benowitz et al., 2002), the cut-off used in the present study was selected so that heavy smokers who adhered to abstinence requirements would not be excluded from participation. When post hoc analyses were run using only the data from participants who met a CO cut-off of ≤10ppm, all three-way interactions remained significant, suggesting that the observed effects are not a result of failure to adhere to the abstinence requirement. Fourth, the sample size of the present study was modest, but within the norms of within/between subject balanced placebo designs. While a number of the observed interactions approached marginal significance, findings converged across QSU-B factor 1 and factor 2 craving and were consistent with our a priori hypothesis, suggesting that findings are unlikely to be a result of Type I error. In addition, smaller sample sizes are more frequently associated with Type II than with Type I error. Finally, while inhaler self-administration (frequency, number and duration of puffs) was standardized across participants, plasma nicotine levels were not monitored and it is possible that there was some variability in the degree of nicotine exposure among participants. However, because the nicotine administration was found to contribute to craving reductions across participants, this seems unlikely. It is recommended that future research include direct measures of nicotine exposure so that the relationships between nicotine dose and subjective and physiological responses can be reported.

In conclusion, findings from the current study demonstrate that quitting motivated and unmotivated dependent smokers display unique physiological and subjective

responses to nicotine expectancy and administration components of acute NRT use. Nicotine expectancy and administration were observed to interact to curb craving in quitting motivated smokers, yet exerted their effects independently in quitting unmotivated smokers. In addition, quitting motivated smokers displayed blunted heart rate reactivity following nicotine consumption relative to quitting unmotivated smokers. Taken together, these findings suggest that quitting motivated smokers may be less sensitive to the rewarding aspects of nicotine consumption, and that a combination of pharmacological and psychological factors may be necessary for NRT to impact craving in this population. Given that quitting motivated smokers are more likely to use NRT than quitting unmotivated smokers, it is important for future research to continue to examine how pharmacological and non-pharmacological mechanisms interact to influence cessation-related outcomes in quitting motivated dependent smokers.

CHAPTER 6. GENERAL DISCUSSION

6.1 Overview of dissertation aims and methodology

The primary purpose of the present work was to assess the relative contribution of expectancy and pharmacology to drug responses using nicotine and tobacco as a model. In order to achieve this aim, the four experiments included in this dissertation used a balanced placebo design, in which drug content instructions (i.e., told contains active drug vs. told contains no active drug) were crossed with actual drug administration (i.e., administered active drug vs. administered inert drug/placebo), such that the independent and combined impact of drug expectancy and drug administration on drug responses could be quantified (Sutton, 1991). Previous balanced placebo research assessing the relative contribution of nicotine expectancy and administration to responses to NRT and tobacco administration demonstrate that nicotine expectancy has an important impact on behavioural and subjective responses; however, the impact of nicotine administration on same remains less certain (Dar & Barrett, 2014). Therefore, an additional aim of the present dissertation was to further examine the relative contribution of nicotine expectancy and pharmacology to subjective and behavioural NRT and tobacco responses, with the goal of contributing to an improved understanding of the mechanisms underlying NRT and tobacco responses, as these may have important implications for the development of smoking cessation interventions with improved treatment outcomes.

More broadly, an improved understanding of the relative contribution of non-pharmacological (i.e., expectancy) and pharmacological contributions to drug responses has important implications for research assessing drug effects and clinical efficacy, as randomized clinical trials, which are primarily used to assess same, rarely directly assess

or control for expectancy (Correa et al., 2014; Dar et al., 2005; Stewart-Williams & Podd, 2004; Sutton, 1991; Thomas et al., 2008), despite accumulating evidence that expectancy makes important contributions to the therapeutic benefits of varied substances (e.g., Correa et al., 2014; Dar et al., 2005; Thomas et al., 2008). If non-pharmacological factors, such as expectancy, are found to confer therapeutic benefits to drug responses, then targeting these in interventions may improve treatment outcomes.

6.2 Overview of main findings

The main novel findings presented in this work are that nicotine expectancy makes a critical contribution to acute subjective and behavioural responses to NRT and tobacco administration. A number of additional non-pharmacological factors, including exposure to smoking-related stimuli, sex, perceptions regarding the availability of a future smoking opportunity, and varied motivations to quit smoking were also found to have an important impact on NRT and tobacco responses. Taken together, these findings suggest that non-pharmacological factors make an important contribution to drug responses, and thus potentially clinical responses and therapeutic efficacy. Targeting non-pharmacological factors in interventions may therefore contribute to improved treatment responses, particularly within the context of smoking cessation interventions.

Experiments 1, 3 and 4 used the balanced placebo design to assess the relative contribution of nicotine expectancy and administration to NRT responses. Nicotine content instructions were consistently associated with curbed subjective craving to smoke; however, findings regarding nicotine administration were less consistent. In experiment 1, nicotine content instructions and administration were found to interact to reduce craving following nicotine lozenge administration; however, no independent

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effects of nicotine administration were observed. In experiment 3, nicotine administration was observed to independently reduce both intention to smoke and withdrawal-related craving when data were analysed with all participants; however, these effects were not significant when analyses were restricted to only those participants who believed nicotine content instructions. Rather, independent effects of nicotine content instructions on withdrawal-related craving emerged in analyses using 'believers' only. Finally, in experiment 4, nicotine administration was independently associated with curbed withdrawal-related craving regardless of whether analyses used all participants or 'believers' only. These findings are consistent with previous reports of nicotine expectancy effects on NRT responses (Darredeau & Barrett, 2010; Fucito & Juliano, 2007; Gottlieb et al., 1987; Hughes et al., 1989; Perkins, Grottenthaler, et al., 2009); however, the effects of nicotine administration on subjective craving observed in experiments 3 and 4 are less consistent with the available literature. Indeed, Perkins et al. (2009) were the only other group to previously document independent effects of nicotine administration on NRT responses.

It is possible that discrepant findings regarding the impact of nicotine administration on responses to NRT administration may have been a result of differences in the products administered during each experiment and/or varied abstinence requirements prior to the onset of experimental sessions. Indeed, while experiments 1 and 3 used lozenges, experiment 4 used inhalers. Experiments 1 and 3 appear to be the first in the available literature to use the 4mg nicotine lozenge in a balanced placebo design. Comparison of nicotine absorption across various nicotine products (i.e., the cannon, inhalator, nasal spray, microtab, 2mg and 4mg gum, and 2mg and 4mg lozenge) suggests

that, across all products, the 4mg lozenge is associated with the highest blood nicotine concentration over 60 minutes following product administration (McEwen et al., 2008), suggesting that effects of nicotine administration may be more pronounced when 4mg lozenges are used relative to other nicotine delivery devices, including the inhaler. Additionally, while participants were required to arrive at experimental sessions after overnight ($\geq$12 hour abstinence) in experiments 3 and 4, they were permitted to smoke their preferred brand of cigarette one hour prior to lozenge administration in experiment 1. It is therefore possible that the effects of nicotine administration on responses to the nicotine lozenge in experiment 1 may have been blunted, due to an already elevated blood nicotine concentration relative to that in experiments 3 and 4. Indeed, the half-life of venous blood concentrations of nicotine following cigarette smoking is two hours (Le Houezec, 2003), suggesting that nicotine levels would have, indeed, been elevated one hour following smoking in experiment 1 relative to experiments 3 and 4.

Experiment 2 was the only one to use the balanced placebo design to assess the impact of nicotine expectancy and administration on acute responses to tobacco smoking. Findings demonstrated that both nicotine content instructions and administration were associated with curbed craving following tobacco smoking. These findings are largely consistent with previous studies which have also documented both nicotine expectancy and administration effects (Darredeau et al., 2013; Juliano & Brandon, 2002; Juliano et al., 2011; Kelemen & Kaighobadi, 2007; Perkins, Ciccocioppo, et al., 2008; Perkins, Jacobs, Ciccocioppo, et al., 2004; Robinson et al., 2016). Collectively, findings suggest that nicotine administration may make a more substantial contribution to tobacco responses than NRT responses.

6.3 Implications

Nicotine administration effects on responses to tobacco consumption must be interpreted with caution, as findings are more consistent with the difference between smoking nicotine-containing and denicotinized cigarettes than the difference between consuming nicotine versus placebo (Dar & Barrett, 2014). Tobacco smoke contains a number of non-nicotine pharmacologically active constituents, which may interact with nicotine to produce subjective effects (Caine et al., 2014; Clemens et al., 2009; Harris et al., 2010; Hoffman & Evans, 2013). Further, evidence suggests that nicotine smoked in tobacco may be more effective in curbing craving than nicotine consumed via NRT (Barrett, 2010), which may be a result of differing sensory (e.g., inhaling smoke) and pharmacodynamic characteristics (e.g., speed of nicotine delivery; Rose, 2006). Finally, smokers may have differing expectancies for NRT compared to tobacco effects. Indeed, Juliano and Brandon (2004) demonstrated that smokers report stronger expectancies that cigarette smoking is effective in controlling negative affect and craving compared to NRT. These differing expectancies may also contribute to the divergent findings of balanced placebo research using tobacco and NRT.

While the current dissertation exclusively examined the acute effects of nicotine expectancy and administration, previous balanced placebo research have assessed longer-term effects. Indeed, Gottlieb et al. (1987) and Hughes et al. (1989) demonstrated expectancy effects on smoking behaviour and abstinence over the course of 2 two-week smoking cessation trials, suggesting that expectancy may indeed have important therapeutic benefits. A similar conclusion can be drawn from placebo-controlled smoking cessation trials which directly assess the contribution of perceived treatment assignment

to outcome measures. For example, Dar, Stronguin, and Etter (2005) demonstrated that, regardless of actual treatment assignment (i.e., NRT vs. placebo), the belief that one had received NRT was associated with improved treatment outcomes (i.e., reduced smoking and increased abstinence). Further, the association between NRT and improved cessation outcome was not found to be significant after beliefs regarding treatment assignment were controlled for. Similar findings have also been documented in placebo-controlled smoking cessation trials of varenicline (Correa et al., 2014) and buproprion (Schnoll et al., 2008).

The importance of assessing perceived treatment assignment is critical, given that blinding regarding treatment assignment is frequently unsuccessful (Fisher & Greenberg, 1993; Greenberg et al., 1992; Margraf et al., 1991). Blinding failure may be particularly relevant to trials of smoking cessation, as meta-analyses of same have demonstrated that the blind was unsuccessful in the majority of studies that assessed perceived treatment assignment (Mooney et al., 2004). Of greater concern, is that the majority of trials included in the meta-analysis did not assess perceived treatment assignment (Mooney et al., 2004). Therefore the extent to which findings are a result of treatment pharmacology, expectancy, or some combination of these is unknown. Directly assessing and/or manipulating perceived treatment assignment in clinical trials is critical in order to better clarify the mechanisms that mediate drug responses, including therapeutic benefits and clinical efficacy.

6.4 Limitations

While the four experiments included in this work manipulated stimulus expectancies (i.e., beliefs about the active drug content of an administered substance),

none of the studies directly manipulated response expectancies (i.e., beliefs about the subjective, cognitive, physiological and/or behavioural effects of a particular substance). Participants were given explicit instructions about whether or not study products contained nicotine; however, no instructions regarding the expected effects of nicotine consumption were provided.

While it has been demonstrated that smokers expect that both NRT and tobacco are effective in curbing craving (Juliano & Brandon, 2004), manipulations of response expectancies have been demonstrated to significantly alter drug responses. For example, Fucito and Juliano (2007) demonstrated that placebo responses to transdermal patches are maximized when both stimulus expectancy (i.e., told patch contains nicotine vs. placebo) and response expectancies (i.e., given information maximizing patch's benefits vs. given routine information such as the side effect profile) were manipulated. In addition, Copp et al. (2015) recently found that female dependent smokers initiated placebo e-cigarette self-administration more rapidly when they were instructed that the e-cigarette contained nicotine and when they had strong a-priori beliefs about the effectiveness of nicotine in curbing craving to smoke, suggesting that stimulus and response expectancies may interact to impact self-administration, particularly in female smokers.

It has been demonstrated that smokers have weak expectancies regarding the therapeutic effects of NRT (Juliano & Brandon, 2004). Indeed, in a mail out survey of 494 current and former smokers, Etter and Perneger (2001) found that only 16% of participants believed that NRT helps people quit smoking and 26% feared NRT side effects. Smokers' perceptions about cessation aid effectiveness may also be associated with outcomes of cessation attempts, as Hammond, McDonald, Fong, and Borland (2004)

documented that smokers who perceived smoking cessation aids to be effective were more likely to intend to quit, to engage in a cessation attempt, and to use a cessation aid during same. Taken together, these findings suggest that exclusively manipulating stimulus expectancies may underestimate expectancy effects, particularly if participants hold negative or ambivalent response expectancies about the product being administered. It is possible that the expectancy effects observed in the current work may have been maximized had manipulations of response expectancies (i.e., given instructions maximizing product benefits vs. no instructions) also been included, particularly in the experiments assessing NRT responses. It is recommended that future research directly manipulate both stimulus and response expectancies in order to better ascertain the role that each of these play in mediating drug responses.

Findings from the present dissertation and the available body of balanced placebo research provide strong evidence for the important contribution of expectancy to drug responses; however, it remains unclear whether such responses are a result of physiological processes or other factors (e.g., experimental demand characteristics). Functional neuroimaging studies have recently begun to assess the neurobiological mechanisms that underlie NRT responses, including reduced craving and withdrawal. Sutherland et al. (2013) reported that withdrawal relief following acute NRT use was associated with reduced resting state functional connectivity between the amygdala and insula. Cole et al. (2010) also demonstrated that NRT-induced withdrawal relief was associated with reduced resting state functional connectivity in regions associated with reward processing (e.g., the orbitofrontal cortex, prefrontal cortex, and thalamus) and in the insula. Activity within the insula has also been demonstrated to be positively

associated with cue-induced (McBride et al., 2006) and abstinence-precipitated craving (Wang et al., 2014); however, none of these studies assessed the relative impact of nicotine expectancy and administration on neurobiological responses to NRT administration.

Gu et al. (2016) recently used a balanced placebo design to assess the impact of nicotine expectancy and administration on subjective craving and associated neural activation as measured with functional magnetic resonance imaging (fMRI). Twenty eight daily smokers completed all four conditions of the balanced placebo design, during which nicotine content instructions (told nicotine-containing vs. told no-nicotine cigarette) and administration (administered a 0.6mg vs. 0.06mg nicotine cigarette) were crossed. Immediately after smoking the study cigarette, participants completed a reward learning task while undergoing fMRI scanning. Results demonstrated that, when participants smoked a nicotine-containing cigarette, nicotine content instructions were associated with significantly reduced subjective craving. Additionally, the observed reductions in craving were associated with reduced blood oxygen level dependent (BOLD) activity in the insula. These findings suggest that nicotine expectancy exerts an important influence on insula-related neural activity in the presence of nicotine administration. More broadly, this study is the first to demonstrate that non-pharmacological factors exert important top down influences on nicotine responses at the neural and subjective level, and thus provides compelling evidence that expectancy effects on drug responses are not merely a result of demand characteristics. While there do not yet appear to be any neuroimaging studies assessing nicotine expectancy and administration effects on subjective craving and neural activity following NRT

administration, the findings of Gu et al. (2016) provide strong support for the mediating role of both drug expectancy and administration in generating acute drug responses, thus highlighting the critical importance of assessing both expectancy and administration in studies of drug effects.

A final limitation of the present work is that the relative influence of all non-pharmacological factors (e.g., stimulus expectancy, sex, exposure to smoking-associated cues, expectations about the temporal proximity of a future smoking opportunity, quitting motivation, and duration of abstinence from smoking and/or nicotine use) on NRT and tobacco responses were not assessed simultaneously, and thus the extent to which each of these factors interact with one another to alter NRT and tobacco responses remains uncertain. Indeed, recent work provides evidence that these factors may interact with one another in a unique manner. For example, Donohue et al. (2016) demonstrated that quitting motivation (intend to quit smoking vs. no intention to quit smoking) and duration of abstinence from smoking (3 hour abstinence vs. non-abstinent) interact to impact neural responses associated with craving, as measured with EEG in 24 regular cigarette smokers. It is therefore recommended that future research evaluate the relative contribution of each of these non-pharmacological factors and of pharmacological factors to drug responses.

6.5 Conclusions

In conclusion, the findings of this work suggest that a number of non-pharmacological factors make important contributions to drug responses. While the main focus of the work was documenting the impact of expectancy on subjective and behavioural drug responses, findings also demonstrated that sex, exposure to drug-

associated cues, varied motivations to quit smoking, and varied perceptions about the availability of a future smoking opportunity exert important influences on drug responses. Findings highlight the importance of considering both pharmacological and non-pharmacological factors when designing and interpreting research assessing drug responses and effects. Improved knowledge of the contribution of non-pharmacological factors to drug responses may ultimately lead to the development of improved interventions, as findings from this work suggest that non-pharmacological factors may make important contributions to the therapeutic benefits and efficacy of various substances.

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