Sensorimotor Replacement with Electronic and De-nicotinised cigarettes:

Short-term Effects on Urges to Smoke, Withdrawal Symptoms and Smoking Cessation

by

Dunja Przulj

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

Queen Mary, University of London

Statement of Originality

I, Dunja Przulj, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

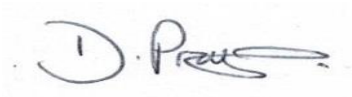
I attest that I have exercised reasonable care to ensure that the work is original, and does not to the best of my knowledge break any UK law, infringe any third party's copyright or other Intellectual Property Right, or contain any confidential material.

I accept that the College has the right to use plagiarism detection software to check the electronic version of the thesis.

I confirm that this thesis has not been previously submitted for the award of a degree by this or any other university.

The copyright of this thesis rests with the author and no quotation from it or information derived from it may be published without the prior written consent of the author.

Signature: Date: 29th January 2014



Collaboration

Data for the thesis was in part collected in collaboration with the following study, conducted at the Tobacco Dependence Research Unit, Queen Mary, University of London.

Complementing Current NHS Stop Smoking Service Treatment with Behavioural Replacement: The role of de-nicotinised cigarettes.

Principle Investigator: Dr. Hayden McRobbie

Co-investigators: Dr. Katherine Myers Smith, Dunja Przulj, Danielle Cornwall

Trial Registration: Clinicaltrials.gov (www.clinicaltrials.gov); Registration Number: NCT01250301

Funding: This study was funded by a grant from the Global Research Awards for Nicotine Dependence (GRAND).

Contribution: I assisted the study team with protocol development, study set-up, including ethical approval and research governance, participant recruitment, delivery of interventions and data collection, data analysis and write-up. Collection of data specific to the thesis was assisted by DC; all other work relating to thesis-specific data (i.e. selection of measures, data analysis and interpretation) was conducted by myself.

All other work included in the thesis was supported by the Economic and Social Research Council and the UK Centre for Tobacco and Alcohol Studies.

Publications:

Przulj, D., McRobbie, H., & Hajek, P. (2012). The Effect of Sensorimotor Replacement on Smoking Cessation and Craving. *The Open Addiction Journal,* 5: 41-50.

Acknowledgements

I am very grateful for all the help and support from my supervisors, Prof. Peter Hajek and Dr. Hayden McRobbie, and a big thank-you to all my wonderful colleagues at the RLH Smokers' Clinic who helped me along the way.

To my parents, Mirza and Vlado, and all my friends and family, thank you for your continued support and encouragement.

Abstract

Background: Current smoking-cessation medicines can assist smokers to quit, but have limited efficacy. Supplementing them with a replacement for the sensory and behavioural aspects of smoking, which are hypothesised to act as secondary reinforcers, could in theory help to alleviate urges to smoke and withdrawal, and may assist smoking cessation.

Methods: Three studies were conducted to examine sensorimotor replacement (SMR) effects. The first two employed a cross-over design to assess the effects of two SMR products, nicotine-free electronic cigarettes (ECs) and de-nicotinised cigarettes (DNCs), on short-term withdrawal, urges to smoke, and user acceptability. Study 1 (N= 35), compared EC to a stress ball (SB) to control for behavioural distraction and Study 2 (N=41) tested whether SMR effects were 'dose dependent' by comparing DNCs with ECs. The final study was part of a randomised controlled trial (N= 200) of DNCs in combination with standard treatment. It examined whether SMR effects on abstinence are moderated by scores on a 'behavioural' dependence measure (GN-SBQ).

Results: The EC was preferred over the SB, and alleviated urge to smoke more than SB, but the effect was modest and short-lived. The DNC and EC had similar effects acutely, but DNC suppressed urges to smoke and withdrawal to a somewhat greater extent over a day of abstinence. DNCs combined with standard smoking-cessation treatment improved short-term abstinence regardless of GN-SBQ scores.

Conclusion: SMR effects on urge and withdrawal alleviation were modest and a 'dose response' effect was not clearly established. An attempt to identify smokers for whom SMR may be of particular benefit was not successful. SMR however, was perceived as helpful and appealing, and results from the trial suggest that adding SMR may enhance existing treatments. It was proposed that rather than directly alleviating urges/withdrawal, SMR may operate as a coping tool in 'high-risk' situations, by providing an alternative to smoking.

Contents

List of Tables and Figures 9
List of abbreviations 12
1 Introduction 14
2 Theoretical Background 16
2.1 Differential drug effects within the nucleus accumbens 18
2.2 Behavioural Withdrawal 19
2.3 Other non-nicotine factors 21
2.3.1 Tobacco smoke constituents 21
2.3.2 Expectancy theory 21
2.4 Treatment implications 23
3 Literature review 25
3.1 How important are the sensory effects of smoking? 25
3.1.1 Depth of smoke inhalation 25
3.1.2 Refined smoke 26
3.1.3 Sensory blockade 27
3.1.4 Intravenous (IV) nicotine administration 29
3.1.5 Summary 31
3.2 Sensorimotor Replacement Products 31
3.2.1 Non-nicotine inhalators and aerosols 32
3.2.2 De-nicotinised cigarettes 36
3.2.3 Electronic Cigarettes 51
3.3 Conclusions and further research 56
4 Study 1: Can sensorimotor replacement with the electronic cigarette surpass behavioural distraction? 60
4.1 Methodology 60
4.1.1 Aims 60
4.1.2 Hypotheses 60
4.1.3 Research approach and Design 60
4.1.4 Participants 63
4.1.5 Measures and Outcomes 63
4.1.6 Sample size 66
4.1.7 Products 66

4.1.8 Procedures 67
4.1.9 Data analysis 68
4.2 Results 71
4.2.1 Participant characteristics 71
4.2.2 Compliance with abstinence 71
4.2.3 Product use 71
4.2.4 Primary outcome: Acute effects on urges to smoke after overnight abstinence 72
4.2.5 Cue exposure effects 73
4.2.6 Urges to smoke and withdrawal symptoms over 1 hour 76
4.2.7 Supplementary analyses: Acute effects on urges to smoke and withdrawal 84
4.2.8 Urges to smoke and withdrawal symptoms during the day 94
4.2.9 Supplementary analyses: Baseline ratings during morning and evening sessions 95
4.2.10 Product perceptions, preferences and adverse effects 98
4.3 Discussion 101
5 Study 2: Are sensorimotor effects 'dose' dependent? 104
5.1 Methodology 104
5.1.1 Aims 104
5.1.2 Hypotheses 104
5.1.3 Design 104
5.1.4 Participants 104
5.1.5 Measures and Outcomes 105
5.1.6 Sample size 106
5.1.7 Products 106
5.1.8 Procedures 107
5.1.9 Data analysis 107
5.2 Results 108
5.2.1 Participant characteristics 108
5.2.2 Compliance with abstinence 108
5.2.3 Product use 109
5.2.4 Primary outcome: Acute effects on urges to smoke after overnight abstinence 110
5.2.5 Cue-exposure effects 110
5.2.6 Urges to smoke and withdrawal symptoms over 1 hour 113

5.2.7 Supplementary analyses: Acute effects on urges to smoke and withdrawal 123
5.2.8 Urges to smoke and withdrawal symptoms during the day 132
5.2.9 Supplementary analyses: baseline ratings during morning and evening sessions 133
5.2.10 Product perceptions, preferences and adverse effects 136
5.2.11 Supplementary analyses: Comparison of EC effects across studies 139
5.3 Discussion 142
6 Study 3: Are sensorimotor replacement treatment effects moderated by 'behavioural' dependence? 144
6.1 Study synopsis 144
6.2 Methodology 144
6.2.1 Aims 144
6.2.2 Hypotheses 145
6.2.3 Design 145
6.2.4 Participants 145
6.2.5 Procedures 146
6.2.6 Measures and Outcomes 148
6.2.7 Sample size 149
6.2.8 Data analysis 150
6.3 Results 150
6.3.1 Participant characteristics 150
6.3.2 De-nicotinised cigarette use 153
6.3.3 Smoking cessation 153
6.3.4 Predictors of abstinence 154
6.4 Discussion 155
7 General Discussion and Conclusions 159
7.1 Sensorimotor replacement vs. behavioural distraction 161
7.2 Proximity of sensorimotor replacement to smoking 163
7.3 Moderators of sensorimotor replacement effects 164
7.4 Effects of sensorimotor replacement on urges to smoke: Implications for the central SMR hypothesis. 166
7.5 Cue-exposure effects 168
7.6 Strengths and Limitations 171
7.7 Future research 174
7.8 Conclusions 177

8 References 178
9 Appendix 192
1 Study Advertisements 192
2 Clinical records form (Studies 1 and 2) 193
3 Baseline Questionnaire (used in all studies) 204
4 Study 1 Participant Information Sheet 209
5 Example Consent Form (Studies 1 and 2) 212
6 Summry of sensitivity analysis on primary outcome (Study 1) 213
7 Mean ratings and standard deviations for urge to smoke over 1 hour (Study1) 214
8 Mean ratings and standard deviations for irritability over 1 hour (Study 1) 215
9 Mean ratings and standard deviations for restlessness over 1 hour (Study 1) 216
10 Mean ratings and standard deviations of difficulty concentrating over 1 hour (Study 1) 217
11 Mean ratings and standard deviations of composite withdrawal over 1 hour (Study 1) 218
12 Summary statistics: Simple contrasts for urge to smoke over 1 hour during morning session (Study 1; whole sample) 219
13 Summary of mean scores and test statistics for individual MPSS items (Study 1) 220
14 Study 2 Participant Information Sheet 221
15 Summary of sensitivity analysis on primary outcome (Study 2) 224
16 Mean ratings and standard deviations of urge to smoke over 1 hour (Study 2) 225
17 Mean ratings and standard deviations of irritability over 1 hour (Study 2) 226
18 Mean ratings and standard deviations of restlessness over 1 hour (Study 2) 227
19 Mean ratings and standard deviations for difficulty concentrating over 1 hour (Study 2) 228
20 Mean ratings and standard deviations of composite withdrawal over 1 hour (Study 2) 229
21 Summary of mean scores and test statistics for individual MPSS items (Study 2) 230
22 Study 3 Participant Information Sheet 231
23 Study 3 Consent Form 235
24 Summary of test statistics for between groups baseline comparisons (Study 3; DNC+ST vs. ST) 236
Supplementary Material: Published Papers 237

List of Tables and Figures

Study 1 Tables

Table 4.1: Summary of Study 1 Procedures and Measures..... 69
Table 4.2: Study 1 Participant Characteristics..... 71
Table 4.3: Mean ratings and summary of ANOVA analysis of urges and withdrawal symptoms pre and post cue-exposure in abstainers..... 74
Table 4.4: Mean ratings and summary of ANOVA analysis of urges and withdrawal symptoms pre and post cue-exposure (whole sample). 74
Table 4.5: Summary of ANOVA analysis for urges and withdrawal ratings over 1 hour in abstainers..... 77
Table 4.6: Summary of ANOVA analysis for urges and withdrawal ratings over 1 hour (whole sample) 78
Table 4.7: Summary of ANOVA analysis on the acute effects of products on urges and withdrawal ratings in abstainers. 87
Table 4.8: Mean area under the curve (AUC), reduction maximum (Rmax), and time to Rmax (Tmax) values and summary test statistics for acute urges and withdrawal ratings in abstainers..... 88
Table 4.9: Summary of ANOVA analysis on the acute effects of products on urges and withdrawal ratings (whole sample). 91
Table 4.10: Mean area under the curve (AUC), reduction maximum (Rmax), and time to Rmax (Tmax) values and summary test statistics for acute urges and withdrawal ratings (whole sample). 92
Table 4.11: Mean scores and summary test statistics for composite MPSS and urges to smoke..... 94
Table 4.12: Summary of ANOVA analysis on baseline urge and withdrawal ratings in the morning and evening. 97
Table 4.13: Mean product ratings and preferences. 99
Table 4.14: Open responses to questions “What did you like most/least about the product you used today?” 100

Study 2 Tables:

Table 5.1: Study 2 Participants Characteristics. 109
Table 5.2: Mean ratings and summary of ANOVA analysis of urges and withdrawal symptoms pre and post cue-exposure in abstainers..... 110
Table 5.3: Mean ratings and summary of ANOVA analysis of urges and withdrawal symptoms pre and post cue-exposure (whole sample). 112
Table 5.4: Summary of ANOVA analysis for urges and withdrawal ratings over 1 hour in abstainers..... 115
Table 5.5: Summary of ANOVA analysis for urges and withdrawal ratings over 1 hour (whole sample). 116
Table 5.6: Summary of ANOVA analysis on the acute effects of products on urges and withdrawal ratings in abstainers. 125

Table 5.7: Mean area under the curve (AUC), reduction maximum (Rmax), and time to Rmax (Tmax) values and summary test statistics for acute urges and withdrawal ratings in abstainers..... 126
Table 5.8: Summary of ANOVA analysis on the acute effects of products on urges and withdrawal ratings in abstainers (whole sample)..... 129
Table 5.9: Mean area under the curve (AUC), reduction maximum (Rmax), and time to Rmax (Tmax) values and summary test statistics for acute urges and withdrawal ratings (whole sample). 130
Table 5.10: Mean scores and summary test statistics for composite MPSS and urges to smoke..... 132
Table 5.11: Summary of ANOVA analysis on baseline urge and withdrawal ratings in the morning and evening. 135
Table 5.12: Mean product ratings and preferences. 136
Table 5.13: Open responses to questions "What did you like most/least about the product you used today?" 138
Table 5.14: Participant characteristics of 'abstainer' samples in Studies 1 and 2. 140

Study 3 Tables:

Table 6.1: Summary of Study 3 Procedures. 147
Table 6.2: Study 3 Participant Characteristics 152
Table 6.3: Abstinence rates within high and low GN-SBQ sub-groups. 153
Table 6.4: Abstinence rates within high and low SM-MFS sub-groups. 154
Table 6.5: Summary of logistic regression analyses for GN-SBQ and SM-MFS as predictors of abstinence..... 154

Study 1 Figures

Figure 4.1: The Halo Electronic Cigarette 67
Figure 4.2: Mean urge to smoke ratings over 1 hour 79
Figure 4.3: Mean irritability ratings over 1 hour 80
Figure 4.4: Mean restlessness ratings over 1 hour..... 81
Figure 4.5 Mean ratings of difficulty concentrating over 1 hour 82
Figure 4.6: Mean composite withdrawal ratings over 1 hour 83
Figure 4.7: Acute effects of products on urge to smoke in abstainers 86
Figure 4.8: Acute effects of products on composite withdrawal in abstainers..... 89
Figure 4.9: Acute effects of products on urge to smoke (whole sample) 90
Figure 4.10: Acute effects of products on composite withdrawal (whole sample) 93
Figure 4.11: Mean baseline ratings of urge to smoke and composite withdrawal in the morning and evening 96

Study 2 Figures

Figure 5.1: Mean urge to smoke ratings over 1 hour 117

Figure 5.2: Mean irritability ratings over 1 hour 118
Figure 5.3: Mean restlessness ratings over 1 hour..... 119
Figure 5.4: Mean ratings of difficulty concentrating over 1 hour 120
Figure 5.5: Mean composite withdrawal ratings over 1 hour..... 121
Figure 5.6: Acute effects of products on urge to smoke in abstainers 124
Figure 5.7: Acute effects of products on composite withdrawal in abstainers..... 127
Figure 5.8: Acute effects of products on urge to smoke (whole sample) 128
Figure 5.9: Acute effects of products on composite withdrawal (whole sample) 131
F**igure 5.10:** Mean baseline ratings of urge to smoke and composite withdrawal in the morning and evening..... 134
Figure 5.11: Mean ratings of urge to smoke for EC in Studies 1 and 2 in abstainers..... 141

Study 3 Figures

Figure 6.1: Study 3 Participant flow diagram 151

List of abbreviations

ANOVA: Analysis Of Variance

AUC: Area Under the Curve

BPD: Balanced Placebo Design

CO: Carbon monoxide

CPD: Cigarettes Per Day

DA: Dopamine

Df: Degrees of Freedom

DNC: De-nicotinised Cigarette

EC: Electronic Cigarette

FTND: Fagerstrom Test of Nicotine Dependence

GN-SBQ: Glover-Nilsson Smoking Behavioural Questionnaire

ISO: International Organisation for Standardisation

IV: Intravenous

M: Mean

MAO: Monoamine Oxidase

MNWS: Minnesota Nicotine Withdrawal Scale

MPSS: Mood and Physical Symptoms Scale

NHS-SSS: National Health Service Stop Smoking Service

NRT: Nicotine Replacement Therapy

PC: Post Cue

QSU: Questionnaire of Smoking Urges

RCT: Randomised Controlled Trial

Rmax: Reduction Maximum

SB: Stress Ball

SD: Standard Deviation

SM-MFS: Sensorimotor Motives For Smoking

SMR: Sensorimotor Replacement

ST: Standard Treatment

Tmax: Time to Maximum reduction

TQD: Target Quit Day

1 Introduction

Smoking still remains one of the leading causes of mortality in England, with an estimated one in five deaths in those aged over 35 attributed to it (The Health and Social Care Information Centre, 2013). Prevalence has steadily reduced over the last 30 years with 39% of adults reporting smoking in 1980 to 20% in 2010. This is mostly due to a rise in never or occasional smokers (from 43% to 55%), whilst the proportion of ex-smokers increased by only 2% (The Health and Social Care Information Centre, 2013). Helping smokers to quit and achieve abstinence long-term still remains a significant challenge.

Nicotine has long been identified as the fundamental component in tobacco addiction. Recognising the addictive nature of nicotine and the nicotine withdrawal syndrome which accompanies smoking cessation, led to the development of effective treatments for smokers. Nicotine Replacement Therapy (NRT) was introduced over 20 years ago on the assumption that if smokers were smoking primarily to obtain nicotine, replacing the source of nicotine via a clean and safe method would help lower the prevalence of smoking (Rose, 2006). It is well documented that NRT and other medications such as varenicline and bupropion can enhance people's chances of successfully quitting long-term (Stead et al., 2008), but their efficacy is limited. The quantity of nicotine delivered via NRT for example, is considerably less than from cigarettes and the speed of delivery is slower, meaning that NRT helps at best to moderate the intensity of urges to smoke and other withdrawal symptoms.

The NHS Stop Smoking Service (NHS-SSS) provides a combination of medication and weekly behavioural support that incorporates cognitive and behavioural techniques to help facilitate cessation, as well as encouraging correct and adequate medication use. Although the NHS-SSS is currently the most effective approach, with over 50% of service users setting a quit date abstinent at four weeks (The Health and Social Care Information Centre, 2012), there is still considerable room for improvement.

There is no denying the primacy of nicotine in the development and maintenance of tobacco addiction, but there is evidence to suggest that non-nicotine factors may also contribute, and that addressing these could help improve smoking cessation treatment (Rose, 2006). Many smokers attempting to quit miss the behaviour of smoking (e.g. holding the cigarette, puffing, inhaling/exhaling) and sensations that accompany it (e.g. smell/taste of smoke, throat 'scratch', and other airway sensations), yet there is little focus of these

sensorimotor factors in treatment. The nicotine inhalator is currently the only licensed smoking cessation medication which attempts to address these factors, but it provides only limited sensorimotor input. Providing an adequate replacement for the sensory and behavioural aspects of smoking may theoretically help aid cessation by alleviating urges to smoke and withdrawal acutely; extinguishing smokers' reactions to the cues/triggers associated with smoking; or by providing a concrete behavioural coping strategy during high-risk relapse situations.

This thesis will aim to answer a number of theoretical questions still outstanding in the sensorimotor literature, and provide further data on whether or not sensorimotor replacement (SMR) may have clinical utility. SMR will be investigated through the use of two products which provide at least some of the sensations of smoking, but contain no or negligible amounts nicotine: de-nicotinised cigarettes (DNCs) and nicotine-free electronic cigarettes (ECs). Briefly, DNCs are tobacco cigarettes which are smoked as per conventional cigarettes, but have an extremely low nicotine content (machine yield <0.1 mg nicotine), believed to have no central effects (Rose, 2006). ECs on the other hand, are tobacco-free battery powered devices, where with each puff, a visible vapour or mist is created which resembles smoke. They are comprised of a battery, atomizer and cartridge containing propylene glycol/glycerine and other flavourings, and can be purchased with or without nicotine.

The thesis will begin with the theoretical background of how sensorimotor factors may contribute to tobacco dependence and what the implications of this are for treatment. Next, the literature in support of SMR will be reviewed. This includes a summary of early research which highlights the importance of sensorimotor factors, and the effects of SMR products (non-nicotine inhalators/aerosols, DNCs and ECs) on key outcomes of craving/urges to smoke[1], withdrawal alleviation and smoking cessation. Where applicable, the effect of SMR on other measures of reinforcement and user acceptability will be summarised. The current research undertaken will then be presented. Each study is reported separately (i.e. methods, results and discussion), followed by an overall discussion and considerations for future research.

[1] The terms 'urges to smoke' and 'craving' are used interchangeably throughout; there is little evidence that these terms differ semantically (see Tiffany & Wray, 2012).

2 Theoretical Background

The contribution of sensorimotor factors to the development and maintenance of tobacco addiction may be explained by an instrumental learning approach (Rose and Levin, 1991). At its most basic, this view identifies nicotine as a primary reinforcer, and sensorimotor stimuli as secondary or conditioned reinforcers. Nicotine acts as both a positive and negative reinforcer by stimulating the reward areas of the brain, and by providing escape from or avoidance of nicotine withdrawal symptoms, respectively. Sensorimotor stimuli reinforce smoking behaviour through their association with the pharmacological effects of nicotine. This happens through classical or 'Pavlovian' conditioning, whereby a previously neutral stimulus becomes rewarding if it is closely followed by a real reward. For example, the throat 'scratch' that smokers experience when smoke is inhaled after each puff is quickly followed by the rewarding effects of nicotine. Given many pairings of this over time, smokers come to like and expect this sensation (West and Hardy, 2006).

The mechanisms behind instrumental learning are widely believed to stem from the increase in the neurotransmitter dopamine (DA) in the reward circuitry of the brain, specifically the nucleus accumbens (West and Hardy, 2006). The increase in DA in this area has been noted as a key characteristic of drugs of dependence in animal models and accordingly, research suggests that the ability of nicotine to stimulate the DA projections to the nucleus accumbens is what gives nicotine its reinforcing properties (Balfour, 2004). Although nicotine, like other drugs of dependence, stimulates DA overflow in the nucleus accumbens, this alone may be over simplistic to explain the highly addictive nature of smoking. Firstly, unlike other psychostimulant drugs such as cocaine and amphetamine, nicotine does not have strong euphoriant effects, and the amount of DA overflow in the nucleus accumbens is relatively small compared to other drugs of dependence (Balfour, 2004). Indeed, smokers sometimes report not enjoying smoking, but still continue to do so. Secondly and on a related note, Balfour (2004), highlights that habitual smoking throughout the day can lead to concentrations of nicotine which desensitize neuronal nicotinic receptors and prevent further stimulation of DA overflow, yet smokers continue to smoke despite receiving no hedonic reward from nicotine. Of course, instrumental learning also postulates that nicotine is a negative reinforcer, thus one probable explanation for this is that smokers are avoiding the unpleasant effects of nicotine withdrawal. Balfour's variation on the DA theory of reward attempts to provide an explanation as to why nicotine is highly addictive despite its weak euphoriant effects, and in doing so, suggests that conditioned

stimuli, namely sensorimotor factors, are important contributors to tobacco dependence (Balfour, 2004, Balfour, 2008).

This hypothesis is underpinned by a wealth of research utilising animal models. These studies typically use a self-administration paradigm, whereby animals learn to administer nicotine via an intravenous infusion, by performing a response such as lever pressing (Chaudhri et al., 2006). Early studies reported inconsistent results with regards to voluntary nicotine self-administration; it became apparent that in order to generate high and stable rates of responding for nicotine, a strict set of experimental parameters was required, suggesting that nicotine alone is a relatively weak reinforcer (Henningfield and Goldberg, 1983).

One such parameter is the pairing of nicotine with a non-pharmacological stimulus, which is now a common feature of animal nicotine self-administration models. In one of the pioneering investigations, Goldberg (1981), reported high rates of operant responding when a light was paired with nicotine delivery. The removal of the light cue subsequently reduced responding, despite the continued availability of nicotine. This provided some preliminary evidence that such stimuli could contribute to nicotine reinforcement.

Further research has supported the contribution of conditioned stimuli to various stages of nicotine reinforcement in animal models (Chaudhri et al., 2006). The acquisition of lever pressing for nicotine in rats is facilitated by the paring of nicotine delivery with a visual stimulus (a light cue), compared to when either are presented alone (Caggiula et al., 2002). In addition, given this pairing, lever pressing can be maintained with a wide range of nicotine doses; on the other hand, when there is no stimulus pairing, sustained and stable responding is only maintained with higher doses of nicotine (Chaudhri et al., 2006). Finally, during extinction procedures where nicotine delivery is replaced with saline, if these paired stimuli are present, lever pressing is reduced but continues at a stable rate. When the stimulus is then removed, lever pressing reduces further, until it is finally extinguished. Lever pressing can then be reinstated by priming with nicotine, or notably, by the presentation of the previously paired stimulus (Caggiula et al., 2001). It should be noted, however, that additional parameters are required to facilitate these responses, such as diet restriction and experimental testing during the dark phase of a rat's light/dark cycle.

Together, this body of research demonstrates that (i) nicotine is a relatively weak primary reinforcer on its own (unless administered at high doses); (ii) the pairing of a non-pharmacological stimulus with nicotine can enhance responding; and (iii) resistance to

extinction results mostly from the presence of these paired stimuli, suggesting a role for non-nicotine factors in tobacco dependence.

2.1 Differential drug effects within the nucleus accumbens

Balfour's theory makes a distinction between DA overflow in two subdivisions of the nucleus accumbens: the medial shell and the core. Importantly, both are hypothesised to have complementary roles in tobacco addiction. The increase in DA in the medial shell is proposed to give *behaviours* associated with this DA overflow hedonic properties. It is important to note that it is the behaviour (smoking) not the outcome (pharmacological effect of nicotine) that then becomes enjoyable. This enables the behaviour of smoking, as well as other stimuli associated with the delivery of nicotine, to acquire reinforcing properties and smoking is then more likely to be repeated. On the other hand, the increase in DA in the core of the accumbens is presumed to give cues which are associated with the delivery of nicotine 'incentive salience', which then facilitates stimulus-response behaviour. Thus DA in the core is hypothesised to play a significant role in promoting the effects of conditioned reinforcers and stimuli on smoking behaviour. Furthermore, there is sensitisation of this effect of nicotine on DA levels in the core, and it is thought that this is what leads to the transition from normal use to addiction. The theory therefore explicitly suggests a role for sensory and behavioural factors and other smoking-related cues, in the development and maintenance of tobacco addiction.

As noted previously, the accumulation of nicotine throughout the day can desensitise nicotinic receptors, preventing the release of subsequent DA. Balfour's theory suggests that smoking behaviour still continues under these circumstances because of conditioned stimuli, as well as the motivation to avoid unpleasant withdrawal symptoms. Importantly, when smokers do experience periods of abstinence, such as at work or when they sleep, these receptors are no longer desensitised so that when a cigarette is smoked, DA overflow is stimulated and the associations between sensorimotor factors or other stimuli and DA overflow are once again strengthened (Balfour, 2004).

One of the main concerns of this theory relates to the fact that much of the research in this area utilises animal models with intravenous (IV) nicotine, making the findings less generalisable to the effects of inhaled tobacco smoke in humans (Balfour, 2004). Additionally, the quantities of nicotine injected in animal studies often leads to significantly

higher venous levels compared to when a cigarette is smoked, again limiting generalisations. There is however some support for the use of animal models; research suggests that there are similarities between IV nicotine and the nicotine inhaled in each bolus of tobacco smoke; that increases in DA in the nucleus accumbens do occur following inhalation of tobacco smoke in human brains; and that this mediates the reinforcing properties of nicotine administered via tobacco smoke (Balfour, 2004). Thus concerns regarding the generalisation from animal models to humans may be mitigated. A more pressing concern with the hypothesis is that strong evidence in support of the role of excess DA in the core specifically, is currently lacking (Balfour, 2008).

The theoretical account outlined above proposes that sensorimotor factors contribute to tobacco dependence via their associations with nicotine-related DA overflow, whereby these sensorimotor factors themselves are able to acquire reinforcing properties. Balfour suggests this to be of importance during times when blood nicotine is raised and DA is no longer released. In addition, other cues related to nicotine delivery may trigger smoking behaviour. Although acknowledged in the model, the relative contribution of negative reinforcement (i.e. the avoidance of nicotine withdrawal symptoms) in the maintenance of smoking is not entirely clear, and the hypothesis places more emphasis on the role of positive reinforcement of conditioned stimuli.

In a distinct but related vein, Baker *et al* (2006), have stressed the importance of negative reinforcement in tobacco dependence, in that avoidance of withdrawal symptoms is the main motivator behind continued drug use. This view still conforms to an instrumental learning account, and suggests a role for sensorimotor factors by proposing that cessation of smoking results in a second form of withdrawal, termed 'behavioural' withdrawal.

2.2 **Behavioural Withdrawal**

The model of behavioural withdrawal asserts that many dependent drug users continue to use drugs in order to regulate affect. Thus when blood nicotine levels fall and smokers experience withdrawal symptoms, and in particular negative affect and urges, smoking a cigarette helps them to cope with or regulate these symptoms (termed 'symptom-regulation'). This, as with the conventional instrumental learning account, occurs because of a learned association between drug use and symptom relief (Baker et al., 2006). It is important to note that it is the self-administration ritual or behaviour (i.e. smoking) which

allows smokers to cope with or regulate their negative affect and/or urges. It is therefore proposed that when smokers quit they will experience both pharmacological withdrawal as well as behavioural withdrawal (i.e. the absence of the self-administration ritual). As a result, there will be a disruption in symptom-regulation, and withdrawal symptoms will be exacerbated because individuals cannot revert to their usual means of coping, (i.e. smoking a cigarette). Moreover, symptoms such as negative affect and craving, may be triggered months later by stress or negative life events and smoking-related cues (e.g. sight or smell of cigarettes, environments previously associated with smoking), respectively. Each time this occurs, it is proposed that individuals will experience behavioural withdrawal as they cannot perform the self-administration ritual to regulate these symptoms. Baker *et al* argue that withdrawal should be seen as 'symptom-dysregulation', and it is proposed that symptom-dysregulation will continue until the value of smoking-related cues extinguish, or the individual finds an effective coping strategy which replaces smoking (Baker et al., 2006). In this way, the model can help to explain why ex-smokers may still report strong craving or negative affect months after cessation, after pharmacological withdrawal (which typically lasts 2-4 weeks post-cessation) has dissipated.

Symptom-dysregulation is suggested to be a cause of both pharmacological and behavioural withdrawal. However, behavioural withdrawal is hypothesised to account for prolonged symptom-dysregulation, volatility and variability of symptoms as well as exacerbated reactions to environmental events or smoking-related cues (Baker et al., 2006). It is also hypothesised that pharmacological nicotine withdrawal symptoms should be eased even if the self-administration ritual is performed without delivery of nicotine (e.g. with DNCs). Equally, if nicotine is administered without the usual ritual, such as in the case of NRT, withdrawal symptoms will not be fully alleviated and this may help to explain why the success of NRT is limited.

This view is consistent with Balfour's notion that it is the behaviour which is reinforced rather than the effect of the drug, and proposes that both nicotine and non-nicotine factors are important in tobacco dependence. It also recognises the role of smoking-related cues, which may trigger smoking behaviour. Underlying both of these accounts is of course the assumption that an association has been formed, via classical conditioning, between the behaviour/sensations of smoking and other stimuli, and the pharmacological effects of nicotine in the first place.

2.3 Other non-nicotine factors

2.3.1 Tobacco smoke constituents

Sensorimotor factors are not the sole non-nicotine factors which could be contributing to tobacco dependence. Rose (2006), summarised the evidence with respect to tobacco smoke constituents which could have direct pharmacological effects on the brain or could be potentiating the reinforcing effects of nicotine. Acetaldehyde for example, may increase the reinforcing effects of nicotine, and ammonia may increase the absorption of nicotine. Menthol is thought to interact with nicotine to control its perception (i.e. reduces irritation of nicotine), delivery and uptake, as it is believed to increase permeability of membranes. Tobacco smoke is also believed to contain monoamine oxidase (MAO) inhibitors which may have direct anti-depressant effects, and/or may increase the lifetime of DA neurotransmitters released by nicotine; whatever the mechanism may be, research points to some role for MAO inhibitors in smoking cessation treatment, withdrawal symptoms, and nicotine self-administration in animal models (Rose, 2006).

2.3.2 Expectancy theory

So far it has been argued that sensorimotor stimuli become reinforcing due to a classical conditioning process. However, some of these reinforcing effects may be in part explained by expectancy theory, a theory often applied to a wide range of placebo effects. This is of particular relevance for DNCs as they are still smoked as per conventional cigarettes, but the nicotine has been removed, though the same principles could be applied to ECs.

Expectancy theory asserts that DNCs may alleviate urges to smoke and withdrawal, because the smoker has the belief or expectation that they are smoking a nicotine cigarette (known as the stimulus or dose expectancy) together with the expectation that nicotine alleviates urges to smoke (known as the response expectancy; Perkins et al., 2003). Both classical conditioning and expectancy theory have been put forward as mechanisms for placebo effects in general, but it is likely that both mechanisms play a role (Perkins et al., 2003, Stewart-Williams and Podd, 2004). In an attempt to clarify the mechanisms involved, Stewart-Williams and Podd (2004), concluded that both classical conditioning and verbal information can be sources of learning for placebo effects. Furthermore, when the source is verbal information, placebo effects are mediated only through conscious expectations. For

classical conditioning however, placebo effects may be mediated by both conscious expectation or automatic, non-cognitive processes. They further hypothesise that in the case of pharmacological placebo effects, automatic processes and conscious expectations may have an additive effect, but that non-pharmacological placebo effects are mediated solely through expectation.

Even if the sensorimotor stimulation provided by DNCs acted as conditioned reinforcers, it still remains that the expectation of receiving nicotine could contribute to their potential reinforcing efficacy. In support of expectancy theory, a number of studies have directly explored the relationship between nicotine dose and nicotine dose expectancies on smoking related outcomes. To do this, studies have employed the balanced placebo design (BPD; Rohsenow and Marlatt, 1981), in which participants are randomised to receive nicotine or placebo cigarettes (DNCs), with half of the participants in each group told they have received nicotine, and the other half told they have received a placebo.

Research in this area has found that when participants believe they are smoking nicotine, regardless of nicotine content, they show reduced urges to smoke (Perkins et al., 2008, Kelemen and Kaighobadi, 2007), increased satisfaction/liking and other subjective effects such as improved concentration, reduced irritability, feeling more calm etc. (Kelemen and Kaighobadi, 2007, Perkins et al., 2004, Perkins et al., 2008, Juliano et al., 2011), and less mood disturbance (Juliano et al., 2011). No effects of dose expectancies have been reported on measures of withdrawal symptoms however (Perkins et al., 2004, Perkins et al., 2008, Juliano and Brandon, 2002). Latency to first puff has also been found to be shorter in those told they are smoking nicotine vs. placebo, though the total number of puffs taken did not differ (Perkins et al., 2008). In one study (Darredeau et al., 2013), nicotine expectancy showed less consistent effects, whereby those participants told they were smoking nicotine vs. placebo reported greater intention to smoke (Factor 1 of the Questionnaire of Smoking Urges [QSU]; Tiffany and Drobes, 1991), but there was no effect evident on withdrawal relief (Factor 2, QSU). Participants did however work harder on the progressive ratio task to earn more puffs when told nicotine vs. placebo, regardless of actual nicotine content.

Significant interactions between nicotine expectancy and actual nicotine intake were also reported. Here, the expectation of nicotine reduced craving in those smoking DNCs but no effects of dose expectancies were found in those smoking nicotine cigarettes (Juliano et al., 2011, Juliano and Brandon, 2002). The number of puffs earned on a progressive ratio task was greater in those told they were smoking nicotine in the DNC group, but no differences

were found in the nicotine cigarette group (Perkins et al., 2004). In contrast however, Juliano *et al* (2011), found that the total number of puffs taken in the nicotine group was greater for those told they were smoking nicotine; amongst those smoking DNCs, those who were told nicotine took less puffs than those told they were smoking placebos.

One limitation of the BPD is that results can only be interpreted meaningfully if participants have successfully been deceived. There is mixed evidence as to which condition (given nicotine/told placebo or given placebo/told nicotine) is more problematic in this respect and differences may lie in the procedural aspects of the studies and measures used to assess disbelief (Juliano et al., 2011). Previous research has attempted to counteract this problem by assessing participants' level of belief/disbelief, and excluding the data from those participants whose beliefs were not consistent with the condition they were assigned to.

Aside from some inconsistencies, there is some evidence to suggest that any reinforcing effects of DNCs may be boosted by the expectation of nicotine delivery.

2.4 Treatment implications

Given the probable role of sensorimotor factors as secondary reinforcers in tobacco dependence, it stands to reason that treatments for smoking cessation may be improved if these reinforcers are also addressed, alongside the primary reinforcer, nicotine. This could be implemented by providing a substitute which mimics the sensory and behavioural aspects of smoking, i.e. a sensorimotor replacement (SMR) product, to help moderate urges to smoke and withdrawal symptoms during abstinence.

In theory, SMR could also aid cessation via extinction of the previously learnt associations between nicotine and the behaviours and sensations of smoking; and/or by extinguishing other cues associated with smoking, which also result from classical conditioning processes. Extinguishing smoking-related cues has been tried and tested with cue-exposure therapy but with limited success (Ferguson and Shiffman, 2009). The efficacy of cue-exposure therapy may in part be limited by 'renewal' effects, where a conditioned response returns after extinction, because of a change in context to the one where extinction originally took place. Moreover, there is evidence to suggest that removing the reward (i.e. nicotine), whilst still engaging in the behaviour (smoking), is a more effective approach to extinguish

learnt behaviours (Conklin and Tiffany, 2002). SMR could therefore enhance extinction by (i) allowing unreinforced smoking behaviour (e.g. with DNCs) and (ii) enabling this to occur in a variety of contexts, therefore mitigating renewal effects.

SMR could potentially also provide a concrete behavioural tool or coping strategy during high-risk situations in which a lapse back to smoking may be likely. This may not necessarily directly alleviate any urge to smoke, but may help the individual to cope with and manage the situation.

There is of course a risk that SMR could itself be a trigger for smoking; indeed Balfour highlights the fact that sensorimotor cues could be just that- cues or conditioned stimuli which enhance responding for the primary reinforcer (Balfour, 2004). However, these stimuli are also hypothesised to be conditioned reinforcers, which by definition, become rewarding in themselves. In the context of treatment mechanisms then, the central hypothesis is that SMR may acutely alleviate urges to smoke and potentially also other nicotine withdrawal symptoms.

3 Literature review

The literature review is presented in two main sections. The first will examine the evidence that the sensorimotor aspects of smoking have some significance in tobacco dependence, and builds a foundation for the SMR hypothesis. The second will review the evidence in support of the SMR hypothesis, i.e. the impact of SMR on key outcomes of craving/urges to smoke, withdrawal and smoking cessation.

3.1 How important are the sensory effects of smoking?

The majority of research on sensorimotor factors originates from Dr. Jed Rose and colleagues, though the contribution of sensory reward to tobacco addiction was recognised prior to this (Russell, 1971, Russell et al., 1974). In an early study, 60% of smokers reported at least a little enjoyment from the sensory effects of cigarettes (i.e. feeling of smoke in the throat and chest) and 10% of smokers liked this 'very much' (Rose, 1988). This observation led to further investigations regarding the independent effects of nicotine and tobacco smoke, and specifically the sensorimotor effects, via a number of different research paradigms. The findings of these studies are discussed further below.

3.1.1 Depth of smoke inhalation

Firstly, in a study where the depth of inhalation of smoke was controlled, shallow inhalations were found to be just as satisfying as deeper inhalations (Rose, 1988). Since deeper inhalations of smoke were assumed to provide more of a pharmacological effect of nicotine, these findings loosely suggested that the sensations elicited by cigarette smoke could be as satisfying as the central effects of nicotine.

3.1.2 **Refined smoke**

Rose and colleagues carried out a series of experiments with a refined smoke aerosol. This device was created by firstly collecting smoke condensate from conventional cigarettes, and then heating in a cigarette-sized tube to generate an aerosol similar to conventional cigarette smoke. Using smoke condensate and heating only moderately, greatly reduced or eliminated many toxic constituents found in tobacco smoke (e.g. carbon monoxide [CO], formaldehyde, ammonia) as well as nicotine (Rose and Behm, 1987). The aim of the refined smoke aerosol was to reduce the harm and nicotine associated with cigarette smoke, much like low nicotine and tar cigarettes, but importantly, without compromising the desired sensory effects of cigarette smoke. Although low nicotine and tar cigarettes were marketed as safer or healthier cigarettes, these cigarettes are often associated with compensatory smoking (i.e. increase in number of puffs, inhaling more deeply, taking larger puffs), thus enabling smokers to maintain high levels of nicotine, tar and CO. They have also been rated low on satisfaction and flavour (Rose and Behm, 1987). Rose and colleagues hypothesised that low nicotine cigarettes could be satisfying if the sensations they elicit were perceived as strong, and aimed to test this with the refined smoke aerosol.

In the first experiment, the refined smoke aerosol was rated higher on liking, similarity to own brand, harshness and strength compared to a conventional low nicotine and tar cigarette, even though nicotine content was lower in the refined smoke aerosol (Rose and Behm, 1987). In the second experiment, these findings were extended by showing that the relatively low level of nicotine afforded by the refined smoke aerosol could be satisfying over repeated use and following overnight abstinence. The aerosol was compared to a conventional low nicotine cigarette with a similar nicotine level. The refined smoke was rated higher on satisfaction, sensory effects and was able to reduce craving to a greater extent than the conventional cigarette (Rose and Behm, 1987). Since both the conventional cigarette and the refined smoke aerosol delivered comparable nicotine levels, it was proposed that the aerosol was more satisfactory because of the stronger sensations it provided.

In further research, the strength of the aerosol in terms of sensory effects was found to be comparable to conventional high nicotine cigarettes, as was the reduction in desire/craving for a cigarette, despite the conventional cigarette containing 20 times more nicotine (Behm et al., 1990). Since the aerosol was rated significantly higher on ‘liking’ compared to an unlit control cigarette, it was argued that this reduction in desire for a cigarette was not simply

due to the aerosol being perceived as aversive. In another experiment, Rose *et al* (1993), investigated ad-libitum smoking behaviour over 3 hours, of refined smoke compared to a conventional high nicotine cigarette and a low nicotine cigarette. As expected, the low nicotine smoke led to compensatory smoking, whereas refined and high nicotine smoke did not, and were puffed and inhaled in a similar way. These findings seemed to suggest that smokers were regulating their smoke intake to achieve satisfying sensory effects rather than regulating nicotine levels. Craving reduction with refined smoke was comparable to the high nicotine cigarette, but greater versus the low nicotine condition. Despite this, results should be taken with caution as differences between refined smoke and low nicotine were marginal at the end of the 3 hour session. In addition, the low nicotine cigarette was in fact rated as more satisfying than refined smoke.

Taken together, these studies suggest that refined smoke, despite containing minimal amounts of nicotine, could be satisfying and reduce craving acutely and importantly, without the need for compensatory smoking. Although hypothesised to be because of the strong sensory effects provided by the refined smoke, the sensory ratings reported in the last experiment (Rose et al., 1993) may somewhat negate this hypothesis. With the exception of strength ratings in the windpipe, all other sensory ratings (perceived strength on tongue, throat, nose and chest) were comparable across conditions; thus despite somewhat better craving alleviation with refined smoke vs. the low nicotine cigarette, the sensory effects were rated similarly between the two. Moreover, the low nicotine cigarette was rated as more satisfying. This may of course be a result of the compensatory smoking that occurred in the low nicotine cigarette condition, but this is not entirely clear.

3.1.3 **Sensory blockade**

Further support for sensorimotor factors in smoking has emerged from experiments where the sensory effects of cigarette smoke have been blocked by anaesthetising the upper and lower respiratory tract. This line of research aimed to show that if nicotine intake was the sole motivation for smoking, removing the sensations from cigarette smoke should not greatly impact upon a smoker's desire for a cigarette or the enjoyment/satisfaction gained from smoking.

In the first experiment, craving (measured before smoking, but after anaesthetisation) reduced linearly as the area of partial anaesthesia increased (Rose et al., 1984). For

example, craving was significantly higher when only the mouth was anaesthetised compared to when the mouth and the upper and lower airways were anaesthetised. Craving reduction (taking into account pre-smoking craving), was not significantly affected by anaesthetisation. Given the reduction in craving via the anaesthetisation procedure itself, the insignificant findings may be a result of floor effects. Desire for a cigarette was reduced by anaesthetisation only for the first few puffs; the effect diminished by the end of the smoking periods. This seems to provide little support for the role of sensory factors, but the ratings of cigarette puffs suggest the extent of sensory blockade may have been insufficient. Ratings of harshness and strength of puffs were not affected by anaesthesia and participants reported feeling the smoke in their chest. It is possible that this un-anaesthetised area may have been enough to allow them to discriminate how strong and harsh the puffs were, or alternatively as puff volume was not controlled, participants may have taken larger puffs and/or inhaled more to gain the same sensory effect (Rose et al., 1984); the findings of the next experiment support the former explanation.

The second experiment (Rose et al., 1985) reported significantly less reduction in craving following smoking after anaesthetisation compared to saline (control condition). This effect remained even when pre-smoking craving ratings were taken into account. Sensory blockade also reduced the desirability of puffs, but had no effect on subsequent ad-libitum smoking behaviour (though the anaesthetic had mostly dissipated by this stage). As before, craving measured before smoking but after anaesthetisation, was reduced by anaesthetisation and there were no differences in ratings of strength and harshness between the two conditions. Since smoking topography was controlled in this study unlike in the previous one, it is likely that this was due to incomplete sensory blockade of the lower respiratory tract.

In addition to the experiments above, Perkins *et al* (2001) and Baldinger *et al* (1995c) examined the effect of blocking visual and olfactory cues on ratings of cigarettes, and subsequent smoking behaviour. Baldinger *et al* (1995c), reported that blocking olfactory cues reduced enjoyment and taste of cigarettes and average puff volume, but did not impact upon craving or ratings of strength. In the first experiment by Perkins *et al* (2001), blockade of both visual and olfactory cues reduced hedonic ratings of puffs (ratings of 'like puff' and 'satisfaction'), similarity to own brand, and the amount that people were willing to pay for another cigarette, but overall ratings of strength of cigarettes did not differ between the sensory blockade and no blockade conditions. The number of puffs and CO boost in the subsequent ad-libitum smoking session was also reduced by sensory blockade.

The second experiment confirmed that these effects were due to the blockade of olfactory rather than visual cues.

It could of course be argued that the procedures used to block sensations (nose clips, goggles, anaesthetic solutions etc.) contribute to reduced satisfaction, in that participants may have felt uncomfortable in these conditions. It was clear that anaesthetisation procedures for example had an impact on subjective craving ratings before smoking even took place (Rose et al., 1984, Rose et al., 1985). To control for this, during the no blockade condition in the Perkins *et al* (2001) study, participants still wore goggles that did not obscure vision (i.e. they were clear) and nose clips positioned in a way which did not block the nostrils and as such would not obscure olfactory cues. Additionally, to examine whether sensory blockade procedures had any non-specific effects, participants also rated classical music, with and without visual and olfactory blockade. No main effects of condition were reported on ratings of music, suggesting any potential discomfort from these procedures did not contribute to the findings (Perkins et al., 2001).

The findings of these experiments suggest that sensory blockade may impact upon the hedonic properties of smoking, but perhaps not on the actual sensations of smoking. As noted previously, this is likely due to inadequate sensory blockade procedures. There were mixed results on the effect of sensory blockade on craving; it is not unrealistic to expect little difference in craving however, especially where participants were smoking nicotine cigarettes in both sensory blockade or no blockade conditions. Instead, this research paradigm lends some support for the *positive* reinforcing effects of sensory factors, whereby even partial sensory blockade may attenuate smoking satisfaction/enjoyment.

3.1.4 **Intravenous (IV) nicotine administration**

The distinction between nicotine and sensory effects has also been highlighted with procedures where nicotine has been delivered independently from tobacco smoke. Since conventional NRT delivers smaller amounts of nicotine at a much slower rate than cigarettes, Rose and colleagues used a procedure whereby nicotine was administered intravenously and importantly, in a similar way to the puff-by-puff bolus delivery of cigarette smoke (Westman et al., 1996b).

Research using such procedures showed that DNCs, in combination with saline or IV nicotine, provided greater immediate relief from craving compared to conditions where IV

nicotine/saline was presented without smoking (Rose et al., 2000, Westman et al., 1996b). Both of these studies however reported no differences between conditions on the Shiffman-Jarvik craving measure (Shiffman and Jarvik, 1976). One study did report significantly less craving on this measure following administration of DNCs with saline vs. saline alone, but equivalent craving relief between DNCs and saline vs. IV nicotine alone (Rose et al., 2003). Another study found greater immediate craving relief and craving reduction measured by the Shiffman-Jarvik questionnaire, in conditions where IV nicotine/saline were presented alongside de-nicotinised smoke vs. puffs of air, or so called 'sham' smoking (Rose et al., 2010).

Other subjective effects such as satisfaction and reward were also noted to be greater with de-nicotinised smoke vs. IV nicotine/saline conditions (Rose et al., 2000), and DNCs were able to satiate smokers to a greater extent than IV nicotine, indicating that satiation was more dependent on the delivery of smoke and sensory effects than nicotine itself (Rose et al., 2003, Rose et al., 2010). De-nicotinised smoke was also preferred over IV nicotine in a concurrent choice paradigm by most participants (Rose et al., 2010).

This line of research also demonstrates that when IV nicotine is combined with DNCs, many of the effects of conventional cigarettes can be replicated, such as craving and withdrawal reduction, satisfaction, enjoyment, reward and satiation (Rose et al., 2000, Rose et al., 2003, Westman et al., 1996b). In one study, the combination of IV nicotine with DNCs reduced craving to a greater extent than either alone (Rose et al., 2010). These studies have however typically assessed the effects of IV nicotine and DNCs over relatively short periods of time, and given longer periods of abstinence from smoking, DNCs may become less rewarding and satiating, and nicotine delivery more so.

Although there is some support here for the role of sensorimotor factors, the assumption that inhaled nicotine smoke should be more rewarding than nicotine administered without the sensorimotor aspects (i.e. intravenously), has not always been supported. Some studies discussed here (Rose et al., 2003), and previous work (Henningfield et al., 1985) have reported comparable effects of IV nicotine to inhaled (nicotine) smoke. For example, Henningfield *et al* reported that nicotine delivery via either of these routes resulted in similar increases in "drug liking" and decreases in craving. These comparable effects of IV nicotine to inhaled smoke could be explained by the IV nicotine administration procedure used, whereby extremely fast and large doses were delivered; in contrast, Rose and colleagues matched the dose of IV nicotine to that inhaled from conventional cigarettes by participants (Rose, 2006).

3.1.5 **Summary**

Through a variety of research paradigms, Rose and colleagues and other research groups have demonstrated that sensorimotor factors likely play some role in the maintenance of smoking and are considered important to smokers. The more recent research with IV nicotine and DNCs has been a particularly useful research paradigm, enabling the independent and combined effects of nicotine and sensory cues to be examined, and provides additional evidence in support of SMR.

3.2 **Sensorimotor Replacement Products**

As described previously, replacing the sensorimotor aspects of smoking may have potential in smoking cessation, especially if combined with current treatments so that both the primary and secondary reinforcers of smoking are addressed. This however is not a novel idea; the nicotine inhalator was designed for this purpose - to provide both nicotine and SMR. The inhalator however, needs to be puffed intensely over 20 minutes to provide an adequate level of nicotine (Russell et al., 1987), but compliance with its recommended use has been reported to be low (Hajek et al., 1999). Thus the limited nicotine delivery may cancel out any gains it provides in terms of behavioural replacement. Furthermore, it remains a poor sensory replacement as the airway sensations do not resemble cigarette effects closely enough.

Several other products which provide sensorimotor stimuli have been developed and evaluated. These are non-nicotine inhalators and aerosols, DNCs, and more recently ECs. The evidence in support of SMR with these products will be reviewed in turn. Given the theory that sensorimotor factors have become conditioned reinforcers in smoking, central to the SMR hypothesis is the alleviation of urges to smoke and withdrawal symptoms, which may translate to smoking cessation success. The review will therefore include data on craving/urges to smoke, withdrawal, and where available, smoking cessation outcomes. SMR could theoretically also aid cessation via extinction; evidence pertaining to this will also be considered. To further ascertain the clinical utility of these products, results from other subjective and objective measures will also be summarised.

3.2.1 **Non-nicotine inhalators and aerosols**

Rose and colleagues developed and evaluated several non-nicotine inhalators/aerosols using various substances designed to replace some of the airway sensory effects of smoking. Citric acid, ascorbic acid (Vitamin C), and black pepper extract were chosen because of their ability to mimic the throat 'scratch' of smoke inhalation (Westman et al., 1996a).

3.2.1.1 **Citric Acid**

Studies with citric acid have reported significantly reduced craving compared to controlled puffs of air (Rose and Hickman, 1987), to an unflavoured placebo aerosol (Levin et al., 1990, Behm et al., 1993), and effects comparable to a low nicotine and tar cigarette (Rose and Hickman, 1987). Any craving relief from citric acid may however be short-lived; Levin *et al* (1990) found significant craving reduction in the morning compared to the placebo group, but no differences between groups at later time points during 8 hours of abstinence. Additionally, Behm *et al* (1993) found a significant difference between the citric acid group and placebo controls on the first day of abstinence, but equivalent craving ratings from day 5 of abstinence. A similar pattern of results was also noted for negative affect ratings. In a smoking cessation trial comparing a combination of the citric acid inhaler with the nicotine patch (Westman et al., 1995), relief from craving on the quit day was significantly higher in the citric acid group vs. placebo inhaler; however, no differences were found on the Shiffman-Jarvik withdrawal questionnaire. Other effects noted with citric acid were that it was significantly more likable and similar to usual brand cigarettes compared to both the low nicotine and tar cigarette and air; strength and harshness ratings were comparable to the usual brand cigarette; and it was significantly more satisfying than air, and as satisfying as the low nicotine and tar cigarette (Rose and Hickman, 1987).

Two randomised, placebo-controlled studies investigated the efficacy of the citric acid inhaler on smoking cessation outcomes. In the first (Behm et al., 1993), there was a significantly higher point prevalence abstinence rate in the citric acid group (20% abstinent vs. 0% of controls; N= 74) at day 19 post-quit, as verified with CO readings, but only in a sub group of participants with high baseline CO readings. Overall abstinence rates were not reported. In the second trial (Westman et al., 1995) participants (N=100), were randomised

to use the citric acid inhaler or a lactose placebo inhaler for 10 weeks after quitting, in combination with a nicotine patch for the first 6 weeks. Ten-week CO-validated continuous abstinence rates were significantly higher in the citric acid group than placebo (19.5% vs. 6.8%, respectively). However, when adjusted for baseline differences in participant characteristics (number of cigarettes smoked per day, number of years smoked, baseline CO) this effect was marginal (p= 0.06). At the 24 week follow-up, virtually all participants had relapsed and abstinence rates were 0% and 5.1% in the citric acid and placebo groups, respectively.

In summary, the citric acid aerosol/inhaler may have some benefit in alleviating withdrawal, but effects are likely to be short lived. There is some suggestion that the respiratory sensations provided by citric acid may not have been strong enough. For example, 72% of participants stated they would have liked stronger throat sensations from the inhaler (Behm et al., 1993). This may be of particular importance as perception of strength from the inhaler was significantly correlated to satisfaction and liking (Levin et al., 1990), and to craving relief, help in refraining from smoking, and abstinence rates (Westman et al., 1995). Although the last trial was placebo controlled, use of the placebo inhaler may still have afforded some SMR, and at the very least a distraction from smoking. In fact, the positive association between perception of sensations and craving relief, help in refraining from smoking and even abstinence rates, were evident for both the citric acid inhaler and the placebo inhaler.

3.2.1.2 **Ascorbic Acid**

Two trials examined an ascorbic acid aerosol on craving relief and smoking cessation (Levin et al., 1993). In study 1, participants (N= 63), were randomised to use either the aerosol in combination with behavioural support, or behavioural support alone. In addition to this, all participants were asked to switch to low-nicotine cigarettes prior to quitting. CO-validated point prevalence abstinence rates were significantly higher in the ascorbic acid group at days 3 (~84% vs. ~60%, p= 0.05) and 22 post-cessation (~58% vs. ~22%, p< 0.01), with a trend evident at one week post-cessation (~73% vs. ~52%, p= 0.09). Abstinence rates by the 6 and 12 week follow ups fell below 20%, with no differences between groups.

With respects to craving, *greater* levels were reported one week post-cessation in those using the aerosol compared to controls using nothing. Three weeks post-cessation, this effect was marginal. Since only abstainers were included in the analysis of craving, it could be the case that participants with high craving in the control group relapsed, whereas the aerosol helped those participants remain abstinent despite high levels of craving (Levin et al., 1993). Alternatively, the sensations provided by the aerosol may have had the unwanted effect of triggering or cueing craving much like other conditioned stimuli. This may be unlikely though, as the aerosol was rated as moderately helpful in both alleviating craving immediately, and craving reduction over all, and in helping participants to remain abstinent. Furthermore, the difference in craving between groups, although significant, was small with a mean difference of 0.82 on a 7-point scale. There were no differences between groups on other withdrawal symptoms, apart from 'habit' withdrawal which was significantly higher in the experimental group, but only at 6-weeks post-quit.

In study 2, two different types of ascorbic acid aerosols were compared (fine vs. coarse particles). Since fine particles would provide more of a throat 'scratch', it was hypothesised that this aerosol would be more effective. There were, however, no significant differences in overall abstinence rates between the two groups or with craving ratings during aerosol use. Participants who had used the coarse aerosol did report a significant increase in craving one week after stopping use, whereas craving continued to reduce in the fine aerosol condition. The authors propose that this may have been a result of more effective extinction with the fine particle aerosol (Levin et al., 1993). Despite this, the initial hypothesis that the fine particle aerosol would be more effective due to stronger airway sensations specifically in the throat is difficult to accept or reject with these findings, as the throat sensations delivered from the coarse aerosol were also reported to be somewhat strong. The coarse aerosol therefore may not have been an adequate control device.

3.2.1.3 **Black Pepper Extract**

One study investigated the use of a black pepper inhalator on withdrawal symptoms and other subjective effects (Rose and Behm, 1994). Participants were randomly assigned to one of 3 inhalator conditions: black pepper, mint/menthol or no flavour (empty cartridge). Following 8 hours of abstinence, participants used their allocated inhalators ad-libitum for 3

hours at the study centre and completed subjective measures every hour. The black pepper inhalator decreased craving to a greater extent compared to both control conditions.

Additionally, compared to the placebo inhalator, negative affect and anxiety were also significantly reduced in the black pepper condition, but satisfaction ratings were comparable across all conditions. It could be argued that these results may be due to the aversive or irritating effects of black pepper, although this seems unlikely as participants reported liking the black pepper and menthol inhalators more than the placebo, and airway sensory effects were only rated stronger for the black pepper inhalator in the chest, with no differences between inhalators in other areas. Furthermore, as with previous studies with citric acid (Levin et al., 1990, Westman et al., 1995) craving reduction was found to be significantly correlated with sensations in the chest.

3.2.1.4 **Substitute/'dummy cigarettes'**

No further work has been conducted with the citric acid, ascorbic acid and black pepper inhalators/aerosols due to extensive regulatory requirements. With few consistent results available it is difficult to draw any conclusions as to whether these products could have any value in smoking cessation treatment. Various substitute or 'dummy cigarettes' are available to buy which claim to provide smokers with some SMR and are often marketed to smokers as a stop smoking aid. They typically resemble cigarettes (though some are more akin to the inhalator) and are often tobacco flavoured but cannot be smoked (e.g. the Crafe Away Smokeless Cigarette). Until recently, no trials have been conducted to substantiate these claims.

In the first study of its kind, the use of a tobacco flavoured nicotine-free inhalator in combination with pharmacological (nicotine patch plus bupropion) and behavioural treatment was conducted (Caponnetto et al., 2011a). One hundred and twenty smokers seeking treatment were randomised to use either the inhalator with standard treatment or standard treatment alone. The inhalator had no effect on abstinence rates at 4 or 24 weeks overall, though there was a significant effect of the inhalator in smokers who reported high levels of 'behavioural dependence' at baseline, a construct purported to be measured by the Glover-Nilsson Smoking Behavioural Questionnaire (GN-SBQ; Glover et al., 2005). For

example, at 4 weeks post-quit, 67% of participants were abstinent in the inhalator group compared to 35% of controls (p= 0.024). These findings were however post-hoc.

3.2.1.5 **Summary**

Taken together, these studies suggest that flavoured non-nicotine inhalators/aerosols used alone or in combination with standard treatment may be of some help in craving alleviation, but only in the short term. The utility of these products as a smoking cessation tool is difficult to ascertain as data are limited, and what is available is somewhat mixed. One study indicated that SMR may be of benefit for those who are 'behaviourally' dependent to smoking (Caponnetto et al., 2011a), but this finding requires replication.

3.2.2 **De-nicotinised cigarettes**

The development of a cigarette which contains negligible amounts of nicotine has allowed researchers to examine more clearly the role that nicotine and non-nicotine factors play in tobacco dependence. DNCs contain tobacco and other harmful constituents and are smoked as per conventional cigarettes. However, the nicotine content is extremely low (machine yield <0.1 mg nicotine), and is believed to have no central effects (Rose, 2006). DNCs differ from low-nicotine yield cigarettes (referred to as 'light' or 'ultra-light' cigarettes), which typically yield low levels of nicotine and tar. These cigarettes deliver diluted smoke, which when tested by machine, register low levels of nicotine. However, smokers can overcome this by intentionally blocking the ventilation holes in the filter, or by adjusting their smoking behaviour; thus these 'light' cigarettes can still deliver considerable amounts of nicotine (Robinson et al., 2000). This is possible because the nicotine content in these cigarettes is similar to high nicotine yield cigarettes (Kozlowski et al., 1998).

DNCs on the other hand contain tobacco where almost all the nicotine has been removed from the tobacco leaf. Thus the nicotine content is lowered as opposed to the yield, and cannot be altered by the design of the cigarette or through smoking behaviour. Even after rapid smoking of DNCs, no significant increase in nicotine plasma levels is evident (Dallery et al., 2003). Various methods exist for manufacturing DNCs, such as washing tobacco with an alkaline solution, or more recently with genetic modification/selective breeding. These cigarettes also still contain high levels of tar, and at similar levels to conventional cigarettes.

It has been suggested that this characteristic of DNCs may reduce the need for compensatory smoking commonly seen with 'light' cigarettes (Walker et al., 2009), possibly because reductions in tar are thought to compromise the sensory qualities of smoke (Hasenfratz et al., 1993). This resonates with the early work of Rose and colleagues who hypothesised that low nicotine cigarettes would be appealing providing adequate sensory effects (Rose and Behm, 1987) .

DNCs provide an almost complete behavioural and sensory replacement for cigarettes and deliver most of the chemicals found in conventional cigarettes, including those which may enhance the effects of nicotine. A considerable amount of literature exists regarding the effects of DNCs, particularly on craving/urges to smoke and withdrawal, but also on other subjective effects, smoking behaviour and other objective indicators of reinforcement. Recently, research has also focused on the efficacy of DNCs in smoking cessation.

3.2.2.1 **Acute effects on urges to smoke and withdrawal**

The majority of studies involving DNCs have examined their acute effects on urges to smoke/craving, following overnight abstinence, with measures varying from single item questions to more comprehensive questionnaires. Craving reduction in comparison to conventional nicotine cigarettes has, in a fair number of studies, been reported to be equivalent (Hasenfratz et al., 1993, Butschky et al., 1995, Rose et al., 1994, Baldinger et al., 1995c, Baldinger et al., 1995b, Westman et al., 1996b, Gross et al., 1997, Pickworth et al., 1999, Breland et al., 2002, Buchhalter et al., 2001, Dallery et al., 2003, Rose and Behm, 2004, Eid et al., 2005, Buchhalter et al., 2005, Juliano et al., 2006, Donny et al., 2007, Brody et al., 2009, Cobb et al., 2010, Perkins et al., 2010, Barrett, 2010, Attwood et al., 2009, Domino et al., 2013). In one report, which pooled data from 9 studies, DNC effects (craving reduction together with satisfaction ratings) were found to be weaker than conventional cigarettes (Brauer et al., 2001), though males and more dependent smokers reported more similar ratings between the two, suggesting gender and dependency as potential moderators of the rewards gained from DNCs. Type of study was also a significant predictor of reward variability, perhaps reflecting differences between studies in terms of participants' intentions to quit, ad-libitum vs. controlled smoking procedures, or the primary focus of the study.

In addition, other studies have also reported, as expected, greater urge relief with conventional cigarettes (Baldinger et al., 1995a, Rose et al., 2003, Pritchard et al., 1996, Hasenfratz et al., 1993, Hutchison et al., 2004, Juliano et al., 2011, Tidey et al., 2012). One recent study found greater craving relief scores with conventional cigarettes vs. DNCs on the first smoking bout only, and equivalent relief between the two cigarettes during the 3 subsequent bouts (MacQueen et al., 2012). In another recent study, craving during smoking reduced to a similar extent with DNCs in comparison to conventional cigarettes, with effects most pronounced during the first smoking bout compared to the second. When craving was examined over the course of 25 minutes however, craving reduction was greater with the nicotine cigarette (Lindsey et al., 2013). Hatsukami *et al* (2013a) reported a dose-response whereby there was no difference in craving reduction between DNCs and medium-nicotine cigarettes, but high-nicotine cigarettes generated better craving reduction than DNCs.

There is good evidence that DNCs can alleviate craving acutely compared to no intervention (Lane et al., 1995, Juliano et al., 2006, Perkins et al., 2010, Tidey et al., 2012) and control procedures such as puffing on an unlit cigarette or taking in puffs of air (Cobb et al., 2010, Rose et al., 2010).

A limited number of studies have compared the acute effects of DNCs to alternative methods of nicotine delivery. Buchhalter *et al* (2001) and Breland *et al* (2002) examined potentially reduced exposure products (PREPs), Accord and Eclipse - which heat tobacco and deliver less nicotine than conventional cigarettes - in comparison to DNCs. DNCs were able to decrease craving to a greater extent than the Accord, on at least one measure of craving, the QSU. Craving reduction between DNCs and the Eclipse was however equivalent (Breland et al., 2002). Cobb *et al* (2010) examined DNCs and non-combustible products such as snus, lozenge, and Ariva (a compressed tobacco tablet). DNCs were able to reduce craving (relative to baseline) at almost all time points over a 2 hour period, where as non-combustible products did not, with the exception of one brand of snus. Direct comparisons between the DNCs and non-combustible products were not reported.

One study has also compared DNCs to a nicotine and placebo inhalator over 2 hours, following overnight abstinence (Barrett, 2010). DNCs significantly reduced craving relative to the placebo inhalator, and also relative to the nicotine inhalator but only on Factor 1 of the QSU (intention to smoke). Withdrawal/negative affect relief (Factor 2, QSU) was equivalent between the nicotine inhalator and DNCs. In a different design to previous

studies, one study reported the effects of DNCs smoked 30 minutes after administration of nicotine or placebo lozenges (Barrett and Darredeau, 2012). Here, both placebo and nicotine lozenges reduced Factor 1 scores of the QSU (from baseline to 30 minutes, measured prior to smoking a DNC) as did DNCs; Factor 2 scores on the other hand were only reduced following administration of DNCs. DNCs have also shown either similar craving relief in comparison to IV nicotine delivery (Rose et al., 2003, Rose et al., 2000, Westman et al., 1996b), or superior craving alleviation (Rose et al., 2010, Westman et al., 1996b, Rose et al., 2000), depending on the craving measure used.

With respect to short-term alleviation of other withdrawal symptoms, findings have been more inconsistent, with research typically showing that DNCs can alleviate at least some withdrawal symptoms (Rose et al., 2000, Rose et al., 2003, Hutchison et al., 2004, Rose and Behm, 2004, Brody et al., 2009, Rose et al., 2010, Attwood et al., 2009, Kassel et al., 2007, Tidey et al., 2012), and in some cases to the same extent as nicotine-containing cigarettes (Butschky et al., 1995, Pickworth et al., 1999, Lane et al., 1995, Rose et al., 1994, Westman et al., 1996b, Breland et al., 2002, Buchhalter et al., 2001, Juliano et al., 2006, Gross et al., 1997, Perkins et al., 2010, Dallery et al., 2003, Lindsey et al., 2013).

3.2.2.2 **Prolonged effects on urges to smoke and withdrawal**

A limited number of studies have investigated the effects of DNCs over longer periods of time. Over 24 hours of abstinence, craving and withdrawal were significantly lower with DNCs than with no intervention, and craving, impatience and irritability were comparable between DNCs and conventional cigarettes (Baldinger et al., 1995b). In the second study (Buchhalter et al., 2005), craving reduction over 4 days of DNC use was observed on some, though not all measures, in comparison to no intervention (i.e. complete abstinence), and was comparable to nicotine cigarettes. DNCs did not alleviate all withdrawal symptoms. In another study, participants in the DNC and no-smoking conditions did not differ in daily ratings of craving over 11 days of abstinence, whereas craving was significantly lower in the nicotine-cigarette group vs. the no-smoking group (Donny et al., 2007). No differences between any of the conditions were found with respect to withdrawal symptoms. Finally, Donny and Jones (2009), reported similar withdrawal symptom ratings over 6 days, between participants smoking DNCs and those smoking conventional cigarettes, whilst wearing a placebo patch. Although participants in the DNC group were more irritable, this

dissipated over time. Due to methodological problems, craving ratings could not be reliably interpreted in this study and were not reported.

In a study which randomised participants to use one of three types of cigarettes (DNCs, medium-nicotine, and high nicotine; double-blinded), for one week, there were no differences in ratings of craving reduction between the three cigarettes (Hatsukami et al., 2013a). However, not all participants remained abstinent from their conventional cigarettes during the study.

3.2.2.3 **Subjective measures and user acceptability**

Along with measurements of craving and withdrawal, studies with DNCs have also included assessments of subjective reinforcing effects such as satisfaction, enjoyment, and airway sensory effects. These are important to consider if DNCs are to be utilised in smoking cessation treatment as they need to be acceptable to users to ensure adherence. Research has also found ratings of sensory effects, as opposed to nicotine content, to be related to reductions in desire to smoke (Pritchard et al., 1996); additionally, there was an indication of a relationship between sensory effects and craving relief from studies with the citric acid and black pepper inhalators (Rose and Behm, 1994, Levin et al., 1990, Westman et al., 1995).

Unsurprisingly, nicotine cigarettes have typically been rated more positive than DNCs used in both the short and long term (Butschky et al., 1995, Cobb et al., 2010, Hasenfratz et al., 1993, Baldinger et al., 1995a, Baldinger et al., 1995b, Baldinger et al., 1995c, Brauer et al., 2001, Rose and Behm, 2004, Hutchison et al., 2004, Donny et al., 2007, Naqvi and Bechara, 2005, Naqvi and Bechara, 2006, Perkins et al., 2010, Donny and Jones, 2009, Shahan et al., 1999, Pritchard et al., 1996, MacQueen et al., 2012, Brauer et al., 1999, Juliano et al., 2011, King et al., 2009, Kassel et al., 2007, Tidey et al., 2012, Lindsey et al., 2013, Buchhalter et al., 2005, Tidey et al., 2013, Hatsukami et al., 2013a). However, some exceptions have been noted (Dallery et al., 2003, Lane et al., 1995, Juliano et al., 2006, Pritchard et al., 1996, Gross et al., 1997, Pickworth et al., 1999, Westman et al., 1996b, Barrett, 2010, Kassel et al., 2007, Strasser et al., 2007). For example, Westman *et al* (1996b), found no main effects of cigarette type on satisfaction, liking and airway sensory effects, and no significant differences in satisfaction, strength, harshness, or 'smoke vs. air' were reported in another

study (Dallery et al., 2003). Barrett (2010), found no difference between the two cigarette types on any subjective measures, except 'stimulation', where nicotine cigarettes were rated higher. A nicotine dose-response was reported by Hatsukami *et al* (2013a), whereby high-nicotine cigarettes were rated more positively than DNCs and medium-nicotine cigarettes when used over 1 week, with no differences evident between these latter two cigarettes.

DNCs were also rated as more pleasant and satisfying than a nicotine inhalator (Barrett, 2010); more psychologically rewarding, more satisfying and gave more enjoyable airway sensations than sham smoking (Rose et al., 2010); plus as more pleasant, desirable and stronger than puffs from an unlit cigarette (Naqvi and Bechara, 2005). DNCs were reported to acutely increase ratings of pleasantness, stimulation, relaxation and satisfaction, and decreased anxiety, whereas administration of a nicotine or placebo lozenge did not (Barrett and Darredeau, 2012).The duration of abstinence prior to smoking DNCs (short term vs. overnight abstinence) has not been found to affect subjective ratings despite predictions that longer periods of abstinence may warrant more positive ratings (Pritchard et al., 1996, Pickworth et al., 1999).

3.2.2.4 **Objective measures of reinforcing efficacy**

The reinforcing effects of DNCs have mostly been inferred from self-report measures such as craving and withdrawal questionnaires, satisfaction ratings, and so on. It has been argued that the relationship between self-report data and actual smoking behaviour is unclear, and often seemingly related measures can provide inconsistent results (Shahan et al., 1999). Indeed recently, a review found that the predictive relationship between craving and smoking cessation was inconsistent (Wray et al., 2013). Even with the data reviewed so far, different measures of urges/craving have shown inconsistent results within studies (e.g.Westman et al., 1995, Breland et al., 2002). A number of studies have utilised objective measures of reinforcement such as progressive ratio tasks, preferences between cigarettes in a concurrent choice paradigm, and ad-libitum smoking behaviour. Although these studies do not directly contribute to the main evidence base on craving and withdrawal alleviation, they provide a more comprehensive indication of the reinforcing efficacy of sensorimotor input.

DNCs have been shown to be as acutely reinforcing as conventional cigarettes when each was presented alone, on a variety of indicators during a progressive ratio task; once the two cigarettes were provided concurrently however, nicotine cigarettes were preferred (Shahan et al., 1999). Shahan *et al* (2001), also found that consumption rates of nicotine cigarettes and DNCs reduced to a similar extent on a progressive ratio task as unit price increased, and reduced to the same extent when an alternative reinforcer (money) was available, suggesting similar levels of reinforcement. Tidey *et al* (2013) however reported slightly greater preferences for nicotine cigarettes vs. DNCs during a blinded choice task.

Studies assessing short term ad-libitum smoking behaviour have found no differences in the amount of DNCs and nicotine cigarettes smoked (Baldinger et al., 1995b) and puff volume (Perkins et al., 2010, Tidey et al., 2012), though Rose and Behm (2004) did report significantly more nicotine cigarettes smoked vs. DNCs. Additionally, MacQueen *et al* (2012) reported some compensatory smoking for DNCs (e.g. increased total puff volume and puff length) compared to conventional cigarettes, but this effect of nicotine content reduced over the four smoking bouts. Finally, participants have also demonstrated a preference for DNC puffs compared to IV nicotine administration and sham puffs (Rose et al., 2010).

Four studies have objectively explored the reinforcing efficacy of DNCs over longer periods of time. The number of puffs earned on a progressive ratio task was reported to have significantly reduced over 13 days with DNCS, but did not in the no-smoking and nicotine-cigarette condition (Donny et al., 2007). The number of cigarettes smoked daily also significantly reduced over time with DNCs, but increased with nicotine cigarettes. The authors concluded that although the reinforcing effects of DNCs did reduce over time, DNCs remained somewhat reinforcing as participants still continued to smoke them. In a shorter study (Buchhalter et al., 2005), there was no change over time in the daily number of DNCs or nicotine cigarettes smoked over 4 days, but significantly more nicotine cigarettes were smoked vs. DNCs. This was also reported in another study where significantly less DNCs were smoked over one week vs. high-nicotine cigarettes (Hatsukami et al., 2013a). There were no differences in comparison to baseline measures of usual-brand cigarette smoking for the DNC group. Donny and Jones (2009) found that DNCs were as reinforcing as nicotine cigarettes over 9 days, as indexed by no difference in number of cigarettes smoked per day and no difference in average puff volume, total puff volume and total puff count, during a 1 hour self-administration session on days 3 and 9.

The degree to which DNCs can satiate smokers has also been investigated by assessing smoking behaviour (of conventional cigarettes) following administration of DNCs. No differences between DNCs and conventional cigarettes in latency to first puff were found, but latency was significantly greater compared to when placebo and nicotine inhalators were used (Barrett, 2010). However, there was significantly less administration of puffs in the conventional cigarette condition compared to DNCs and inhalator conditions, suggesting as expected, that DNCs were less satiating than conventional cigarettes. DNCs were able to satiate smokers compared to a no smoking condition (Rose et al., 2003, Tidey et al., 2012), and in comparison to IV nicotine delivery (Rose et al., 2010). Following smoking of DNCs or conventional cigarettes, latency to smoke preferred cigarettes, number of puffs, number of cigarettes over 3 hours, and number of cigarettes each hour, did not differ between cigarette type in another study (Dallery et al., 2003).

In summary, as with subjective measures, the available literature is somewhat mixed. Nevertheless there is some evidence to suggest that with the removal of nicotine, conditioned sensorimotor stimuli may remain reinforcing even over longer periods of abstinence. Research investigating the satiating effects of DNCs in particular, provides additional support other than craving or urge alleviation for the use of SMR in treatment. Given that DNCs still contain tobacco, there may be concerns over prolonged DNC use and this may pose a barrier to utilisation in smoking-cessation treatment. It is important to note then, the reduction in use of DNCs over time and in comparison to conventional cigarettes, reported in these longer-term studies.

3.2.2.5 Acute effects of de-nicotinised cigarettes: Additional data from the Balanced Placebo Design paradigm

Evidence in support of SMR with DNCs also derives from studies examining the role of nicotine expectancy. The results of these studies with respect to main effects of dose expectancies and interactions with actual nicotine intake were described earlier (see theoretical background), but with the use of a balance placebo design (BPD), these studies also offer direct comparisons between conventional nicotine cigarettes and DNCs. Nicotine cigarettes were reported to better alleviate craving (Juliano et al., 2011, Kelemen and Kaighobadi, 2007, Juliano and Brandon, 2002, Darredeau et al., 2013); were rated higher than DNCs on satisfaction, liking, and other subjective rewarding effects (Perkins et al.,

2008, Perkins et al., 2004, Kelemen and Kaighobadi, 2007, Juliano et al., 2011, Juliano and Brandon, 2002, Darredeau et al., 2013); reduced anxiety to a greater extent (Juliano and Brandon, 2002) and improved mood (Juliano et al., 2011). Two studies, in contrast, reported no differences between the two cigarettes on craving (Perkins et al., 2004, Perkins et al., 2008), and few main effects of nicotine were found with regard to withdrawal measures (Perkins et al., 2004, Juliano and Brandon, 2002), with the exception of one study (Perkins et al., 2008).

In terms of objective measures, the number of puffs earned on a progressive ratio task was greater with nicotine cigarettes (Perkins et al., 2004). In another study, latency to first puff did not differ between DNCs and nicotine cigarettes (Perkins et al., 2008), and Darredeau *et al* (2013), also reported no main effect of actual nicotine content on various indicators on a progressive ratio task.

These studies (with the exception of one, detailed below) did not include a 'no smoking' control group, thus the effects of smoking per se, independent of nicotine content or dose expectancies are unknown. The effects of DNCs in comparison to no intervention or control conditions such as sham smoking were summarised previously, but one BPD study adds to this literature (Perkins et al., 2008). In exploratory analyses, Perkins *et al* compared a no-smoking control group to the DNC group (i.e. both those told placebo and told nicotine). Following either positive or negative mood inducement, DNCs reduced craving vs. no smoking. Additionally, following negative mood inducement, DNCs also reduced negative affect and withdrawal. The DNC group was also compared to a sham smoking control group (puffing on an unlit cigarette). Following negative mood inducement, DNCs again reduced craving and negative affect, but no effects were found on withdrawal or positive affect. The sham smoking control group was not tested under positive mood inducement.

In summary, this line of research adds to the literature on the acute effects of DNCs, firstly in comparison to no intervention and to conventional cigarettes, but as outlined previously, also suggests that the expectation of receiving nicotine may boost the reinforcing efficacy of DNCs (Juliano et al., 2011, Juliano and Brandon, 2002, Perkins et al., 2004). Thus some of the reinforcing effects reported in previous (blinded) studies with DNCs may be a result of nicotine expectancy *and/or* conditioned sensorimotor stimulation. As Perkins *et al* (2003) points out, many of the (non-BPD) studies examining DNC effects employed double or single blind designs, in which participants were given vague information on nicotine content. Thus stimulus expectancies (i.e. the belief that they are getting nicotine) may vary between participants, and may impact upon outcome. Indeed one non-BPD study found

that those participants who could discriminate between nicotine cigarettes and DNCs, rated nicotine cigarettes more positively (e.g. more satisfying, stronger) than DNCs (Strasser et al., 2007). Amongst those who could not discriminate nicotine content, DNCs and nicotine cigarettes were rated the same. Together with the BPD literature, this suggests that nicotine expectancy may have some role to play in the reinforcing efficacy of DNCs.

3.2.2.6 **Combining de-nicotinised cigarettes with nicotine delivery**

A handful of experimental studies have examined the effects of combining DNCs with nicotine delivery, either with a nicotine patch or intravenously (IV). Combining DNCs with nicotine should prove most beneficial as both primary and secondary reinforcers of tobacco addiction are addressed simultaneously. These studies have shown that a combination of the two reduced craving the most compared to IV nicotine, saline or DNCs alone (Rose et al., 2010), and produced effects similar to conventional cigarettes (Rose et al., 2000, Westman et al., 1996b, Rose et al., 2003). A study which combined DNCs with the nicotine patch also reported no differences in urges and withdrawal symptoms in comparison to smoking own brand cigarettes (Tidey et al., 2012). Donny and Jones (2009), included a further two conditions in their study examining the use of DNCs over 6 days - DNCs with either a 7mg or 21mg patch - but few consistent effects of either patch type or cigarette type were found on withdrawal symptoms.

In addition to the above, one study found a reduction in craving when participants smoked DNCs in combination with a nicotine patch, in comparison to craving calculated as an average of their baseline craving and craving after 2 weeks of own brand smoking (Rose et al., 2007). Withdrawal symptoms were not affected. This study, however, was designed primarily to examine brain correlates of nicotine dependence, and the study procedures make it difficult to interpret the data for the purposes of this review. For example, conditions were not counterbalanced: all participants completed baseline measures, used DNCs and patches for 2 weeks, and then smoked their usual cigarettes for 2 weeks; no control group was included, thus any effects could be due to the nicotine patch alone; and some participants continued to smoke their usual cigarettes during the 2 weeks of DNC use (on average 18 per day), though it is not clear whether or not participants were instructed to smoke only DNCs during this period.

DNCs have also been combined with NRT in smoking cessation trials; the findings of these studies and others are discussed next.

3.2.2.7 **De-nicotinised cigarettes and smoking cessation**

In the past few years, research with DNCs has begun to focus on their clinical utility in smoking cessation. As reported above, DNCs appear to offer some acute craving/urge relief during abstinence, and therefore may aid cessation by helping to moderate urges to smoke if used as a replacement following the quit day. They could also aid cessation through extinction, that is, extinguishing the previously learnt associations between nicotine and the behaviour and sensations of smoking. In support of this, it has been proposed that the process of extinction may be more effective when the reinforcing effects of a drug are removed, as opposed to the drug-taking behaviour (Conklin and Tiffany, 2002). Furthermore, as DNCs can be smoked in the same situations and environments as regular cigarettes, extinction can occur in a wide variety of contexts, and 'renewal' effects are theoretically less likely to occur. If used prior to quitting, extinction could aid cessation in a number of ways, such as reducing the enjoyment and/reward of cigarettes and dependence in the lead up to the quit day, and in turn, potentially easing urges to smoke and withdrawal during abstinence. Extinction may occur not only for the sensorimotor aspects of smoking, thus devaluing smoking itself, but also for other external/internal conditioned stimuli which trigger urges to smokes and/smoking behaviour.

In three smoking cessation trials, DNCs have been utilised in this way, i.e. for several weeks prior to the quit date but not after it. The first of these trials randomised 96 participants into 6 conditions in a three (DNCs; 'light' cigarettes; own brand) by two (nicotine patch; placebo) design (Rose et al., 2006). Following the quit day, participants then received either 42mg, 21mg or placebo patch in combination with mecamylamine. There was no effect of DNCs on abstinence rates at 1 and 6 months, although there was an effect of pre-cessation nicotine patch. It is likely that the study was underpowered to detect any differences between the cigarette conditions. DNCs did however significantly reduce urges to smoke compared to own brand smoking over the two weeks prior to quitting, as well as on the quit day and one week post-quit; but there were no differences at four weeks post-quit. Following the quit day, DNCs also had an effect on 'habit' withdrawal ratings and negative affect. Habit withdrawal was significantly lower compared to those using own brand

cigarettes before the quit day, and negative affect was reduced in comparison to those using the 'light' cigarettes. Dependence scores, as measured by the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al., 1991), were also reduced over the 2 weeks prior to quitting, indicating a potential reduction in dependence, but again there was only a main effect of pre-cessation nicotine patch with no additional benefit evident with the DNCs.

In the second trial (Rezaishiraz et al., 2007), 98 participants were given nicotine patches and were randomised to smoke DNCs or low-nicotine cigarettes for 2 weeks before quitting. After the quit day all participants received eight weeks of nicotine patch treatment. Self-reported point-prevalence abstinence rates at 3 and 6 months did not differ significantly between groups, but craving was significantly lower in the DNC group, both before the quit day and at 2 weeks post-quit. No differences between groups in other withdrawal symptoms were evident.

Finally, in a larger trial, participants (N=346) used cigarettes with gradually reduced nicotine content over 6 weeks until DNCs were smoked in the final two weeks (Becker et al., 2008). Participants were also randomized to use either a placebo or nicotine patch, before and after the quit day. A control group smoked normal cigarettes during the pre-quit period with a placebo patch 2 weeks pre-quit day, and subsequently used a nicotine patch following the quit day. All groups were asked to stop smoking all cigarettes after the target quit date. Four week CO-validated continuous abstinence rates were significantly higher in the DNC plus nicotine patch group vs. controls (33% vs. 22%, respectively, $p < 0.05$), but the DNC plus placebo patch group did not differ in outcome relative to controls (22% vs. 16%, respectively, *ns*). Differences between the two DNC groups were not reported. By 3 and 6 months, no differences in abstinence rates were present. Effects on urges to smoke and withdrawal were not reported in the study. Use of DNCs in both conditions increased slightly in comparison to the amount of cigarettes smoked in the first week, but this change was not significantly different to the change in cigarettes smoked in the control group. Finally, regular cigarettes in the control condition were rated as significantly more satisfying than DNCs in either condition.

Four studies have examined the use of DNCs following the quit day. In the first (Hatsukami et al., 2010), DNCs were compared to the nicotine lozenge and to low-nicotine cigarettes. Participants (N=165) used their assigned products ad-libitum for a period of 6 weeks

starting on their target quit day. Continuous CO-validated quit rates at four weeks after discontinuation of the products (though use of lozenge was permitted) did not differ across conditions, but the trend favoured the DNC group (43%, 35%, and 21% for DNC, lozenge, and low-nicotine cigarettes, respectively).

With respect to other effects, at one week following the quit day, withdrawal symptoms increased compared to baseline for all groups, though the increase was significantly less for the DNC group vs. lozenge and marginally less vs. the low-nicotine cigarette group. Craving scores did not change in any of the groups. Following cessation of the products however, craving increased significantly for the two cigarette groups in comparison to the previous week, though withdrawal symptoms only increased in the low-nicotine cigarette group. In comparison to the number of cigarettes smoked at baseline, daily smoking of DNCs significantly reduced following 2 weeks of use, whereas use of the low-nicotine cigarettes was significantly greater vs. baseline at each time-point. At 6 weeks post-quit day, the number of DNCs smoked daily was lower than the number of low-nicotine cigarettes smoked. Dependence, measured with the FTND, decreased over the 6 weeks in both the lozenge and DNC groups, but not for the low-nicotine cigarette intervention, with the lowest levels reported in the lozenge group.

In the second trial (Walker et al., 2012), participants (N=1,410) were randomised to either standard care (NRT and behavioural support for 8 weeks) or standard care alongside DNC use for a period of 6 weeks after the quit day. Abstinence rates reported at 3 and 6 weeks and 3 and 6 months were higher in the DNC group at all follow-up points. At 6 months for example, continuous self-reported abstinence rates were 23% vs. 15% in the DNC and control condition, respectively ($p < 0.001$). Time to first lapse was also significantly longer for those in the DNC group vs. controls. Abstinence however was not biochemically verified at any time point. There were no differences between groups in urge to smoke and other withdrawal symptoms from baseline to 6 weeks post-quit. The number of DNCs smoked weekly reduced over the 6 week period, although subjective ratings of the cigarettes (e.g. satisfaction, craving relief, psychological reward, aversion, enjoyment of sensations) did not change from week 3 to week 6.

Recently, Hatsukami *et al* (2013b), reported on a trial comparing the effects of DNCs, nicotine patch and a combination of the two, on smoking behaviour, withdrawal symptoms and long term abstinence rates. Participants (N= 235) were randomised to one of the three

interventions, and provided with the products for 6 weeks, alongside brief behavioural support for 12 weeks. From baseline to one week during the intervention phase, craving decreased in all groups, while withdrawal symptoms increased. The increase in withdrawal was significantly less in the combined DNC and patch group compared to patch alone. At week 7 (i.e. one-week after cessation of the products) craving increased for all groups from week 6. There were also changes in withdrawal from weeks 6 to 7, with the patch-only group reporting lower withdrawal ratings, and both DNC groups reporting elevated symptoms; differences between treatment groups however were not significant.

During the intervention phase, those in the combined DNC and patch group were significantly less likely to smoke conventional cigarettes compared to the other groups. For example, at week 6, 33% and 43% in the DNC and patch only groups, respectively, reported smoking conventional cigarettes in the previous week, compared to just 14% in the combined DNC and patch group (p= 0.002). These reports however were point-prevalence and self-report only. The number of DNCs smoked per day over 6 weeks reduced, but the reduction was significantly greater in the DNC plus patch group vs. DNCs alone. Follow-ups at 12, 24 and 36 weeks revealed no differences in continuous, CO and cotinine verified abstinence rates between groups. Thus, despite there being some benefit of combined treatment early on, these effects did not appear to translate to long term abstinence success, though it should be noted that abstinence analyses were exploratory only, and the trial was underpowered to detect such long term effects.

Finally, in a trial conducted at our unit, we randomised 200 participants to either use DNCs for two weeks post-quit day, in combination with standard NHS-SSS treatment (NRT/varenicline and weekly behavioural support), or standard treatment alone (McRobbie et al., 2013). Participants using the DNCs reported significantly reduced frequency of urges in the first week post-quit day, although intensity of urge and other withdrawal symptoms did not differ between groups. Continuous, CO-verified abstinence from two weeks post-quit day, was significantly higher in the DNC group at 4 weeks (58% vs. 43%, p= 0.034), but by 12 weeks, abstinence rates were similar in the two groups (39% vs. 31%, *ns*). The findings therefore point to some benefit of SMR though the effects may be short lived.

3.2.2.8 **Summary**

The existing evidence suggests that DNCs can acutely alleviate urges to smoke and some withdrawal symptoms; in some cases these effects may extend over longer periods of abstinence. Objective measures have shown them to be as reinforcing as nicotine cigarettes in some short-term studies, but it is not clear for how long they can remain reinforcing. Studies utilising the BPD have further added to the DNC literature and have shown, unsurprisingly, that under double-blind conditions nicotine cigarettes are more acutely rewarding than DNCs. Importantly, merely having the expectation of smoking a nicotine cigarette can have an impact on the rewarding effects of smoking. There is some evidence that dose expectancies may have interactive effects with nicotine pharmacology on urge reduction and smoking behaviour, in that the expectation of nicotine decreases urge when DNCs are smoked, but adds little to the effect of nicotine (Juliano et al., 2011).

DNCs appear to have little impact on smoking cessation if used prior to quitting, although data is only available from three trials (Rose et al., 2006, Becker et al., 2008, Rezaishiraz et al., 2007), which may have been underpowered to detect any differences in cessation outcomes. Additionally, in all three studies, DNCs were only used for 2 weeks prior to quitting. It is likely that a longer period of use would be needed to facilitate any potential extinction processes. It may be that DNCs offer more utility for cessation when used post-quit and alongside NRT, possibly because this could offer a way of both extinguishing the associations between sensorimotor factors and nicotine and at the same time providing a way of alleviating urges to smoke in the first few weeks post-quit. However, the evidence is far from conclusive as studies have reported mixed findings of DNC effects on general craving during the quit attempt (Walker et al., 2012, Hatsukami et al., 2010, Hatsukami et al., 2013b). Also, whether or not DNCs extinguish or at least diminish the effects of other conditioned stimuli has not been empirically tested.

Although it is unlikely that people can become dependent upon DNCs (given that the primary reinforcer has been removed), there may be some concerns with using DNCs in treatment. Since they do still contain tobacco, use of DNCs in treatment may appear counterintuitive to patients and still harmful to health; these concerns may however be mitigated by presenting DNCs as a temporary tool, and a ‘stepping stone’ towards complete tobacco abstinence. Importantly, current data show that DNC use gradually reduces over time, and the amount smoked per day is less than baseline cigarette consumption

(McRobbie et al., 2013, Walker et al., 2012, Hatsukami et al., 2010, Hatsukami et al., 2013b).

Secondly, DNCs may prevent people from habituating to life without cigarettes. One experimental study found that smokers who smoked DNCs following 4 days of abstinence, relapsed back to normal smoking quicker than those who were in the 'no lapse' condition (Juliano et al., 2006). Furthermore, the finding that craving increased following cessation of DNCs (Hatsukami et al., 2010, Hatsukami et al., 2013b), may reflect the loss of a coping tool. The main concerns raised by participants using DNCs in treatment were that they were harmful to health (31%), that they may encourage them to smoke conventional cigarettes again (12%), and that they were habit forming (6%; Walker et al., 2012). Nevertheless, in general, DNCs were acceptable; 90% stated they would recommend DNCs for others wanting to quit, and only 11% of participants raised the above concerns. This may reflect some bias however, as responses were from those participants remaining in the trial at 6 weeks. Overall though, there is some evidence that DNCs, especially when combined with existing treatments, may have a benefit in smoking-cessation treatment at least early on, and further trials are warranted.

3.2.3 **Electronic Cigarettes**

Electronic cigarettes (ECs) are tobacco-free, battery powered devices, where with each puff a visible vapour or mist is created which resembles smoke. They are comprised of a battery, atomizer and cartridge containing propylene glycol/glycerine and other flavourings, and can be purchased with differing levels of nicotine, including nicotine-free. EC technology has quickly evolved; early models of ECs (so called 'first-generation' devices) typically resemble conventional cigarettes in appearance. Second-generation devices are more advanced and allow more choice with respect to nicotine strength and flavours. Third-generation ECs, also known as 'mods', are ECs which have been modified by the user (e.g. battery voltage can be controlled). ECs are a potentially useful tool for assessing the sensorimotor aspects of smoking as they provide sensorimotor stimuli fairly close to smoking (e.g. throat scratch, inhaling/exhaling), and as they can be used with or without nicotine, they offer a way of examining the contribution of SMR per se to smoking behaviour.

3.2.3.1 **Experimental studies with Electronic Cigarettes**

In two studies of nicotine ECs, two different brands (NPRO and Hydro) were compared with own brand cigarettes and a sham smoking control condition, after overnight abstinence (Eissenberg, 2010, Vansickel et al., 2010). As expected, own brand cigarettes were found to reduce craving to a greater extent than ECs. ECs were reported to reduce cravings relative to baseline and sham smoking, at some time points (Vansickel et al., 2010). Furthermore, the ECs were rated as more pleasant and satisfying vs. sham smoking, and these ratings increased compared to baseline, as did ratings of 'taste good', 'calm', 'concentration', 'awake', and 'reduce hunger', at several time points. Ratings of 'smoke another cigarette right now' increased at all time points in the EC conditions, but only increased 30-45 minutes post administration with the nicotine-cigarette conditions. In the other trial they showed little impact on baseline craving or difference from sham smoking (Eissenberg, 2010). It should be noted that both of these early studies allowed only 10 puffs of the EC and no increases in plasma nicotine levels were observed. Any effects in these two studies may therefore be attributed to sensorimotor stimulation rather than nicotine.

In a direct comparison of a nicotine and placebo EC, (Bullen et al., 2010), significantly greater reductions in craving over one hour were evident with the nicotine EC. However, the placebo EC also reduced craving initially, with the differences between the two arms only becoming apparent at 25 minutes post product use and onwards. This study also compared the ECs to own brand cigarettes and a nicotine inhalator. As before, own brand cigarettes reduced craving to a greater extent than all other products, but no differences were found between the ECs and inhalator. Additionally, there were no differences in other withdrawal symptoms (irritability, restlessness, poor concentration) between the two ECs, or between the nicotine EC and inhalator. Following a day's use of the products, the nicotine EC was rated as more pleasant than the inhalator, but they were both comparable in satisfaction ratings. The nicotine EC was also rated better than the other products at helping to keep participants from smoking, and more likely to be used as a potential quitting aid and be recommended to a friend who wanted to stop smoking.

Dawkins *et al* also compared placebo and nicotine ECs on acute effects (Dawkins et al., 2012, Dawkins et al., 2013a). In the first study (Dawkins et al., 2012), there were no differences between groups from baseline to 5 minutes, but both ECs significantly reduced desire to smoke over 20 minutes compared to a control condition where participants were

asked to only hold the EC. The reduction was greater for the nicotine EC vs. placebo in males but no differences between ECs were evident in females. Some reduction in withdrawal symptoms was also reported. At 5 minutes, both ECs reduced anxiety in males vs. controls, but for females only the placebo EC showed reductions in comparison to controls. Over 20 minutes, anxiety, poor concentration, irritability, and restlessness reduced in males using the nicotine EC vs. placebo and control group; for females, only depression reduced significantly in both EC groups vs. controls over 20 minutes. The findings of this study highlight some potential gender differences in SMR effects (i.e. that SMR may be of more benefit for women), though the findings are somewhat inconsistent in this respect. Gender differences have also emerged within the DNC literature (Barrett, 2010). Participants however, were required to remain abstinent for only 1-2 hours prior to starting the study; the effect of the ECs over a longer period of abstinence is therefore unknown. In the second study, Dawkins *et al* (2013a) reported greater withdrawal symptom ratings and desire to smoke (at 15 minutes following ad-libitum EC use, after overnight abstinence) during the placebo EC condition vs. nicotine EC.

In two recent studies with experienced EC users (Vansickel and Eissenberg, 2012, Dawkins and Corcoran, 2013), nicotine-containing ECs significantly reduced craving and some withdrawal symptoms following 10 puffs, and following ad-libitum use of the EC for 60 minutes. Furthermore, positive effects of the EC such as pleasantness, satisfaction, and good taste, increased following use, and peaked during the ad-libitum period (Vansickel and Eissenberg, 2012). Vansickel *et al* (2012), also found effective withdrawal and craving relief following 6 bouts of 10 puffs with a nicotine EC in naïve users. Finally, Nides *et al* (2014), examined nicotine EC use acutely in the laboratory and over one week outside of the study centre in naïve users not seeking treatment. Craving reduced acutely during the experimental sessions, and the majority of participants reported medium to high craving relief in general, when used over the course of the week. Withdrawal symptoms were low at baseline prior to laboratory testing and thus were not examined, with the exception of anxiety which reduced following EC use.

These four studies focused on nicotine EC effects only and there were no control groups included, thus the contribution of sensorimotor effects alone cannot be interpreted, though in one study, a reduction in craving and withdrawal was observed after each bout despite nicotine levels only increasing significantly after the fourth (Vansickel et al., 2012).

3.2.3.2 **Smoking Cessation and Reduction**

At present, one study has been published regarding the use of ECs in smoking cessation treatment (Bullen et al., 2013). Here, participants (N= 657) were randomised to one of three groups: nicotine or placebo EC, or nicotine patch, and were also able to access telephone support throughout their quit attempt. Comparisons were made between the nicotine EC and patch, but also to the placebo EC, enabling an indication of the contribution of sensory and behavioural aspects. Verified, continuous abstinence rates at 1, 3 and 6 months post-quit day were in favour of the nicotine EC. At 6 months these were 7.3% for the nicotine EC, 5.8% for placebo EC, and 4.1% for nicotine patch. Differences between groups were not significant, although with low abstinence rates across the groups, the trial was underpowered to detect these. Time to relapse also favoured the nicotine EC compared to the other products. There were similar reductions in smoking in those who did not remain abstinent across the two EC groups, with 57% of participants using the nicotine EC reducing smoking by at least 50%, and 45% reducing smoking in the placebo EC group. For the nicotine patch this was lower, with 41% reducing their smoking. The data therefore show some support for SMR, particularly with regard to smoking reduction; it is probable though that treatment effects with the nicotine EC would be more pronounced given more effective nicotine delivery with new-generation ECs and when combined with intensive behavioural support.

Several surveys of EC users have also reported that the majority of respondents have replaced their usual cigarettes with ECs, either partially or completely (Etter and Bullen, 2011, Etter, 2010, Foulds et al., 2011, Heavner et al., 2009, Goniewicz et al., 2012, Dawkins et al., 2013b, Adkison et al., 2013, Etter and Bullen, 2014) and two qualitative studies with ex-smokers have provided further anecdotal support for the use of ECs in smoking cessation (Barbeau et al., 2013, Farsalinos et al., 2013). Some of these surveys have been conducted on current EC users, and therefore may be biased in their favour. One survey of Quitline users in the U.S. (Vickerman et al., 2013), reported that EC users were less likely to have quit than never-users, though this may reflect the fact these participants appeared to be harder to treat in general.

In a recent survey conducted on a representative sample in Britain, it was reported that most EC users were current or ex-smokers, with an estimated 170,000 (1.1%) ex-smokers having replaced smoking with ECs (Dockrell et al., 2013). In a pilot survey study of

participants purchasing cigarettes as opposed to EC users (Kralikova et al., 2012), 26% (253) had tried the EC at least once, and of these, around 27% were now using them regularly. The main reasons why those who had ever tried one were not using them were because they did not find them satisfying (33%) or they did not like the taste (32%). A larger study of the same design (Kralikova et al., 2013) found that smoking reduction was the main reason for EC use, with 60% of regular users reporting the EC enabled them to do this. As before the main reasons for those not continuing with regular EC was lack of satisfaction and taste. In a population-based survey in the U.S., approximately 55% of respondents having tried the EC did so for smoking cessation purposes (Zhu et al., 2013).

In addition to survey data, case reports and observational studies have also been conducted. A mean reduction of 39% in cigarettes per day (CPD) over one week was reported in 89% of participants using nicotine ECs, and a 50% reduction in 32% of participants (Nides et al., 2014). Successful cessation with ECs for at least 6 months in highly dependent smokers who were previously hard to treat has also been reported (Caponnetto et al., 2011c), and in those with a history of depression (Caponnetto et al., 2011b). One prospective study gave participants who were not seeking to quit smoking, ECs to use ad-libitum for 6 months. At 6 months, 22.5% had quit smoking (Polosa et al., 2011), and when followed up at 2 years, 16 of the 40 participants were either abstinent (N=5) or had reduced their CPD by at least 50% (Polosa et al., 2013). In a similar study design with heavy smokers diagnosed with schizophrenia, half of the sample (7 of 14) reduced their smoking by 50% at one year follow-up (Caponnetto et al., 2013a).

Caponnetto and colleagues also recently conducted a randomised controlled trial (RCT) of nicotine and nicotine-free ECs for harm reduction in non-treatment seeking smokers (Caponnetto et al., 2013b). Participants (N= 300) were randomised to one of three groups: nicotine EC (7.2mg) for 12 weeks; nicotine EC (7.2mg for 6 weeks and 5.4mg for the remaining 6 weeks); or nicotine-free EC for 12 weeks. With respect to cigarette reduction (excluding abstainers), there were no differences between the nicotine and nicotine-free EC groups in the number of participants reducing their CPD by at least 50% since baseline, at 12 (23% vs. 21%, respectively) and 52 weeks (14.5% vs. 12%, respectively). There were however, significant differences between groups in smoking cessation (CO-verified, not a single puff since last visit) at both time-points, in favour of the nicotine EC groups (14% vs. 4% at 12 weeks; 11% vs. 4% at 52 weeks, respectively).

Some subjective measures were also completed, though at 24 and 52 weeks these were only reported by participants still using the products, and thus may be biased. Here, there

were no differences between the three groups on ratings of satisfaction vs. own brand cigarettes, which were relatively low overall; missing own-brand (moderate); and how likely they were to recommend the product to a friend/relative (moderate). The occurrence of withdrawal symptoms was recorded, though the authors only report on the overall number of participants experiencing each symptom, which was low. Although the results unsurprisingly show some favour for the nicotine ECs at least for abstinence rates, the authors note that the brand of EC used in this study was not particularly efficient at delivering nicotine, and instead believe their findings reflect greater satisfaction with the flavour/taste of the nicotine cartridges. If true, this suggests that these findings could be a result of the sensorimotor input from ECs; salivary cotinine levels, however, were measurable in abstainers in the nicotine EC group, thus the contribution of nicotine cannot be completely dismissed.

3.2.3.3 **Summary**

As ECs are a relatively new product, data are currently limited, but there is some evidence that they can acutely alleviate craving and withdrawal. The efficacy of ECs in smoking cessation is as yet unknown, but considering findings from the first trial published, survey data, observational studies, and evidence of harm reduction, there is clearly potential, and these findings warrant further research. Given the limited, or negligible nicotine delivery, particularly with earlier EC models, some of these effects may be attributed to sensorimotor input, and at least anecdotally, the sensorimotor aspects are perceived by users as a part of their efficacy in smoking cessation (Barbeau et al., 2013).

3.3 **Conclusions and further research**

Of the three SMR products investigated to date, DNCs seem to provide the most support for the SMR hypothesis; despite variable results with withdrawal symptom alleviation, they show good evidence of acute urge relief, and often in comparison to conventional cigarettes; plus their effects may extend over longer periods of time. There is also some suggestion that when coupled with current treatments such as NRT, DNCs may enhance cessation, though the mechanism of action may not necessarily be via moderation of urges

to smoke and withdrawal. Their superior effects are most likely due to the fact that they are the closest replacement to conventional cigarette smoking, and thus offer the most sensorimotor input. Of course, effects may also be enhanced by other chemicals and substances present in tobacco smoke. As they do still contain tobacco, their use may be problematic and unacceptable. In contrast to DNCs, the evidence from flavoured non-nicotine inhalators/aerosols is weaker and somewhat mixed, and this may reflect the level of sensorimotor input (or lack of it) provided by these products. ECs may offer a middle ground; they provide sensorimotor stimulation closer to smoking than inhalators/aerosols (though not as close to DNCs) and are tobacco-free. Although data are currently limited, they may be the most promising of the three approaches as they can combine nicotine delivery contingent on sensorimotor input.

Some methodological issues have emerged from the studies reviewed. Firstly, the majority have been experimental/laboratory studies conducted following overnight, or a given period of abstinence, with few studies examining the longer-term effects of SMR, and outside of a laboratory setting. Research findings between different assessments measuring the same constructs within a study have often conflicted, making it difficult to formulate conclusions. For example Rose *et al* (2000) and Westman *et al* (1996b), both reported greater craving relief with DNCs in comparison to no smoking on one measure, but no group differences on the Shiffman-Jarvik craving subscale. Smoking cessation trials have not always complied with the Russell Standard (West et al., 2005), for example, not reporting continuous abstinence or validating self-reported quitters. Another important design feature which may moderate sensorimotor effects is whether or not nicotine content (or lack of it) is blinded from participants; studies utilising the BPD with DNCs have shown that nicotine expectancy may have a role to play.

There are several areas which require further investigation with SMR. Firstly, it is not clear to what extent the effects of SMR can surpass simple distraction. Although previous research has compared products to placebos or to no intervention, no study has used a distraction control condition which provides no conditioned sensorimotor stimulation. The effects of distraction are important to consider as previous research indicates that cognitive and behavioural techniques (including distraction techniques) may, for example, help to alleviate cue-induced cravings (Ferguson and Shiffman, 2009). From a practical standpoint, if SMR does not add anything above and beyond the effects of distraction, there would be little justification of its use in treatment Secondly, what level of SMR is required is unclear. Theoretically, SMR which is closer to real smoking should be more effective, and evidence

from the DNC literature seems to support this, but direct comparisons have not been made. Until the arrival of the EC, no SMR products have been available that could rival the DNC; a direct comparison of the two products could not only have theoretical implications and address the issue of a potential dose-response, but clinical ones also. If for example, ECs were as effective as DNCs, there may be a preference to integrate ECs into treatment, rather than a tobacco product, which may not be deemed acceptable by all. There is also some suggestion in the literature that SMR may be of most benefit for a certain sub-group of smoker. In one study (Caponnetto et al., 2011a), exploratory examination of the data found that SMR aided cessation only in participants who were deemed to be highly 'behaviourally dependent', and other research has pointed to a benefit for those who smoke more/are generally more dependent (Brauer et al., 2001, Behm et al., 1993).

The current project therefore aimed to answer the following research questions:

1. Can SMR surpass simple distraction effects?
2. Are sensorimotor effects 'dose-dependent'?
3. Are smokers who are 'behaviourally dependent' more likely to benefit from SMR in treatment?

These questions were examined via three separate research studies, which focused on two non-nicotine SMR products, ECs and DNCs. To answer whether SMR could surpass distraction effects, a nicotine-free EC was compared to a stress ball in Study 1. The EC, as opposed to DNC, was chosen for this purpose as it does not contain tobacco and smoke constituents, which themselves could have reinforcing effects. As such, this would provide a clearer indication as to the contribution of conditioned sensorimotor stimuli per se, without the contamination of tobacco smoke constituents. In addition, there is currently limited experimental research with ECs, and the study would therefore contribute not only to the wider literature on non-nicotine and sensorimotor aspects of smoking behaviour, but also provide data on ECs, a topic currently of high interest. To examine whether sensorimotor effects are dose-dependent, the nicotine-free EC, which provides some level of sensorimotor input, was compared with the DNC that gives a virtually complete replacement to conventional cigarette smoking. As noted previously, these products showed the most promise for SMR, and a direct comparison of the two would have theoretical and clinical implications. Data for the final research question was collected as part of an existing randomised controlled trial, examining the effect of DNCs in combination

with standard NHS-SSS treatment (McRobbie et al., 2013). The trial provided an opportunity to replicate the novel findings of a recent trial which reported favourable results with SMR in combination with standard treatment, but only in a sub-group of smokers who scored highly on the GN-SBQ measure at baseline (Caponnetto et al., 2011a). There has been little empirical work conducted with the GN-SBQ which purports to measure behavioural dependence to smoking, and what is available is mixed (Nerín et al., 2005, Bullen et al., 2013, Rath et al., 2013); the final study would therefore not only add to the evidence base on potential moderators of SMR treatment effects, but would also allow an examination of the measures' general clinical utility.

4 Study 1: Can sensorimotor replacement with the electronic cigarette surpass behavioural distraction?

4.1 Methodology

4.1.1 Aims

The aim of the first study was to examine whether sensorimotor stimuli delivered by nicotine-free ECs could help alleviate urges to smoke and withdrawal symptoms compared to a behavioural distraction control condition (stress ball; SB).

4.1.2 Hypotheses

Since ECs provide some level of SMR, it was hypothesised that ECs would be more effective at alleviating urges and withdrawal symptoms and would be perceived as more satisfying and helpful than SBs.

4.1.3 Research approach and Design

In order to examine any potential effects of SMR, this study employed a controlled experimental/'laboratory' approach. Such an approach has been previously used to evaluate potentially reduced exposure products such as DNCs, the Accord, Eclipse (Breland et al., 2002, Buchhalter et al., 2001), and more recently with ECs (Bullen et al., 2010, Eissenberg, 2010, Vansickel et al., 2010, Vansickel et al., 2012, Dawkins et al., 2012, Nides et al., 2014). Laboratory methods for evaluating such products/aids are usually conducted in the following way: participants attend the study centre following a period of abstinence (typically overnight abstinence). Baseline measures (e.g. withdrawal) are completed, and participants then use the allocated product for a set period of time (e.g. 5 minutes) or a particular number of times (e.g. 10 puffs from a cigarette). Following this, measures completed at baseline are then repeated at particular time points. In some designs the product will be used once, and measures completed over the following hour; in other designs, the product may be administered again after 30 minutes or 1 hour, and the measures repeated as before.

The product of interest will often be compared to a conventional cigarette and/or another similar product or control condition (e.g. sham smoking). Thus, this method typically employs a cross-over design, where the sequence of conditions is counterbalanced and randomised to prevent order effects, and different conditions are completed following a period of 'wash-out'. With a cross-over design, individual variability can be reduced.

The main advantage of this method is that it can help to reveal whether a product/ intervention etc., is effective in principle, before time, money and other resources are spent on large clinical outcome trials. It can also provide an indication of user acceptability and adverse effects etc., which may be barriers to use. Importantly, this method also allows the examination of changes over time, and interactions between time and product or intervention type.

An important drawback of this method when evaluating potential aids for withdrawal relief is that the setting is highly controlled and artificial, meaning results may not necessarily generalise to use of the products or interventions in a 'real-life' setting. This is especially poignant given that smoking behaviour is highly contextual and associated with many different cues, which are undoubtedly lacking in a controlled laboratory environment. Furthermore, laboratory methods typically assess acute effects (e.g. up to 1 hour), though it could be possible that any treatment benefits dissipate over time as withdrawal symptoms intensify or as novelty effects disappear. Another problem concerns the use of repeated measurement over time, which in some studies is repeated as often as every 5 minutes. This may be of particular concern with questionnaires of self-reported craving or urges as there has been some suggestion that they may be subject to reactivity bias, whereby the act of answering questions about craving may inadvertently cue craving (Sayette et al., 2000). Research into this has not necessarily supported these claims though. Shadel *et al* (2001), for example, found that the QSU at least, was not related to higher craving vs. a questionnaire unrelated to smoking and a time-based control condition. Significant increases in craving were however reported for the time-based control condition, leading to a suggestion that a task which is structured and focused (such as a questionnaire, regardless of content) may supress craving via distraction.

Despite these limitations, using a controlled laboratory method is appropriate for the aims of the present study, and can offer important information on the acute effects of SMR.

Given the limitations, the present study combined controlled experimental methods with ad-libitum use of SMR products outside of the study centre. This approach was used in previous studies with ECs (Bullen et al., 2010, Nides et al., 2014), and NRT (McRobbie et al., 2010), and enables examination of both immediate effects under controlled conditions as well those in a naturalistic setting. Additionally, the controlled experiment was conducted both after overnight abstinence and abstinence over the day. In this way, possible effects over a longer period of time and after familiarity with the products could be evaluated. Repeated questionnaire measures completed over the hour were kept to a minimum to avoid possible reactivity bias.

The present study also employed cue-exposure methods to not only help amplify urges to smoke and withdrawal prior to assessment, but also to increase external validity by exposing participants to a smoking trigger typically experienced in a 'real world' setting. In addition, the impact of SMR on cue-induced urges to smoke could also potentially be assessed, something which is currently lacking in the literature. Cue-induced craving/urge refers to the intense craving triggered by stimuli (e.g. lighters, seeing someone smoke, smoking environments), which have become associated with smoking via conditioning. The general finding from the cue-reactivity literature is that smoking cues generate significant increases in craving compared to neutral cues, inferring that smokers are reactive to these stimuli (Carter and Tiffany, 1999). Recently, the clinical relevance of cue-reactivity has been called into question (Perkins, 2009, Sayette and Tiffany, 2012), but there is some evidence to suggest that smoking-related cues may have implications for relapse, in that lapses are often related to situational cues (Ferguson and Shiffman, 2009). Thus, an intervention which could target both background and cue-induced craving may have added benefit in treatment. In their review, Ferguson and Shiffman (2009), reported little evidence that cue-exposure therapy and chronically administered medications such as the nicotine patch, varenicline and bupropion, had much effect on alleviating cue-induced cravings. In contrast, acutely administered NRT such as nicotine gum and lozenge were reported to be effective, as were behavioural or cognitive interventions aimed at helping people cope with 'high risk' situations. It is possible, therefore, that there may be scope for SMR products to ease these cravings.

In summary, this study used a randomised cross-over design. Participants took part in two conditions (EC and SB, order counterbalanced), with a minimum of 2 days in between. For each condition, participants were required to attend two 1-hour controlled experiments on

the same day (one in the morning following overnight abstinence, one in the evening following abstinence over the day).

4.1.4 Participants

4.1.4.1 Recruitment

Participants were recruited from patients attending the Royal London Hospital Smokers' Clinic, via advertisements in London newspapers and through advertisements in staff bulletins at Queen Mary, University of London (see Appendix 1).

4.1.4.2 Inclusion/exclusion

Participants were included in the study if they were aged 18 or over, smoked at least 10 CPD, and smoked within the first hour of waking. Participants were excluded if they were pregnant/breast feeding, had an acute psychiatric illness, were taking part in other research, or were currently using an EC or NRT.

4.1.5 Measures and Outcomes

A copy of the clinical records form used to collect all data (excluding baseline measures) is shown in Appendix 2.

4.1.5.1 Baseline measures

At baseline, participants completed the standard Royal London Smokers' Clinic baseline questionnaire (see Appendix 3), containing questions regarding demographic details, health status and smoking history. The questionnaire also includes the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al., 1991), a widely used measure for assessing the severity of nicotine dependence.

4.1.5.2 **Withdrawal symptoms and urges to smoke**

Withdrawal symptoms during the one hour controlled experiments were measured by asking participants to rate on an 11-point scale from 0 (“not at all”) to 10 (“extremely”), how they felt “right now”. Three items were adapted from the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes and Hatsukami, 1986): irritability, restlessness, and difficulty concentrating, and were used in a previous study assessing the acute effects of ECs (Bullen et al., 2010). Other withdrawal symptoms such as hunger, depression and sleep problems were not included as they would not be experienced in this short time frame. Urge to smoke was measured with a single item; “Right now, how strong is your urge to smoke?”, also on the same 11-point scale. A single-item measure for urge to smoke was chosen, as a lengthy multi-item questionnaire would not be appropriate to the study deign and could give rise to distraction effects or reactivity bias. Single-item measures have been shown to be as reliable and sensitive as multi-item questionnaires such as the QSU (West and Ussher, 2010).

Withdrawal symptoms experienced over the course of the day were measured with the Mood and Physical Symptoms Scale (MPSS; West and Hajek, 2004), a widely used measure of withdrawal and urges. The MPSS required participants to indicate if they had felt depressed, irritable, restless, hungry, or had difficulty concentrating over the course of the day. These items were rated on a 5-point scale (“not at all”, “slightly”, “somewhat”, “very” or “extremely”). The MPSS also includes two items on a 6-point scale assessing frequency of urges (“not at all”, “a little of the time”, “some of the time”, “a lot of the time”, “almost all of the time”, or “all of the time”) and strength of urges (“no urges”, “slight”, “moderate”, “strong”, “very strong” or “extremely strong”).

4.1.5.3 **Product perceptions and use**

Participants were asked to complete a questionnaire regarding product satisfaction and helpfulness, adapted from previous work with ECs and NRT (Bullen et al., 2010, Hajek et al., 1989, McRobbie et al., 2010). This asked participants on 5-point scales how satisfying their product was in comparison to smoking their usual cigarettes (“much less”, “a little less”, “the same”, “a little more”, “much more”); how helpful it was in enabling them to keep from smoking, how pleasant it was to use, and how embarrassing it was to use (“not at all”,

"slightly", "somewhat", "very", "extremely"); the extent to which they would use the product to help them quit, and if they would recommend it to a friend as an aid to quitting ("definitely not", "probably not", "maybe", "probably", "definitely").

Open questions were used to capture any further information about the products, and asked participants to list what they liked most and least about the products. Any adverse effects experienced were also listed, and rated on strength ("weak", "moderate", "strong"). At the final session, participants completed a product preference questionnaire, where they were asked to indicate which of the two products they liked better, found easier to use, less embarrassing to use, more helpful, and which they would use to help them quit and recommend to a friend for help in quitting.

Frequency of product use was measured by asking participants to record how often they used the product each hour throughout the day. Instead of recording every squeeze of the SB or puff of the EC, one 'use' of the SB was defined as using the SB for a period of time where they squeezed it at least 15 times, and for EC, using the EC for a period of time where they took at least five puffs. Participants were encouraged to record their use throughout the day, to ensure more reliable data collection and avoid retrospective recording. Participants were also asked if they had smoked any of their usual cigarettes over the course of the day ("not a puff", "a few puffs", "1-5 cigarettes", "more than 5 cigarettes"). Abstinence was verified with CO reading of <10ppm, using a Bedfont CO monitor.

4.1.5.4 **Cue exposure and reactivity**

Participants took part in a cue exposure procedure prior to the one hour controlled experiments, where they were asked to light and hold a conventional cigarette for one minute, without smoking it. This method of cue exposure is widely used (Ferguson and Shiffman, 2009), though in the present study all participants were provided with the same brand of cigarettes (Marlboro Lights), as opposed to their preferred brand. This procedure has been shown to induce cigarette craving (Niaura et al., 1998). The impact of the cue exposure was examined by participants completing ratings of withdrawal symptoms and urges (detailed above) pre and post exposure. Since smoking cues have consistently shown to increase cravings compared to neutral cues (Carter and Tiffany, 1999), and a

baseline/pre-exposure rating was completed, a neutral cue condition was deemed not necessary for the present study.

4.1.5.5 **Outcomes**

The primary outcome of interest was the difference between the two conditions in change in urge to smoke from post-cue to 10 minutes post-product use, following overnight abstinence. Secondary outcomes were to compare the EC and SB on (i) urges and withdrawal symptoms over one hour, in the morning and evening; (ii) urges and withdrawal symptoms over one day; and (iii) product satisfaction and preferences.

4.1.6 **Sample size**

A sample of 40 participants was required to detect a minimum difference of 1.6 (at a significance level of 0.05, with 80% probability), on change in urge to smoke from post-cue to 10 minutes post-product use, on an 11-point scale. This was based on previous data (Bullen et al., 2010), where the within-patient standard deviation of the response variable was 2.6.

4.1.7 **Products**

The EC used in this study was the Smoker's Angel Halo Electronic Cigarette, purchased from www.thesmokersangel.co.uk (see Figure 4.1). At the time of study set-up, first generation ECs were more common, and this EC was chosen firstly because a nicotine-free version was available, and secondly because of its appearance and ease of use: unlike other brands and models, it closely resembled a conventional cigarette in size and appearance, with a white battery and orange coloured tip; and used 'cartomizers' (where the cartridge and atomizer are combined), enabling easy assembly and use for participants (i.e. participants were only required to screw in the cartridge to the battery) Participants were provided with 2 fully charged batteries and 2 cartomizers for use throughout the day.

SBs were purchased from an online retailer and were plain and of standard size (70mm in diameter). Participants were provided with one SB to use throughout the day.

Figure 4.1: The Halo Electronic Cigarette

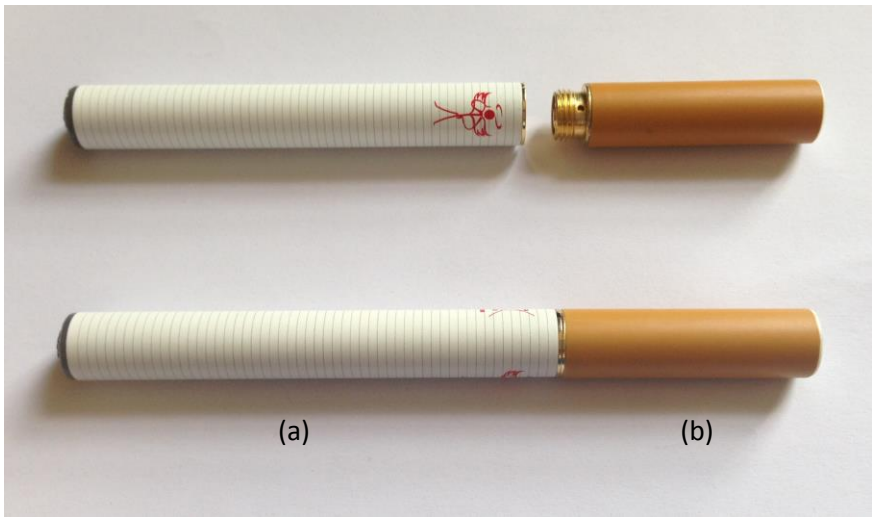


Figure 4.1*: The Halo Electronic Cigarette comprises of a (a) battery and (b) a cartomizer (cartridge with atomizer combined).*

4.1.8 **Procedures**

Participants interested in taking part were initially screened on the telephone, and if eligible, were posted study information (see Appendix 4), the baseline questionnaire, and booked to attend the first study day. Participants were required to attend the study centre in the morning (following overnight abstinence) and evening, on two separate days, with a minimum of 2 days in between sessions (where they were asked to smoke as normal). Morning sessions were scheduled to begin at 9am, and evening at 5pm, though timings were flexible (up to 30 minutes either side) to allow for participants' work commitments, travel disruptions etc. On one of the days participants were given the SB to use, and the other day the EC. The order of conditions was randomised and counterbalanced.

Participants were re-screened and consented (see Appendix 5) at the first morning session and baseline measures were collected. Overnight abstinence was confirmed with a CO reading (cut-off point of 15ppm), as used in previous studies (Bullen et al., 2010, McRobbie et al., 2010). Six participants had readings between 16 and 18ppm at either morning session, and one participant had an average reading of 22.5ppm across the two mornings; exceptions were granted to these participants as they were either heavy smokers (>30 CPD), or reported heavy smoking the night before. Sensitivity analysis of the primary outcome, with these participants removed, revealed similar results between this sub-

sample and the whole sample that completed the study (see Appendix 6). Anyone who reported smoking overnight or in the morning was rescheduled to another day. Following consent and confirmation of overnight abstinence, participants were allocated to their first product.

During each morning and evening session, participants took part in a 1-hour controlled experiment. Withdrawal symptom ratings and urges to smoke were completed pre and post the cue-exposure task. Participants were then given 5 minutes to use their allocated product. When using the EC, participants were asked to take at least 5 puffs and for the SB, to squeeze it at least 15 times, but otherwise they could use their products as they wished over the 5 minutes. Participants then rated their withdrawal and urges at 5, 10, 30 and 60 minutes following initiation of product use.

After the morning session, participants were asked to use their allocated product throughout the day with at least the same frequency as they would normally smoke, to record their product use, and to abstain from their usual cigarettes. Participants returned in the evening and repeated the 1-hour experiment. They also completed the MPSS and questionnaires regarding product perceptions and adverse effects. Self-reported abstinence throughout the day was verified with a CO reading (< 10ppm). At the final evening session, the product preference questionnaire was also completed, participants were paid £40 towards their travel expenses, and offered a referral for smoking cessation treatment. Table 4.1 provides a summary of the procedures and measures.

The study was approved by the National Research Ethics Service committee (Clinical Trials Registration Number: NCT01414998 [www.clinicaltrials.gov]) and ran from May 2012 until October 2012.

4.1.9 **Data analysis**

4.1.9.1 **Cue-exposure effects**

To examine the impact of the cue-exposure procedure on MNWS ratings, a product (EC vs. SB) by time (baseline vs. post-cue) repeated measures analysis of variance (ANOVA) was conducted on urges and withdrawal items, in the morning and evening.

Table 4.1: Summary of Study 1 Procedures and Measures

Procedure/measure	**Session 1**				**Session 2**		
	Morning	Day	Evening		Morning	Day	Evening
Screening + Consent	X						
Baseline demographics	X						
CO	X		X		X		X
Product allocation	X						
Cue-exposure	X		X	**Rest period min. 2 days**	X		X
1-hour post-product use MNWS ratings	X		X		X		X
Product use recording		X				X	
MPSS			X				X
Product rating questionnaire			X				X
Product preference questionnaire							X

These analyses were conducted on the sample of participants who complied with study procedures and abstained over the day in both conditions ('abstainers'), and then separately on the sample of participants who fully completed the study, regardless of abstinence over the day ('whole sample').

4.1.9.2 **Urge and withdrawal symptoms over 1 hour**

To provide an overview of the effects of the products during the experimental sessions, MNWS ratings over the full hour were analysed with a repeated measures ANOVA (product x time) where time had 5 levels (post cue, 5, 10, 30 and 60 minutes), for both the morning and evening sessions. ANOVAs were conducted for each item separately, as well as a composite withdrawal score (irritability, restlessness and difficulty concentrating, averaged). Where assumptions of sphericity were not met, the Greenhouse-Geisser statistic was reported. Any significant interactions were followed up with simple contrasts

comparing ratings at each time-point to post-cue, as differences between products in change from post-cue were of interest. Analyses were conducted on both the abstainer sample and the whole sample.

4.1.9.3 Primary outcome: Acute effects on urge to smoke following overnight abstinence

The primary outcome concerned the acute effect of the products on urge to smoke after overnight abstinence. Urge to smoke change scores, from post-cue to 10 minutes post-product use rated in the morning session, were computed for each condition. The Wilcoxin Signed Ranks Test was used to test for any differences between the products (data were not normally distributed). The analysis was conducted on the whole sample.

4.1.9.4 Urge and withdrawal symptoms over the day

Differences between products in MPSS scores were analysed with paired sample t-tests, or where data was not normally distributed, with the Wilcoxin Signed Ranks Test. These were conducted on individual items and composite scores (depression, irritability, restlessness, difficulty concentrating and hunger averaged for composite withdrawal; urge strength and urge frequency averaged for composite urge). Data was analysed for both abstainers and the whole sample.

4.1.9.5 Product use, perceptions, and abstinence

Differences between products in amount of use (defined as total amount of times used over the day), product satisfaction and other user ratings were also analysed with paired samples t-tests/Wilcoxin. For the open questions, where participants were asked what they liked most and least about the products they used, responses were categorised, and frequencies reported. Any adverse effects listed were reported, along with their strength (averaged across participants if n>1). Chi-square tests were used to examine if there were any differences in the amount of participants choosing one product over the other in the

product preference questionnaire. Differences in abstinence rates over the day were examined with the McNemar test. These analyses were conducted on the whole sample.

4.2 Results

4.2.1 Participant characteristics

Forty-eight participants consented to take part in the study, and 40 of these were randomised and completed the first session (the remaining eight did not return for their first session). Three participants did not attend the second session (N= 1 for EC, N= 2 for SB), and two participants did not fully complete the second evening session (both during the SB condition). A total of 35 participants therefore completed the full study. Participant demographics and baseline characteristics of those who completed are listed in Table 4.2.

4.2.2 Compliance with abstinence

During the EC condition, 22 of the 35 (62.9%) participants who completed the study abstained (CO validated) from cigarettes during the day, and 21 of 35 abstained (60%) during the SB condition. There was no significant difference in abstinence rates between conditions (p= 1.00). Seventeen participants were abstinent during both conditions, and thus made up the 'abstainer' sample.

4.2.3 Product use

There was a significant difference in the amount of product use over the course of the day between the two conditions (z= -2.42, p= 0.015). The EC was used on average 15.9 times (SD= 21.5), and SB, 10.2 times (SD= 12.8).

Table 4.2: Study 1 Participant Characteristics

Demographics and baseline characteristics	**% (N= 35)**
Gender	
Male	65.7
Ethnicity	
Caucasian	68.6
Mixed/other	25.5
Don't wish to answer	5.7
Employment status	
Employed	54.3
Unemployed	14.3
Student	5.7
Other (e.g. retired, sick/disabled)	25.7
Education	
Higher	57.1
Secondary or none	42.9
	Mean (SD)
Age	40.9 (15.5)
CPD*	19.0 (7.2)
FTND	5.8 (2.1)

**Cigarettes per day*

4.2.4 Primary outcome: Acute effects on urges to smoke after overnight abstinence

The hypothesis that the EC would reduce urge to smoke to a greater extent than the SB following overnight abstinence, was examined by comparing change scores from post-cue to 10 minutes in the two conditions. Since all participants were abstinent during the morning sessions, the analysis was conducted on the sample of participants who completed the study. Both the EC and SB reduced urge to smoke from post-cue to 10 minutes (Mean reduction: EC= 1.20 (SD= 1.92); SB= 0.63 (SD= 1.26), but the difference in change was only marginally higher for the EC condition vs. the SB (z= -1.87, p= 0.062).

4.2.5 **Cue exposure effects**

The mean ratings of urge to smoke and withdrawal symptoms pre and post cue-exposure for each condition are shown in Table 4.3 (abstainer sample) and Table 4.4 (whole sample), together with a summary of ANOVA analyses.

Ratings during both morning and evening sessions on the whole were fairly moderate. With regards to the impact of the cue-exposure (i.e. main effects of time), in abstainers, the cue-exposure procedure seemed to have some impact on urges ($F(1, 16) = 9.07$, $p= 0.008$), restlessness ($F(1, 16) = 6.67$, $p= 0.020$) and difficulty concentrating ($F(1, 16) = 9.30$, $p= 0.008$) during the morning session, and on urges ($F(1, 16) = 9.00$, $p= 0.008$) and irritability ($F(1, 16) = 5.88$, $p= 0.028$) in the evening session, indicating increases from pre-cue to post-cue. For the whole sample of participants, no main effects of time were evident.

The repeated measures ANOVA also revealed significant main effects of product for some items, particularly in the morning sessions; since participants were aware of which condition they would be participating in on that morning *prior* to commencing the cue-exposure task, these findings may reflect participants' expectancies of the EC and SB. In the sample of participants who abstained throughout the study, ratings for urge to smoke and difficulty concentrating were on the whole lower when participants were told they would be using the EC vs. the SB (urge to smoke: $F(1, 16) = 6.97$, $p= 0.018$; difficulty concentrating: $F(1, 16) = 7.73$, $p= 0.013$). There was also a trend for lower ratings of irritability and restlessness in the morning, but this did not reach significance. There was, however, a significant interaction between time and product for restlessness in the morning, suggesting that the increase was larger when participants were aware they would be using the SB than EC ($F(1, 16) = 4.92$, $p= 0.041$). No main effects of product were evident during the evening sessions.

For the whole sample (i.e. those who completed the study, regardless of abstinence throughout the day), ratings of urges and irritability in the morning were also lower when participants knew they would be using the EC compared to the SB (urge to smoke: $F(1, 34) = 10.26$, $p= 0.003$; irritability: ($F(1, 34) = 6.46$, $p= 0.016$). The same pattern was evident for restlessness and difficulty concentrating, but it did not reach significance. Urge to smoke

was also on the whole lower in the evening when participants were to use the EC vs. SB (F (1, 34) = 5.02, p= 0.032).

Table 4.3: Mean ratings and summary of ANOVA analysis of urges and withdrawal symptoms pre and post cue-exposure in abstainers.

	Mean rating (SD)				F [1, 16] (p)		
N= 17	**EC baseline**	**EC post-cue**	**SB baseline**	**SB post-cue**	**Time**	**Product**	**Time x Product**
Morning							
Urges	5.94 (2.73)	6.53 (2.83)	6.88 (2.62)	7.29 (2.37)	9.07 (0.008)	6.97 (0.018)	0.46 (0.508)
Irritability	4.59 (2.79)	4.94 (2.90)	5.47 (2.70)	5.53 (3.00)	2.86 (0.110)	3.72 (0.072)	1.74 (0.206)
Restlessness	4.94 (2.95)	5.00 (2.81)	5.47 (2.79)	6.00 (2.72)	6.67 (0.020)	3.97 (0.064)	4.92 (0.041)
Difficulty concentrating	4.24 (2.66)	4.65 (2.83)	5.06 (2.82)	5.24 (2.66)	9.30 (0.008)	7.73 (0.013)	1.36 (0.260)
Evening							
Urges	6.24 (2.66)	6.76 (2.80)	6.29 (2.69)	6.88 (2.89)	9.00 (0.008)	0.04 (0.837)	0.09 (0.773)
Irritability	5.00 (2.65)	5.53 2.65)	5.00 (2.94)	5.24 (3.07)	5.88 (0.028)	0.13 (0.728)	3.13 (0.096)
Restlessness	4.88 (2.60)	5.06 (2.90)	5.06 (2.70)	5.24 (2.99)	1.42 (0.251)	0.21 (0.655)	0 (1.00)
Difficulty concentrating	4.94 (2.73)	4.94 (2.73)	5.24 (2.88)	5.41 (2.94)	1.31 (0.269)	1.04 (0.323)	1.31 (0.269)

Table 4.4: Mean ratings and summary of ANOVA analysis of urges and withdrawal symptoms pre and post cue-exposure (whole sample).

	Mean rating (SD)				F [1, 34] (p)		
N= 35	**EC baseline**	**EC post-cue**	**SB baseline**	**SB post-cue**	**Time**	**Product**	**Time x Product**
Morning							
Urges	5.51 (3.37)	5.66 (2.95)	6.63 (2.90)	6.80 (2.93)	0.66 (0.421)	10.26 (0.003)	0.01 (0.934)
Irritability	4.14 (3.46)	4.31 (3.26)	5.26 (3.13)	5.11 (3.42)	0.01 (0.937)	6.46 (0.016)	1.56 (0.221)
Restlessness	4.26 (3.00)	4.57 (2.98)	5.06 (2.91)	5.20 (3.06)	1.83 (0.160)	3.74 (0.061)	0.28 (0.597)
Difficulty concentrating	3.63 (2.95)	3.94 (2.97)	4.40 (2.86)	4.54 (3.00)	1.51 (0.228)	3.56 (0.071)	0.28 (0.597)
Evening							
Urges	5.69 (3.12)	5.71 (3.30)	6.37 (2.95)	6.63 (3.25)	0.53 (0.474)	5.02 (0.032)	0.53 (0.473)
Irritability	4.23 (2.79)	4.34 (2.95)	4.69 (3.09)	4.83 (3.36)	0.78 (0.383)	1.72 (0.199)	0.02 (0.905)
Restlessness	4.46 (2.76)	4.46 (3.04)	4.91 (2.61)	5.17 (2.82)	0.93 (0.342)	3.03 (0.091)	1.08 (0.305)
Difficulty concentrating	4.17 (2.77)	4.14 (2.96)	4.17 (2.99)	4.46 (3.08)	1.49 (0.230)	0.23 (0.633)	1.74 (0.196)

4.2.6 **Urges to smoke and withdrawal symptoms over 1 hour**

A repeated measures ANOVA was used to examine the pattern of urges and withdrawal symptoms over the course of the hour following the cue exposure, during morning and evening sessions. Table 4.5 (abstainer sample) and Table 4.6 (whole sample) present a summary of the results. Mean scores and standard deviations for each item by condition can be found in Appendices 7-11.

In those who abstained throughout the study, there was a main effect of product during the morning session, indicating that urges and withdrawal symptoms were significantly lower overall during the EC condition (urge to smoke: $F(1, 16) = 20.59$, $p < 0.001$; irritability: $F(1, 16) = 8.32$, $p = 0.011$; restlessness: $F(1, 16) = 14.22$, $p = 0.002$; difficulty concentrating: $F(1, 16) = 5.07$, $p = 0.039$; and composite withdrawal: $F(1, 16) = 13.35$, $p = 0.002$).

There was also a significant main effect of time in the morning for urge to smoke ($F(4, 64) = 9.29$, $p < 0.001$), irritability ($F(2.24, 35.83) = 5.63$, $p = 0.006$), restlessness ($F(1.94, 31.03) = 6.18$, $p = 0.006$), and composite withdrawal ($F(1.81, 28.97) = 5.71$, $p = 0.010$), with reductions from post-cue evident at 5 and 10 minutes post-product use (see Figures 4.2, 4.3, 4.4 and 4.6, respectively, top panel). There were no significant interactions between product and time, for any items, though restlessness tended to decrease to a greater extent early on in the EC condition vs. SB ($F(4, 64) = 2.43$, $p = 0.057$).

A different pattern of results emerged during the evening session; there was only a significant effect of time evident for urge to smoke ($F(2.44, 38.98) = 6.80$, $p = 0.002$). All other withdrawal symptoms remained stable over time, with no differences between products. Figures 4.1-4.5 (top panel) show the ratings for all items by condition, over 1 hour, in those who abstained.

Table 4.5: Summary of ANOVA analysis for urges and withdrawal ratings over 1 hour in abstainers.

	Product	Time	Product x Time
N= 17		**F (df), p value**	
Morning			
Urge to smoke	20.59 (1, 16) p< 0.001	9.29 (4, 64) p< 0.001	1.51 (2.42, 38.73) p= 0.230
Irritability	8.32 (1, 16) p= 0.011	5.63 (2.24, 35.83) p= 0.006	0.74 (4, 64) p= 0.568
Restlessness	14.22 (1, 16) p= 0.002	6.18 (1.94, 31.03) p= 0.006	2.43 (4, 64) p= 0.057
Difficulty Concentrating	5.07 (1, 16) p= 0.039	1.69 (1.95, 31.23) p= 0.201	0.30 (4, 64) p= 0.878
Composite withdrawal	13.35 (1, 16) p= 0.002	5.71 (1.81, 28.97) p= 0.010	0.92 (4, 64) p= 0.457
Evening			
Urges to smoke	0.008 (1, 16) p= 0.932	6.80 (2.44, 38.98) p= 0.002	1.23 (2.44, 39.02) p= 0.312
Irritability	0.05 (1, 16) p= 0.831	1.97 (1.38, 22.07) p= 0.172	1.17 (4, 64) p= 0.332
Restlessness	0.52 (1, 16) p= 0.480	0.95 (1.33, 21.21) p= 0.367	0.26 (4, 64) p= 0.902
Difficulty Concentrating	0.54 (1, 16) p= 0.475	1.02 (1.23, 20.71) p= 0.347	0.79 (4, 64) p= 0.534
Composite withdrawal	0.42 (1, 16) p= 0.525	1.26 (1.27, 3.17) p= 0.286	0.30 (4, 64) p= 0.903

Table 4.6: Summary of ANOVA analysis for urges and withdrawal ratings over 1 hour (whole sample)

	Product	**Time**	**Product x Time**
N= 35		**F (df), p value**	
Morning			
Urge to smoke	14.14 (1, 34) p= 0.001	17.18 (3.15, 106.97) p< 0.001	3.65 (2.71, 92.08) p= 0.019
Irritability	8.08 (1, 34) p= 0.008	5.29 (2.14, 72.88) p= 0.006	0.62 (2.43, 82.54) p= 0.573
Restlessness	12.96 (1, 34) p= 0.001	11.78 (1.92, 65.34) p< 0.001	2.02 (2.41, 81.83) p= 0.130
Difficulty Concentrating	4.82 (1, 34) p= 0.035	3.09 (2.63, 89.43) p= 0.037	0.57 (2.81, 95.61) p= 0.625
Composite withdrawal	10.77 (1, 34) p= 0.002	9.10 (2.11, 2.52) p< 0.001	1.19 (2.52, 85.71) p= 0.316
Evening			
Urges to smoke	4.41 (1, 34) p= 0.043	11.69 (2.69, 91.48) p< 0.001	1.37 (2.66, 90.58) p= 0.258
Irritability	2.50 (1, 34) p= 0.123	1.89 (1.98, 67.32) p= 0.159	1.81 (2.52, 85.65) p= 0.160
Restlessness	3.21 (1, 34) p= 0.082	4.49 (1.96, 66.76) p= 0.015	1.15 (2.10, 71.35) p= 0.326
Difficulty Concentrating	0.43 (1, 34) p= 0.517	2.35 (1.94, 65.99) p= 0.105	0.27 (2.11, 71.66) p= 0.775
Composite withdrawal	2.48 (1, 34) p= 0.125	3.52 (1.81, 61.44) p= 0.040	1.19 (2.24, 76.07) p= 0.315

Figure 4.2: Mean urge to smoke ratings over 1 hour

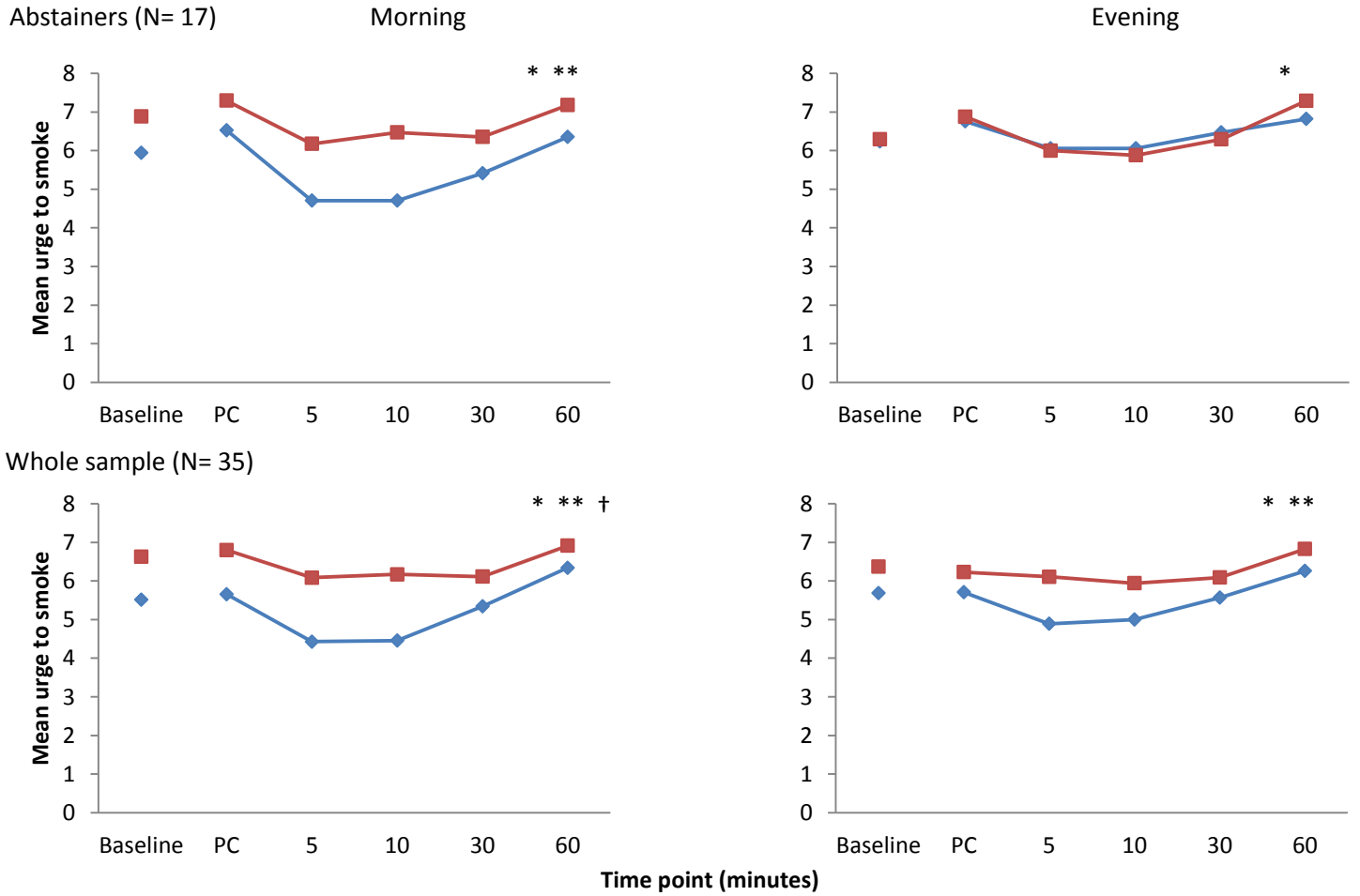


***Figure 4.2** shows the mean urge to smoke during morning and evening sessions over one hour, rated on a scale of 0 (not at all) to 10 (extremely). Product was administered post-cue exposure (PC). *, ** and † indicate significant effects of Time, Product and a Time x Product interaction, respectively (p≤ 0.05)*

Figure 4.3: Mean irritability ratings over 1 hour

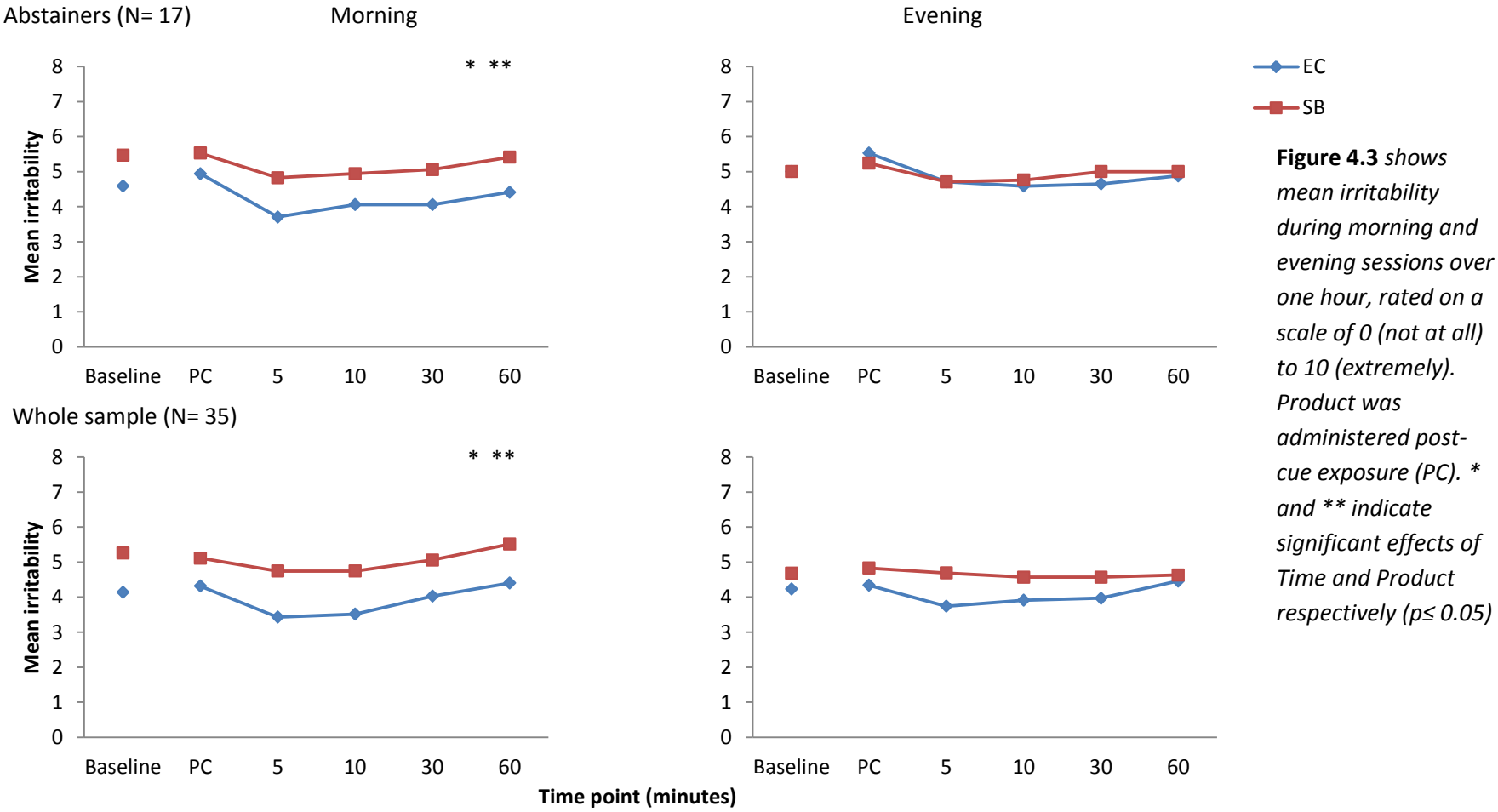


***Figure 4.3** shows mean irritability during morning and evening sessions over one hour, rated on a scale of 0 (not at all) to 10 (extremely). Product was administered post-cue exposure (PC). * and ** indicate significant effects of Time and Product respectively (p≤ 0.05)*

Figure 4.4: Mean restlessness ratings over 1 hour

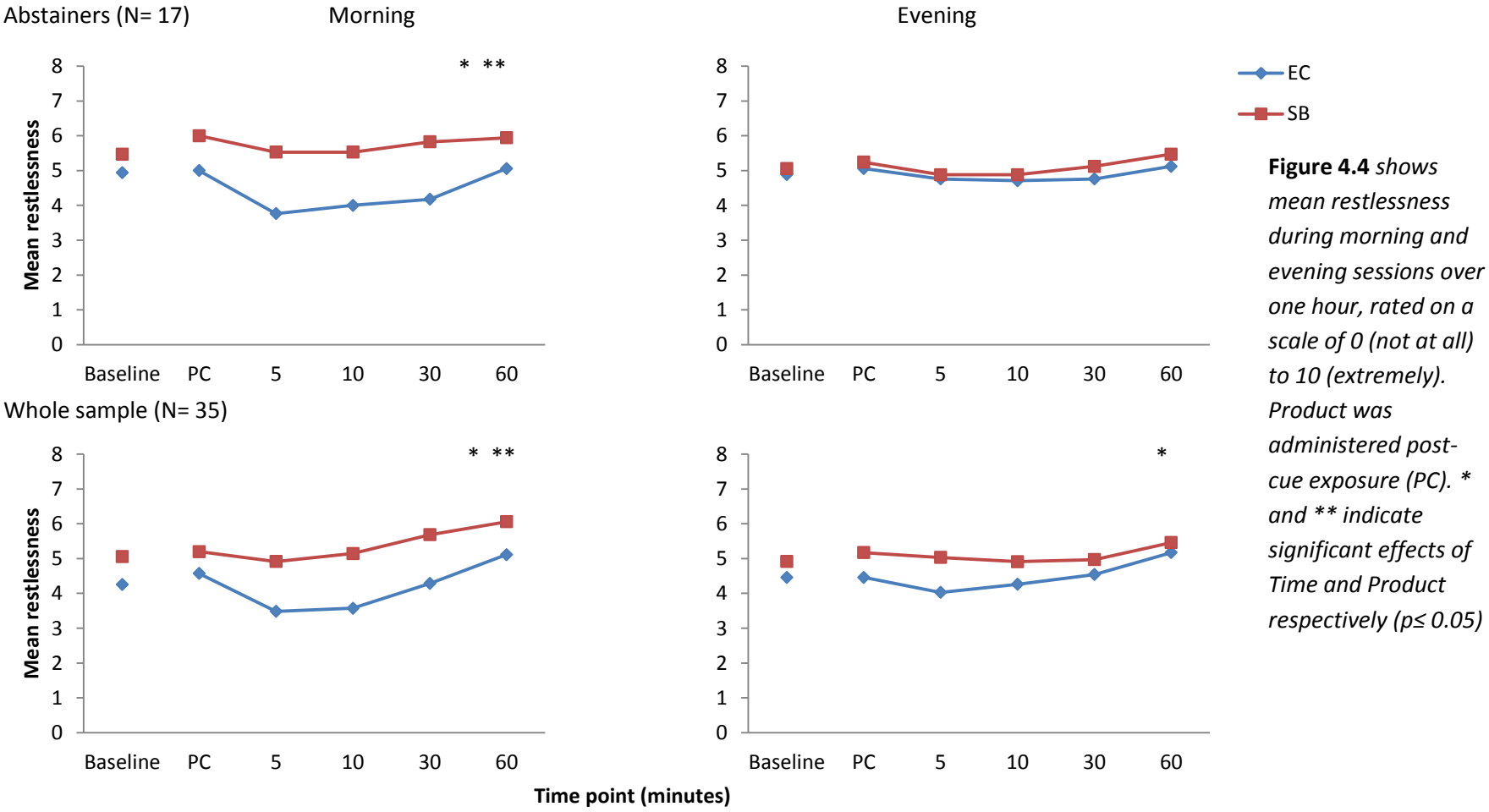


Figure 4.4 *shows mean restlessness during morning and evening sessions over one hour, rated on a scale of 0 (not at all) to 10 (extremely). Product was administered post-cue exposure (PC). * and ** indicate significant effects of Time and Product respectively (p≤ 0.05)*

Figure 4.5 Mean ratings of difficulty concentrating over 1 hour

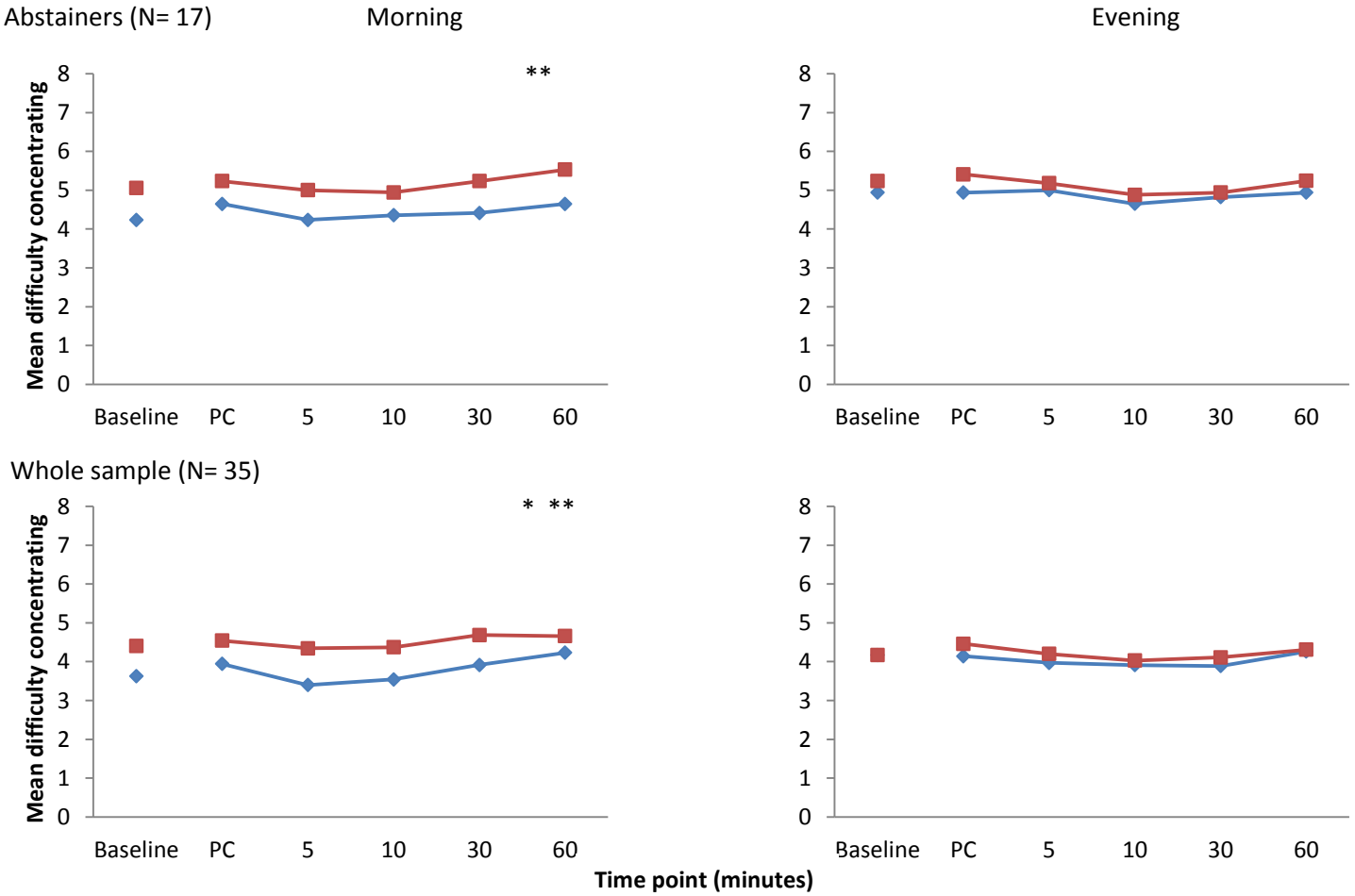


Figure 4.5 *shows mean difficulty concentrating during morning and evening sessions over one hour, rated on a scale of 0 (not at all) to 10 (extremely). Product was administered post-cue exposure (PC). * and ** indicate significant effects of Time and Product respectively (p≤ 0.05)*

Figure 4.6: Mean composite withdrawal ratings over 1 hour

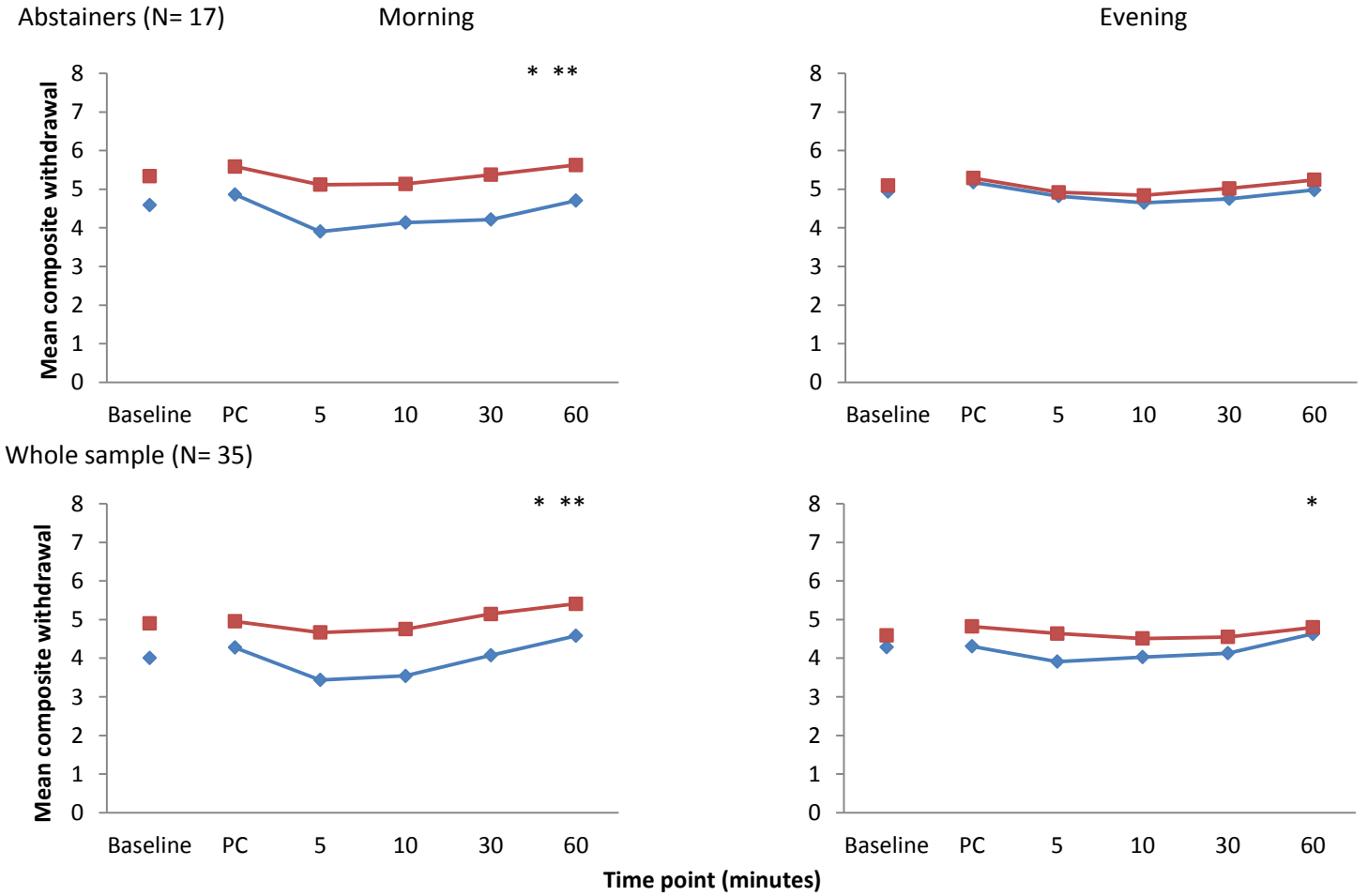


***Figure 4.6** shows mean composite withdrawal during morning and evening sessions over one hour, rated on a scale of 0 (not at all) to 10 (extremely). Product was administered post-cue exposure (PC). * and ** indicate significant effects of Time and Product respectively (p≤ 0.05)*

For the whole sample of participants, all items overall were rated significantly lower during the EC condition vs. SB in the morning (urge to smoke: F (1, 34) = 14.14, p= 0.001; irritability: F (1, 34) = 8.08, p= 0.008; restlessness: F (1, 34) = 12.96, p= 0.001; difficulty concentrating: F (1, 34) = 4.82, p= 0.035; and composite withdrawal: F (1, 34) = 10.77, p= 0.002). There were also significant changes over time (urge to smoke: F (3.15, 106.97) = 17.18, p< 0.001; irritability: F (2.14, 72.88) = 5.29, p= 0.006; restlessness: F 1.92, 65.34) = 11.78 , p< 0.001; difficulty concentrating: F (2.63, 89.43) = 3.09, p= 0.037; and composite withdrawal: F (2.11, 2.52) = 9.10, p< 0.001), with reductions mostly evident within the first 5-10 minutes after product use (see Figures 4.2-4.6, bottom panel).

There was also a significant interaction for urge to smoke (F (2.71, 92.08) = 3.65, p= 0.019); contrasts comparing each time-point to post-cue revealed only a trend for a greater reduction in urge from post-cue to 10 minutes during the EC vs. SB condition (F (1, 34) = 3.28, p= 0.079; see Appendix 12 for a summary of results). This interaction is perhaps more likely explained by the steeper increase in urge during the EC condition from 10 minutes onwards (see Figure 4.2, bottom panel).

In the evening, urge to smoke was rated significantly lower during the EC condition (F (1, 34) = 4.41, p= 0.043), and changes over time were apparent for urges (F (2.69, 91.48) = 11.69, p< 0.001) , restlessness (F (1.96, 66.76) = 4.49, p= 0.015) and composite withdrawal scores (F (1.81, 61.44) = 3.52, p= 0.040); although there were no significant interactions, mean scores are indicative of reductions at 5-10 minutes after product use during the EC condition, with scores during SB use remaining more stable (see Figures 4.2, 4.4 and 4.6, respectively, bottom panel).

4.2.7 Supplementary analyses: Acute effects on urges to smoke and withdrawal

The pattern of symptom ratings over the course of the hour indicated that any effects of the products and potential differences between them were immediate and relatively short-lived. The primary outcome analysis suggested some advantage for the EC. To examine theses acute effects more closely, urge scores and composite withdrawal were entered into a two-by-two repeated measures ANOVA (product [EC vs. SB] by time [post-cue vs. 10 minutes]). To simplify the analysis further, differences from post-cue to 10 minutes for each of the products separately were examined via paired samples t-test (or Wilcoxin Signed Ranks Test where data was not normally distributed).

In addition, area under the curve (AUC) analysis was also conducted for the first 10 minutes post-product use. This approach was used in earlier studies examining both ECs and NRT, with a similar design to the present study (Bullen et al., 2010, McRobbie et al., 2010), and has an advantage over the traditional repeated measures ANOVA approach. It provides a combined summary of the two types of information generated by a repeated measure design: the magnitude of effect and change over time. This simplifies the analysis and reduces the number of statistical comparisons. AUC was calculated from change scores (post-cue minus each time point [5 minutes and 10 minutes]) for urge to smoke and composite withdrawal. Alongside AUC, the greatest reduction in ratings (Rmax) and time at which this occurred (Tmax) were also computed. Paired samples t-test/Wilcoxin was used to test for any differences in these values between products.

These analyses were conducted for both morning and evening sessions, on the sample of participants who abstained throughout the study, and for the whole sample who completed the study.

4.2.7.1 **Results: Abstainer sample**

Separate analyses for each product revealed that both the SB and EC significantly reduced urge to smoke at 10 minutes, during both the morning (SB: t= 2.55, p= 0.022; EC: z= -2.90, p = 0.004) and evening sessions (SB: t= 3.89, p= 0.001; EC: t= 2.40, p= 0.029; see Figure 4.7, top panel). The ANOVA however revealed a significant interaction for the morning session,

Figure 4.7: Acute effects of products on urge to smoke in abstainers

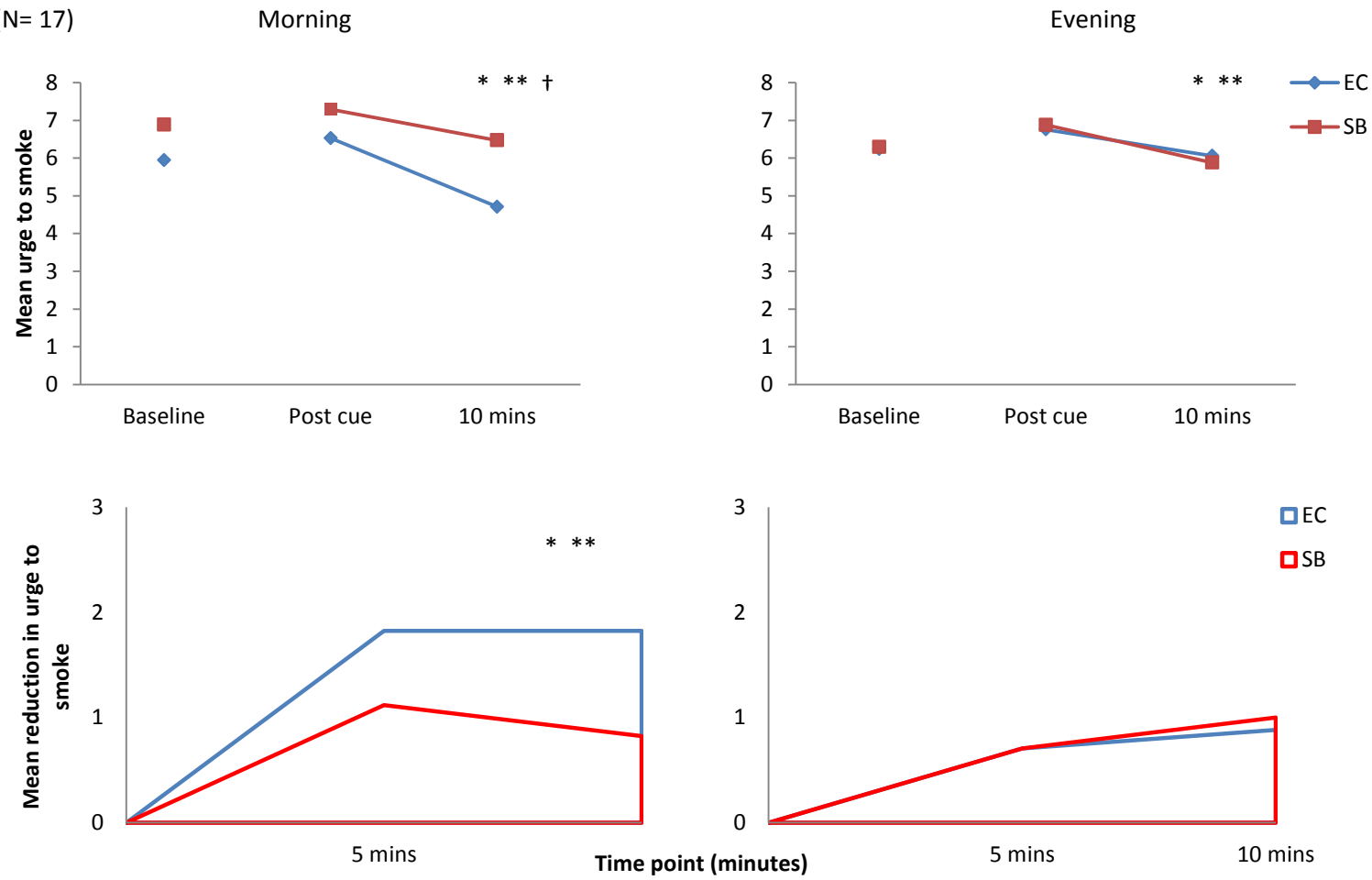


Figure 4.7 *Top panel shows the mean urge to smoke pre-product use and at 10-minutes post-product use. Product was administered post cue-exposure. * and ** indicate a significant change from post-cue to 10 minutes for EC and SB respectively, and † a significant interaction. Bottom panel shows reduction from post-cue in urge to smoke over 5 and 10 minutes post-product use. * and ** indicate a significant difference between products in AUC and Rmax, respectively. Analysis conducted on abstainers only; significance level p ≤ 0.05.*

indicating that reduction with EC was greater than SB (M= 1.82 (2.04) vs. 0.82 (1.33), respectively; F (1, 16) = 8.00, p= 0.012). This interaction was not evident during the evening session. Table 4.7 provides a summary of the repeated measures ANOVA analysis.

AUC analyses were in accordance with these results. During the morning session, mean AUC and Rmax were significantly larger for the EC condition (AUC: z= -2.06, p= 0.040; Rmax: z= -2.25, p= 0.024), with no differences between products apparent in the evening (see Table 4.8). Figure 4.6, bottom panel, shows the mean reduction in urge to smoke over 10 minutes by condition, during morning and evening sessions.

Composite withdrawal scores showed a similar pattern, with the EC significantly reducing withdrawal in the morning (t= 2.73, p= 0.015) and evening (t= 2.70, p= 0.016), as did the SB (morning: t= 2.41, p= 0.028; evening: t= 2.63, p= 0.018; see Figure 4.7, top panel). The ANOVA revealed no significant interaction for either the morning or evening session, indicating no difference in magnitude of reduction between products (see Table 4.7). There were no differences in mean AUC between the products during morning and evening sessions for withdrawal scores. Maximum reduction was significantly larger for the EC condition in the morning only (z= -1.99, p= 0.046; see Table 4.8).

Table 4.7: Summary of ANOVA analysis on the acute effects of products on urges and withdrawal ratings in abstainers.

	Product	**Time**	**Product x Time**
N= 17		**F (df) p value**	
Morning			
Urge to smoke	13.79 (1, 16) p= 0.002	12.23 (1, 16) p= 0.003	8.00 (1, 16) p= 0.012
Composite withdrawal	10.23 (1, 16) p= 0.006	9.96 (1, 16) p= 0.006	1.05 (1, 16) p= 0.322
Evening			
Urges to smoke	0.006 (1, 16) p= 0.940	12.46 (1, 16) p= 0.003	1.21 (1, 16) p= 0.289
Composite withdrawal	0.26 (1, 16) p= 0.616	11.15 (1, 16) p= 0.004	1.24 (1, 16) p= 0.729

Time to maximum reduction was not significantly different at either session (see Table 4.8). Figure 4.7, bottom panel, shows the mean reduction in composite withdrawal over 10 minutes by condition, during morning and evening sessions.

4.2.7.2 **Results: Whole sample**

When the analyses were repeated on the whole sample, a similar pattern emerged for urge to smoke, in that the EC reduced urge to smoke during both sessions (morning: t= 3.69, p= 0.001; evening: (z = -2.78, p= 0.005), as did the SB (morning: z= -2.74, p= 0.006; evening: -2.73, p= 0.006; see Figure 4.8, top panel).

Table 4.8: Mean area under the curve (AUC), reduction maximum (Rmax), and time to Rmax (Tmax) values and summary test statistics for acute urges and withdrawal ratings in abstainers.

N= 17	**EC**	**SB**	**EC vs. SB**	
Morning	Mean (SD)		Test statistic	Sig. (p)
Urge to smoke				
AUC	13.68 (15.89)	7.65 (10.17)	z= - 2.06	0.040
Rmax	2.35 (2.09)	1.41 (1.37)	z= -2.25	0.024
Tmax	6.47 (2.94)	5.00 (3.06)	z= -1.29	0.197
Composite withdrawal				
AUC	6.62 (7.21)	3.48 (4.49)	t= -1.83	0.085
Rmax	1.12 (0.94)	0.75 (0.70)	z= -1.99	0.046
Tmax	5.29 (2.78)	5.29 (4.13)	z= 0	1.00
Evening				
Urge to smoke				
AUC	5.29 (9.18)	6.91 (5.63)	z= -0.91	0.362
Rmax	1.06 (1.14)	1.18 (0.88)	z= -0.28	0.776
Tmax	3.53 (3.43)	5.29 (3.29)	z= -1.51	0.130
Composite withdrawal				
AUC	3.09 (5.89)	2.99 (3.17)	z= -0.78	0.938
Rmax	0.63 (0.73)	0.63 (0.62)	z= -0.48	0.634
Tmax	5.29 (4.13)	5.88 (3.64)	z= -0.42	0.674

Figure 4.8: Acute effects of products on composite withdrawal in abstainers

(N= 17)

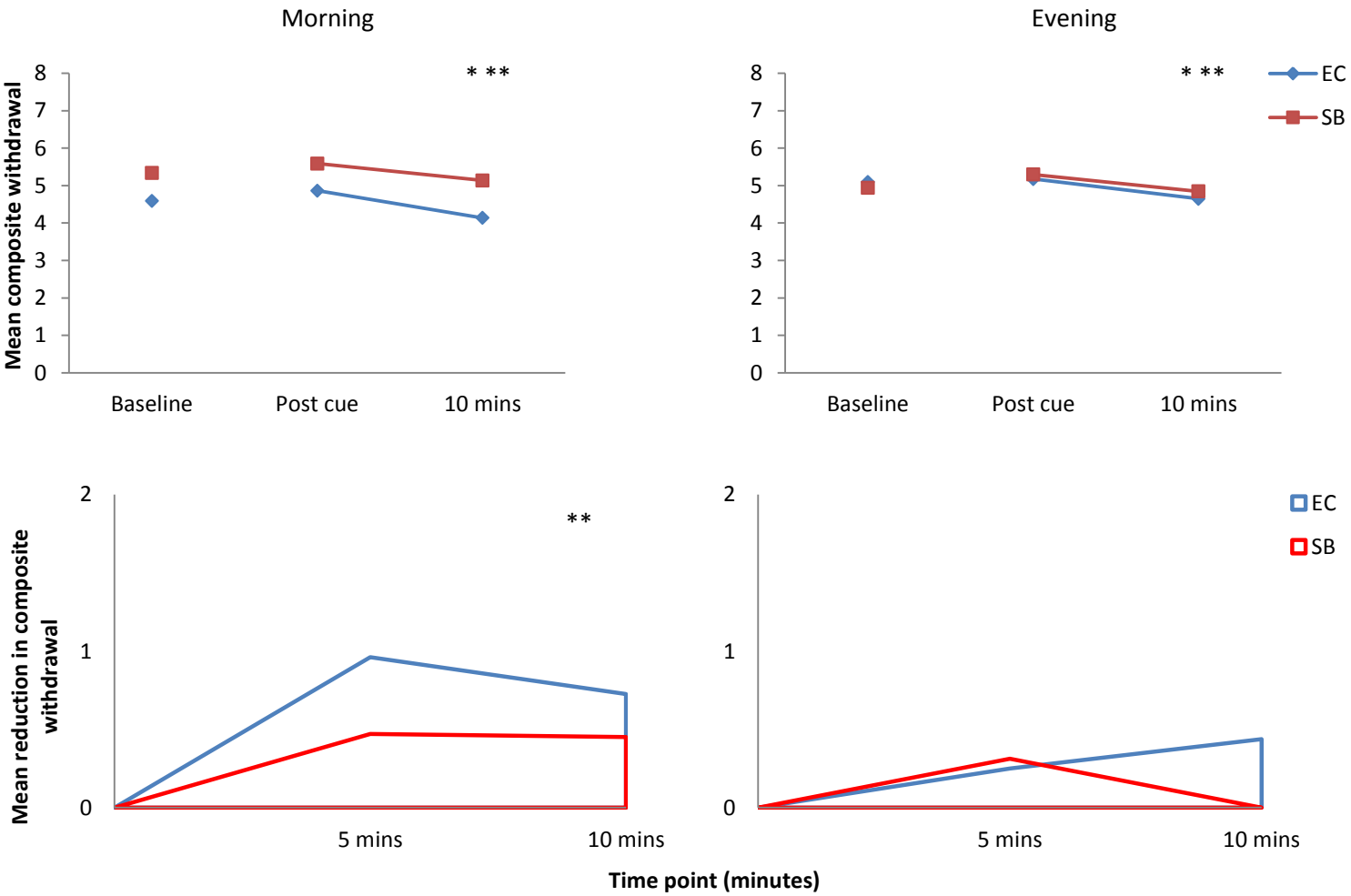


Figure 4.8 *Top panel shows the mean composite withdrawal score pre-product use and at 10-minutes post-product use. Product was administered post cue-exposure. * and ** indicate a significant change from post-cue to 10 minutes for EC and SB respectively. Bottom panel shows reduction from post-cue in composite withdrawal over 5 and 10 minutes post-product use. ** indicates a significant difference between products in Rmax. Analysis conducted on abstainers only; significance level p ≤ 0.05.*

Figure 4.9: Acute effects of products on urge to smoke (whole sample)

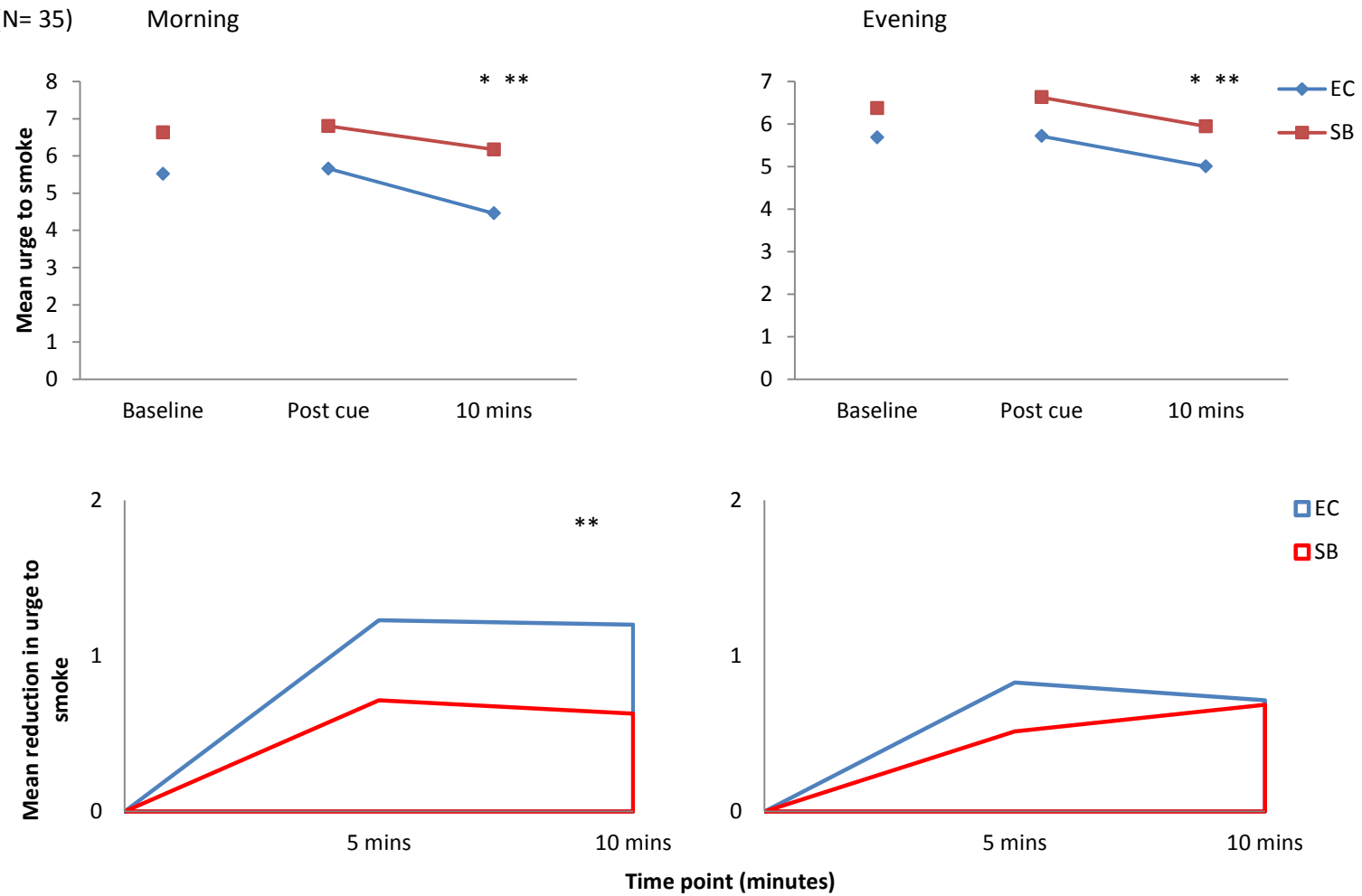


Figure 4.9 *Top panel shows the mean urge to smoke pre-product use and at 10-minutes post-product use. Product was administered post cue-exposure. * and ** indicate a significant change from post-cue to 10 minutes for EC and SB respectively. Bottom panel shows reduction from post-cue in urge to smoke over 5 and 10 minutes post-product use. ** indicates a significant difference between products in Rmax. Analysis includes non-abstainers; significance level p ≤ 0.05.*

Reduction in the morning tended to be larger for the EC, but the interaction did not reach significance (F (1, 34) = 3.28, p= 0.079; see Table 4.9).

Similarly, there was no difference in urge to smoke AUC between products, during the morning and evening, though AUC for the EC in the morning tended to be larger (z= -1.77, p=0.077). Reduction maximum in the morning was significantly larger for the EC (z= -2.59, p= 0.010; see Table 4.10). Figure 4.9, bottom panel, shows the mean reduction in urge to smoke over 10 minutes by condition, during morning and evening sessions.

Composite withdrawal scores followed a slightly different pattern of results. The EC reduced withdrawal acutely in the morning (z= -3.20, p= 0.001), but the reduction was not significant during the evening session (t= 1.47, p= 0.151). In contrast, the SB had no effect during the morning, (t= 1.08, p= 0.288) but reduced withdrawal significantly in the evening (t= 2.16, p= 0.038), though the reduction was modest (see Figure 4.10, top panel). Interactions between product and time in the morning did not quite reach significance (F (1, 34) = 3.53, p= 0.069; see Table 4.9).

Table 4.9: Summary of ANOVA analysis on the acute effects of products on urges and withdrawal ratings (whole sample).

	Product	**Time**	**Product x Time**
N= 35		**F (df) p value**	
Morning			
Urge to smoke	15.46 (1, 34) p< 0.001	16.51 (1, 34) p< 0.001	3.28 (1, 34) p= 0.079
Composite withdrawal	10.45 (1, 34) p= 0.003	9.43 (1, 34) p= 0.004	3.53 (1, 34) p= 0.069
Evening			
Urges to smoke	4.91 (1, 34) p= 0.034	15.30 (1, 34) p< 0.001	0.004 (1, 34) p= 0.947
Composite withdrawal	6.24 (1, 34) p= 0.017	0.004 (1, 34) p= 0.952	3.39 (1, 34) p= 0.919

Table 4.10: Mean area under the curve (AUC), reduction maximum (Rmax), and time to Rmax (Tmax) values and summary test statistics for acute urges and withdrawal ratings (whole sample).

N= 35	**EC**	**SB**	**EC vs. SB**	
Morning	Mean (SD)		Test statistic	Sig. (p)
Urge to smoke				
AUC	9.14 (14.35)	5.14 (9.23)	z= -1.77	0.077
Rmax	1.80 (1.78)	1.03 (1.20)	z= -2.59	0.010
Tmax	5.29 (3.42)	4.00 (3.60)	z= -1.48	0.139
Composite withdrawal				
AUC	6.02 (9.67)	1.93 (7.81)	z= -2.16	0.031
Rmax	1.14 (1.14)	0.69 (0.81)	z= -2.01	0.044
Tmax	5.00 (3.43)	4.43 (4.16)	z= -0.71	0.477
Evening				
Urge to smoke				
AUC	5.93 (11.91)	4.29 (8.57)	z= -0.48	0.628
Rmax	1.17 (1.34)	1.00 (1.14)	z= -0.57	0.589
Tmax	3.57 (3.34)	4.43 (3.98)	z= -1.10	0.273
Composite withdrawal				
AUC	2.71 (6.17)	1.69 (5.64)	z= -0.64	0.520
Rmax	0.60 (0.72)	0.55 (0.67)	z= -0.11	0.991
Tmax	4.43 (3.98)	4.71 (4.19)	z= -0.29	0.771

Differences between products were more apparent with AUC analyses (Table 4.10). AUC and Rmax values for composite withdrawal scores were significantly larger for the EC during the morning session (AUC: z= -2.16, p= 0.031; Rmax: z= -2.01, p= 0.044) but any differences were not significant during the evening. Figure 4.10, bottom panel, shows the mean reduction in urge to smoke over 10 minutes by condition, during morning and evening sessions.

Figure 4.10: Acute effects of products on composite withdrawal (whole sample)

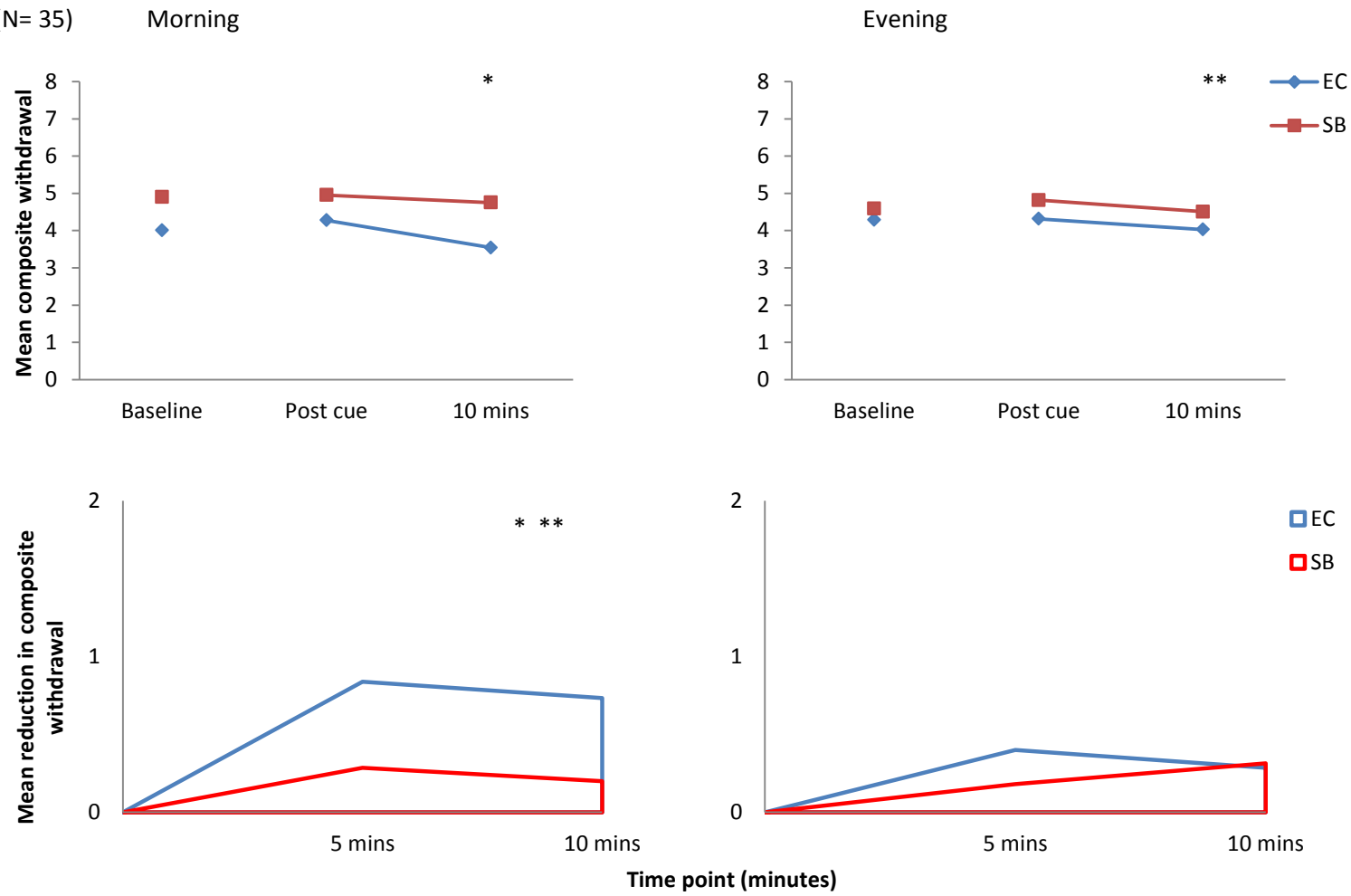


Figure 4.10 *Top panel shows the mean composite withdrawal score pre-product use and at 10-minutes post-product use. Product was administered post cue-exposure. * and ** indicate a significant change from post-cue to 10 minutes for EC and SB respectively. Bottom panel shows reduction from post-cue in composite withdrawal over 5 and 10 minutes post-product use.* and ** indicate a significant difference between products in AUC and Rmax, respectively. Analysis includes non-abstainers; significance level $p \leq 0.05$.*

4.2.8 **Urges to smoke and withdrawal symptoms during the day**

Table 4.11 shows the mean composite MPSS withdrawal and urge scores completed in the evening. In general, participants reported moderate levels of withdrawal and urges over the course of the day. In abstainers, there were no differences between conditions in composite withdrawal scores, but composite urge score was significantly lower in the EC condition (t= -2.26, p= 0.038). When individual urge items were analysed, participants experienced the same frequency of urges in both conditions, but the strength of these urges tended to be lower with EC than SB (z= -1.94, p= 0.052). With respect to individual MPSS items (depression, irritability, restlessness, difficulty concentrating and hunger), there were no differences between conditions on any items. A summary of the analysis can be found in Appendix 13.

When the whole sample was analysed, composite MPSS and urge scores showed a similar pattern, in that there were no differences in MPSS scores, but significantly lower urges to smoke in the EC condition (t= -4.01, p< 0.001; see Table 4.11).

Table 4.11: Mean scores and summary test statistics for composite MPSS and urges to smoke.

	MPSS	**Urge to smoke**	**Urge Frequency**	**Urge Strength**
Abstainers (N= 17)		**M (SD)**		
EC	2.52 (0.76)	3.26 (0.71)	3.35 (1.00)	3.18 (0.81)
SB	2.51 (0.68)	3.65 (1.14)	3.71 (1.21)	3.59 (1.18)
Test statistic	t= 0.09	t= -2.26	z= -1.60	z= -1.94
Sig. (p)	0.933	0.038	0.109	0.052
Whole Sample (N= 37)*				
EC	2.37 (0.78)	3.28 (0.89)	3.44 (1.07)	3.26 (0.94)
SB	2.46 (0.77)	3.82 (1.17)	3.87 (1.23)	3.76 (1.20)
Test statistic	t= -1.02	t= -4.01	t= -2.59	t= -3.51
Sig. (p)	0.314	<0.001	0.010	<0.001

**Two participants who did not attend the evening session gave responses via telephone*

Frequency and urge strength were also significantly lower in the EC condition (z= -2.59, p= 0.01; z= -3.51, p< 0.001, respectively). Irritability was found to be significantly lower for the EC condition (z= -2.08, p= 0.038) though the magnitude of this difference was small (EC: M= 2.49, SD= 1.17; SB: M= 2.84, SD= 1.39). Depression tended to be greater with the EC (M=2.00, SD= 1.20) vs. SB (M= 1.70, SD= 0.88), but ratings for depression were low in both conditions and the difference did not reach significance (z= -1.81, p= 0.070). A summary of the analysis can be found in Appendix 13.

4.2.9 Supplementary analyses: Baseline ratings during morning and evening sessions

To further examine the effect of the products over the course of the day, analyses were conducted to compare morning and evening baseline ratings for MNWS items, urge to smoke and composite withdrawal. Paired samples t-tests/Wilcoxin were used to compare ratings separately for each product, and data were entered into a two-by-two repeated measures ANOVA (product [EC vs. SB] by time [morning vs. evening]) to ascertain any interactional effects. Results are reported for the sample of abstainers, and the whole sample.

4.2.9.1 Results: Abstainer sample

Separate analyses showed that for the EC condition, mean baseline urge to smoke did not change significantly over the course of the day (morning: 5.94 (SD= 2.73), evening: 6.24 (SD= 2.66); t= -0.52, p= 0.611). This was also true for the SB condition (morning: 6.88 (SD= 2.62), evening: 6.29 (SD= 2.69); t= 0.97, p= 0.347; see Figure 4.11, top left panel). The repeated measures ANOVA revealed no significant interactions (see Table 4.12). The same pattern of results was evident for composite withdrawal scores (see Figure 4.11, bottom left panel), with no changes for the EC over the day (morning: 4.59 (SD= 2.60), evening: 4.94 (SD= 2.44); t= -0.71, p= 0.486) or SB (morning: 5.33 (SD= 2.51), evening: 5.10 (SD= 2.71); t= 0.55, p= 0.591). Accordingly, the interaction was not significant (see Table 4.12).

Figure 4.11: Mean baseline ratings of urge to smoke and composite withdrawal in the morning and evening

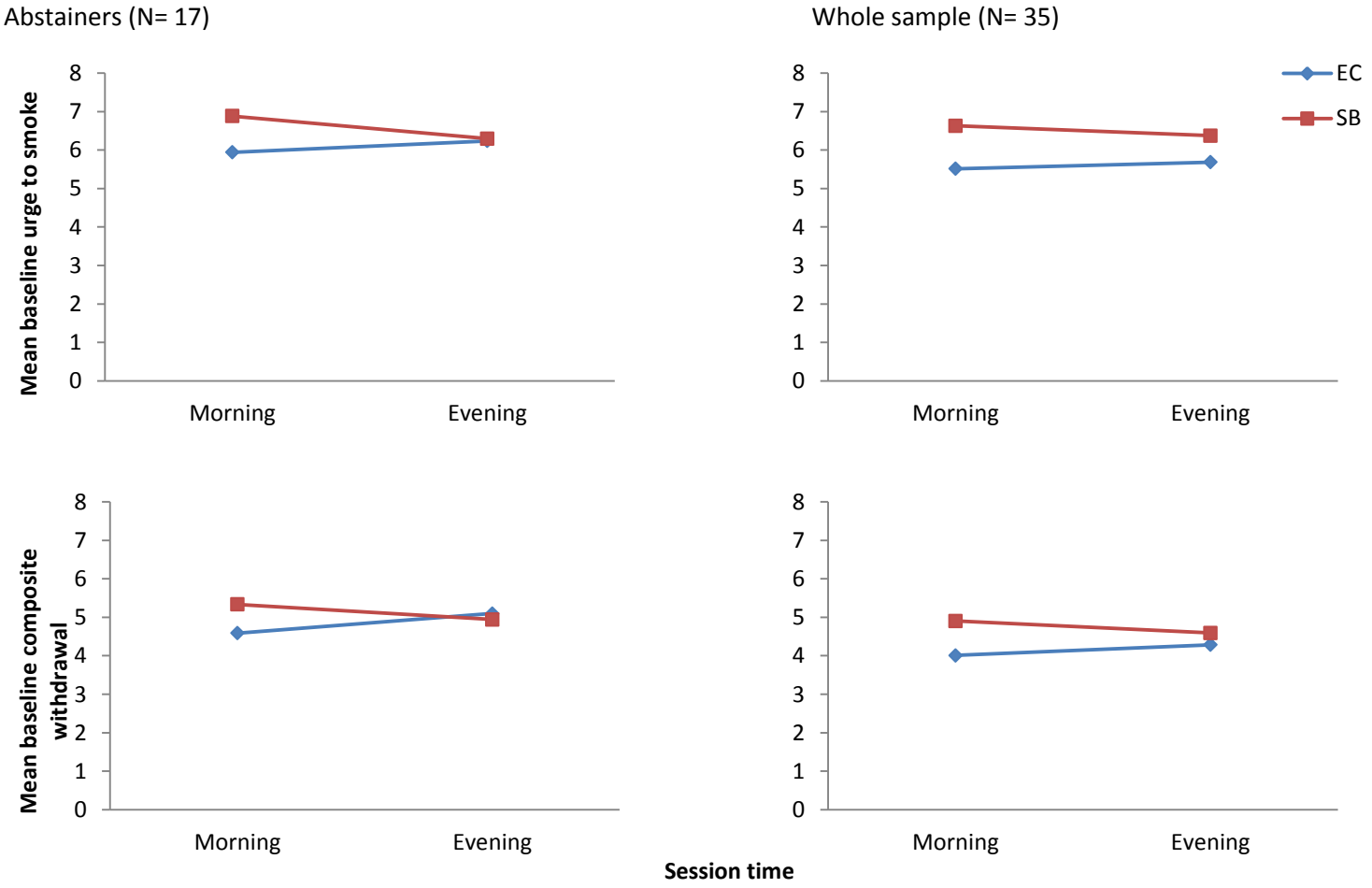


Figure 4.11 *shows the mean baseline ratings of urge to smoke (top panel) and composite withdrawal score (bottom panel) during morning and evening sessions, rated on a scale of 0 (not at all) to 10 (extremely), prior to commencing cue-exposure. There were no significant changes or interactions for either measure.*

Table 4.12: Summary of ANOVA analysis on baseline urge and withdrawal ratings in the morning and evening.

	Product	Time	Product x Time
Abstainers (N=17)		**F (df) p value**	
Urge to smoke	2.03 (1, 16) p= 0.173	0.076 (1, 16) p= 0.786	3.22 (1, 16) p= 0.092
Composite withdrawal	3.62 (1, 16) p= 0.075	0.020 (1, 16) p= 0.890	2.16 (1, 16) p= 0.161
Whole sample (N= 35)			
Urges to smoke	11.03 (1, 34) p= 0.002	0.01 (1, 34) p= 0.912	0.83 (1, 34) p= 0.370
Composite withdrawal	6.24 (1, 34) p= 0.017	0.00 (1, 34) p= 0.952	3.39 (1, 34) p= 0.074

4.2.9.2 **Results: Whole sample**

Analysis conducted on the whole sample revealed the same results, with no changes in mean urge to smoke evident from morning to evening for either the EC (morning: 5.51 (SD= 3.37), evening: 5.69 (SD= 3.12); z= -0.05, p= 0.959) or SB (morning: 6.63 (SD= 2.90), evening: 6.37 (SD= 2.95); z= -0.37, p= 0.710; see Figure 4.11, top right panel). This was also the case for mean composite withdrawal (see Figure 4.11, bottom right panel) for the EC (morning: 4.01 (SD= 2.90), evening: 4.29 (SD= 2.58); t= -0.79, p= 0.436) and SB (morning: 4.90 (SD= 2.61), evening: 4.59 (SD= 2.69); t= 0.90, p = 0.375), and again no significant interaction was evident (see Table 4.12).

4.2.10 **Product perceptions, preferences and adverse effects**

Table 4.13 shows the mean product ratings and percentage of participants choosing each product. Overall, participants perceived the EC more positively than the SB. The ECs were rated as more satisfying (z= -3.01, p= 0.003), and of more help in enabling participants to keep from smoking (z= -4.54, p< 0.001). Satisfaction with the EC still low however. They were also deemed to be less embarrassing to use (z= -2.56, p= 0.011); participants were more likely to use ECs as an aid to quitting in the future (z= -4.83, p< 0.001), and to recommend them to others who wanted to quit smoking (z= -4.59, p< 0.001). There was however no difference between the products in ratings of pleasantness (z= -0.77, p= 0.443).

When participants were asked to choose between the two products, the majority of participants favoured the EC than SB. Significantly more participants liked the EC (x^2= 22.73, p< 0.001), reported it was easier to use (x^2= 22.11, p= 0.011), more helpful in keeping them from smoking (x^2= 22.73, p< 0.001), less embarrassing (x^2= 26.81, p= 0.001), and more likely to use the EC in their own quit attempt (x^2= 22.73, p< 0.001) as well as recommend to others for quitting (x^2= 22.73, p< 0.001).

Seven participants reported adverse effects from the EC. These were moderate throat irritation/sore throat (N= 3); EC becoming hot on the lips/mouth (weak-moderate, N= 2); weak chest irritation (N= 1); moderate stomach ache (N= 1); and a strong feeling of dizziness (N= 1). For the SB condition, two participants reported strong pain from squeezing the ball.

Table 4.14 shows the responses participants gave regarding what they liked most and least about the EC and SB. Most participants liked the EC because of the sensory and behavioural replacement it provided (N= 17), and its similarity to cigarettes (N= 8), though the taste was the least liked aspect (N= 13), followed by the weight and size (N= 10). For the SB, the majority of participants were indifferent, and did not like or dislike anything about the product (N= 17 and 8, respectively). Some did report that the SB was pleasant to use (N= 10), and helped to provide a behavioural distraction (N= 5). The least liked aspects were that it gave no craving or urge relief (N= 9), and that it was impractical (N= 8).

Table 4.13: Mean product ratings and preferences.

Product ratings	**EC**	**SB**	**Sig. (p)**
N = 37[†]		**Mean (SD)**	
Satisfaction compared to usual cigarette	1.77 (0.96)	1.29 (0.80)	0.003
Helpful in keeping from smoking	2.69 (1.10)	1.55 (0.65)	<0.001
Pleasantness	2.69 (0.95)	2.55 (0.72)	0.433
Embarrassing to use	1.72 (0.92)	2.26 (1.13)	0.011
Would use to quit smoking	3.36 (1.14)	1.68 (0.74)	<0.001
Would recommend to others for quitting	3.38 (1.09)	1.89 (0.92)	<0.001
Product preferences		**% of participants**	
Liked more	89.2	10.8	<0.001
Easier to use*	71.4	28.6	0.011
More helpful in keeping from smoking	89.2	10.8	<0.001
More embarrassing to use**	20.6	79.4	0.001
More likely to use for quitting smoking	89.2	10.8	<0.001
More likely to recommend to others for quitting	89.2	10.8	<0.001

[†]*Two participants who did not attend the evening session gave responses via telephone. *N= 2 and **N= 3 did not choose between the two products.*

Table 4.14: Open responses to questions "What did you like most/least about the product you used today?"

Liked Most		**Liked Least**	
EC	**N***		**N***
Sensorimotor replacement	17	Taste	13
Similarity to real cigarettes	8	Weight/size/shape	10
Helped with cravings/prevented smoking	5	No craving relief/satisfaction	5
Less harmful/'clean'/no smell	4	No nicotine rush or 'hit'	4
Taste/flavour	4	Technical problems	1
Can be used anywhere	3	Throat irritation	1
Easy to carry around	1	Increased urge to smoke	1
Nothing	3	Not acceptable to use everywhere	1
		Difficult to puff on	1
		Nothing	7
SB			
Pleasant to use/felt nice/soft	10	No craving relief	9
Behavioural replacement/distraction	5	Size/impractical to use	8
Calming/relaxing	3	No sensory replacement	4
Helpful for keeping from smoking	1	Embarrassing/felt self-conscious	2
Convenient size	1	Difficult/painful to squeeze	2
Nothing	17	Too dissimilar to smoking	1
		Made more irritable/annoyed	1
		Increased urge to smoke	1
		Everything	1
		Nothing	8

**N refers to the frequency of responses. Some participants gave more than one answer.*

4.3 **Discussion**

The aim of the present study was to investigate whether SMR effects could surpass simple distraction. Here, the nicotine-free EC was compared to a SB on urges to smoke and withdrawal following overnight abstinence and abstinence over one day. Both the EC and SB alleviated urge to smoke and most withdrawal symptoms acutely, following overnight abstinence. Ratings were generally lower with the EC over the hour, most likely reflecting lower ratings at baseline. Urge to smoke, the primary outcome of interest, reduced to a lesser extent with the SB, but analysis of change scores at 10 minutes between products did not reach significance. The change seen here with the EC was smaller compared to a previous similar study; Bullen *et al* (2010), reported a mean reduction of 2.8 units with the nicotine-free EC from baseline to 10 minutes following overnight abstinence, compared to 1.82 ('abstainer' sample), and 1.20 (whole sample), seen in the present study. It may be that effects were somewhat diminished as ratings of urge to smoke were slightly lower in the EC condition to begin with compared to SB.

When the data were examined more closely however, and in those who had abstained throughout the study, the EC was more effective in alleviating urges acutely compared to the SB. This was further confirmed with AUC analyses, whereby AUC values and mean reduction maximum were significantly larger for the EC vs. SB. Nevertheless, the magnitude of difference was still fairly modest. Differences between products for composite withdrawal on the other hand were less pronounced.

After participants had used the products throughout the day and continued to abstain, there was a small benefit of the EC with respect to urge to smoke over the course of the day (MPSS ratings), and in particular the intensity of these. As before, the differences between products were modest. Over the course of the hour, there were few changes in urges to smoke and withdrawal, except for a slight dip in urges at 5 and 10 minutes. This occurred regardless of product used, and additional analyses confirmed that both products reduced urges and withdrawal at 10 minutes to a similar extent. This lack of difference appeared to be a result of reduced EC effectiveness, as opposed to an improvement with the SB. These findings suggest that SMR may only have an effect early on in the treatment phase. A similar finding was also reported with the citric acid aerosol, whereby treatment

effects were only evident at the start of the study, and dissipated quickly after repeated use and prolonged abstinence (Levin et al., 1990).

There may be a number of potential explanations for these findings. Firstly, the novelty of using a device which resembles a cigarette and retains similar behaviours to smoking may have been enough to alleviate symptoms when first used, but not after continued use. Related to this is the possibility that the sensorimotor input from the EC was inadequate or even unpleasant. Indeed, the taste of the EC was the most disliked aspect reported by participants, and this may have reduced adherence to the product particularly in the evening when novelty effects had worn off. It should also be considered that ratings of symptoms are also highly subjective and participants may simply have perceived the EC to be more effective in the morning.

With regards to the impact of the cue-exposure procedure, in abstainers at least, the procedure seemed to increase urges, restlessness and difficulty concentrating during the morning session, and urges and irritability in the evening to a modest extent. Interestingly, symptom ratings were on the whole lower in the morning prior to product use, when participants were told they would be using the EC vs. the SB. Furthermore, restlessness increased to a greater extent following cue-exposure, when participants were told they would be using the SB rather than the EC. These findings are suggestive of an expectancy effect; that is, participants may have had the expectation that the EC would be of more help than the SB, resulting in lower symptom ratings.

Overall, there is some evidence that conditioned SMR may surpass distraction effects, but the small differences between products, particularly after continued use, suggest that this effect may be short-lived. On the other hand, the finding that participants had a strong preference for the EC, and primarily reported they liked it because it provided sensorimotor input (in particular the vapour, being able to inhale and exhale) and its similarity to cigarettes, suggest there is an important role for sensorimotor input, if anything at least in terms of user acceptability. Thus, despite somewhat limited EC effects in urge and withdrawal relief, the sensorimotor aspects gave it added appeal over simple behavioural distraction. One notion which should be considered (and would have implications for the central SMR hypothesis), is that these contradictory findings could imply that sensorimotor factors are less involved in urge alleviation than previously hypothesised; smokers may still find ECs helpful, perhaps as a coping tool during abstinence, but this may not necessarily mean that they work by alleviating the urge to smoke.

It also could be possible that the sensorimotor input from the EC was insufficient or inadequate. The next step was to ascertain whether SMR requires a certain level of input or 'dose' to be effective. There is indication in the literature that SMR more proximal to conventional cigarettes would be more effective - and certainly this would hold theoretically - but this has not been empirically tested. The aim of Study 2 was therefore to compare the nicotine-free EC with the DNC, with the same design and procedures used here. Given the modest impact of the EC in this study, this would then also allow comparison between studies, to see how nicotine-free EC effects would compare in a different sample of smokers.

5 Study 2: Are sensorimotor effects 'dose' dependent?

5.1 Methodology

5.1.1 Aims

The aim of Study 2 was to assess whether sensorimotor effects were 'dose-dependent'. Here, the nicotine-free EC and DNC were compared directly to examine whether the proximal SMR delivered by DNCs, would be more effective at reducing urges to smoke and withdrawal symptoms than the EC.

5.1.2 Hypotheses

Since DNCs provide a greater level of SMR (i.e. real tobacco smoke), it was hypothesised that DNCs would be more effective at alleviating urges and withdrawal symptoms and would be perceived as more satisfying and helpful than ECs.

5.1.3 Design

This study followed the same design and procedures as that of Study 1. Participants took part in two conditions (DNC and EC, order counterbalanced), with a minimum of 2 days in between, and attended 2 one-hour controlled experiments on the same day (morning and evening).

5.1.4 Participants

5.1.4.1 Recruitment

Participants were recruited from patients attending the Royal London Hospital Smokers' Clinic, via advertisements in London newspapers, and through advertisements in staff bulletins at Queen Mary, University of London (see Appendix 1).

5.1.4.2 Inclusion/exclusion

Participants were included in the study if they were aged 18 or over, smoked at least 10 cigarettes per day, and smoked within the first hour of waking. Participants were excluded if they were pregnant/breast feeding, had an acute psychiatric illness, were taking part in other research, or were currently using an EC, NRT, or smoking nicotine-free cigarettes (e.g. herbal cigarettes).

5.1.5 Measures and Outcomes

5.1.5.1 Measures

The present study used the same measures as those in Study 1, listed below. A detailed description of the measures used is given in the Study 1 methodology. A copy of the clinical records form and baseline questionnaire can be found in Appendices 2 and 3, respectively.

1. Smokers Clinic Baseline Questionnaire: This is the standard Royal London Hospital baseline questionnaire that includes demographic details, health status, smoking history and the FTND (Heatherton et al., 1991).
2. Minnesota Nicotine Withdrawal Scale (MNWS; Hughes and Hatsukami, 1986): Measure of urges to smoke and withdrawal symptoms (irritability, restlessness, difficulty concentrating).
3. Mood and Physical Symptoms Scale (MPSS; West and Hajek, 2004): Measure of urges to smoke and withdrawal symptoms over the day.
4. Cue-reactivity: Measure of reactions to smoking-related cues.
5. Abstinence from conventional cigarettes: Measured with a Bedfont CO monitor, cut off <10ppm. For the DNC condition, abstinence over the course of the day was self-report only.
6. Product questionnaire: Measure of satisfaction, helpfulness, acceptability, and preferences adapted from previous work (Hajek et al., 1989, Bullen et al., 2010, McRobbie et al., 2010).
7. Adverse effects: Description of any adverse effects and strength of these.
8. Product use: Record of how often the product was used during the day (note one ‘use’ was defined as taking at least 5 puffs from the EC or DNC).

5.1.5.2 **Outcomes**

The primary outcome of interest was the difference between the two conditions in change (from post-cue) in urge to smoke at 10 minutes post-product use, following overnight abstinence. Secondary outcomes were to compare the DNC and EC on (i) urges and withdrawal symptoms over one hour, in the morning and evening; (ii) urges and withdrawal symptoms over the course of a day; and (iii) product satisfaction and preferences.

5.1.6 **Sample size**

As Study 1 used the same design and procedures as the present study, the sample size was calculated from those data, in order to obtain a more accurate idea of how the nicotine-free EC would affect acute urge scores following overnight abstinence. Data from Study 1 showed that the EC generated a mean reduction of 1.20 units (SD= 1.92) from post-cue to 10 minutes post-product use. The present study therefore required 40 participants in order to detect a minimum difference between the two conditions of 1.2 units, with 80% power, at a significance level of 0.05. Taking into account that three participants from Study 1 did not complete the second study session, the total sample size for Study 2 was increased to 45 to allow for some drop-out between sessions.

5.1.7 **Products**

The EC used in Study 1 was also used for the present study (Smoker's Angel Halo Electronic Cigarette, purchased from www.thesmokersangel.co.uk) with nicotine-free cartomizers.

DNCs (XODUS brand) were purchased from 22nd Century Group Inc., USA. These cigarettes contain extremely low levels of nicotine, about 95% reduced compared to most US brands (Xie et al., 2004). The machine yields of nicotine under ISO smoking conditions are approximately 0.088 mg nicotine/cigarette.

5.1.8 **Procedures**

This study followed the same procedures as Study 1, whereby participants attended the study centre on two separate days, following overnight abstinence. A copy of the participant information sheet is shown in Appendix 14. Two participants had CO readings between 18 and 20ppm during both morning sessions, but exceptions were granted as one participant was a heavy smoker (>40 CPD), and the other smoked heavily the night before. Sensitivity analysis of the primary outcome, with these participants removed, revealed similar results between this sub-sample and the whole sample that completed the study (see Appendix 15). Participants were allocated the EC on one day, and DNC the other (randomised, counterbalanced). As before, on each day, participants took part in two 1-hour controlled experiments (morning and evening), and used their allocated product throughout the day whilst remaining abstinent from their conventional cigarettes. The same cue-exposure procedures as those of Study 1 were also used for the present study.

The study was approved by the National Research Ethics Service committee (Clinical Trials Registration Number: NCT01414998 [www.clinicaltrials.gov]), and ran from October 2012 until March 2013.

5.1.9 **Data analysis**

Due to the same study design and procedures, the same sets of analyses outlined previously for Study 1 were conducted for the present study comparing the EC and the DNC.

In summary, these were:

1. Cue-exposure effects on urges and MNWS ratings: Repeated measures ANOVA (Product [DNC vs. EC] x Time [baseline vs. post-cue]) for morning and evening sessions.
2. Urges and MNWS ratings over 1 hour: Repeated measures ANOVA (Product [DNC vs. EC] x Time [post-cue, 5, 10, 30 and 60 minutes]) for morning and evening sessions. Any significant interactions were followed up with simple contrasts (comparing each time point to post-cue).

3. Acute effects of products on urge to smoke following overnight abstinence (primary outcome): paired sample t-test/Wilcoxin Signed Rank Test on change scores (calculated from post-cue to 10 minutes post-product use).
4. Urge to smoke and withdrawal symptoms over the day (MPSS scores): Paired samples t-test/Wilcoxin Signed Rank Test.
5. Differences between products in amount of product use (defined as total us over the day) and product ratings: Paired samples t-test/Wilcoxin Signed Rank Test.
6. Differences in abstinence over the day: McNemar Test.
7. Product preferences: Chi-square test.
8. Open responses to questions "liked most/least about the product used": Categorised and frequencies of responses reported.
9. Adverse effects: Frequency reported along with strength rating (averaged across participants if N>1).

5.2 Results

5.2.1 Participant characteristics

Forty-five participants consented to take part in the study, and all were randomised and completed the first session. Four participants did not attend the second session (N= 3 for DNC; N= 1 for EC). Participant demographics and baseline characteristics of those who completed the study are listed in Table 5.1.

5.2.2 Compliance with abstinence

During the EC condition, 28 of 41 participants (68.3%) abstained (CO validated) from cigarettes during the day, and 38 of 41 (92.7%) abstained during the DNC condition (self-reported). The difference in abstinence rates between the two conditions was significant (p= 0.002). Twenty-eight participants were abstinent during both conditions, and made up the 'abstainer' sample.

Table 5.1: Study 2 Participants Characteristics.

Demographics/baseline characteristics	**% (N= 41)**
Gender	
Male	53.7
Ethnicity	
Caucasian	65.9
Mixed/other	34.1
Don't wish to answer	0
Employment status	
Employed	41.5
Unemployed	26.8
Student	7.3
Other (e.g. retired, sick/disabled)	24.4
Education	
Higher	58.5
Secondary or none	41.5
	Mean (SD)
Age	42.9 (15.6)
CPD	20.6 (9.7)
FTND	5.6 (1.9)

5.2.3 **Product use**

There was a significant difference in the amount of product use over the course of the day between the two conditions (z= -2.39, p= 0.017). The EC was used on average 13.9 times (SD= 13.8), and DNC, 9.4 times (SD= 4.1).

5.2.4 Primary outcome: Acute effects on urges to smoke after overnight abstinence

Urge to smoke change scores (from post-cue to 10 minutes) in the two conditions, following overnight abstinence were compared in order to test the primary hypothesis that the DNC would be more effective compared to the EC. This analysis was conducted on the full sample of participants who completed the study, as all participants were abstinent in the morning session. Both the EC and DNC reduced urge to smoke following product use, (M= 2.95, SD= 2.82 for EC change; M= 3.10, SD= 2.72 for DNC change), but there were no significant differences in magnitude of reduction between the two conditions (z= -0.76, p= 0.448).

5.2.5 Cue-exposure effects

The mean ratings of urge to smoke and withdrawal symptoms pre and post cue-exposure for each condition are shown in Table 5.2 (abstainer sample) and Table 5.3 (whole sample), together with a summary of ANOVA analyses.

On the whole, ratings in the morning prior to product use were fairly moderate. In both samples, the cue-exposure only had a significant impact on ratings of difficulty concentrating (abstainer sample: F (1, 27) = 4.57, p= 0.042; whole sample: (F (1, 40) = 5.53, p= 0.024), whereby these ratings increased following cue-exposure. In the whole sample, there was also a trend for an increase in urge to smoke post cue-exposure (F (1, 40) = 3.32, p= 0.076),

Although there were no significant main effects of product in the morning in either of the samples analysed, there were some interactions between product and time. As in Study 1, participants were aware of which product they would be using prior to completing baseline and post-cue ratings, and as such these interactions could indicate a moderating role of product expectancy on cue reactivity. For the whole sample, there was a significant interaction for restlessness (F (1, 40) = 4.30, p= 0.045), and a marginal interaction for irritability (F (1, 40) = 3.88, p= 0.056), with mean scores reflecting an increase when participants were told they would be using the EC, and no change when they knew they would be using the DNC

There was also a suggestion of an interaction for urge to smoke in the abstainer sample; here, post-cue urge tended to reduce prior to DNC use, but increased prior to EC use (F (1, 27) = 3.71, p= 0.065).

Table 5.2: Mean ratings and summary of ANOVA analysis of urges and withdrawal symptoms pre and post cue-exposure in abstainers.

	Mean rating (SD)				F [1, 27] (p)		
N= 28	**EC baseline**	**EC post-cue**	**DNC baseline**	**DNC post-cue**	**Time**	**Product**	**Time x Product**
Morning							
Urges	6.89 (2.81)	7.54 (2.77)	7.14 (2.19)	6.89 (2.78)	0.49 (0.489)	0.18 (0.678)	3.71 (0.065)
Irritability	4.89 (3.06)	5.57 (3.12)	5.07 (2.45)	4.96 (2.84)	0.98 (0.330)	0.14 (0.708)	2.40 (0.133)
Restlessness	5.07 (2.96)	5.64 (2.95)	4.96 (2.59)	4.96 (2.81)	1.54 (0.226)	0.72 (0.404)	2.78 (0.107)
Difficulty concentrating	4.46 (2.72)	5.04 (3.09)	4.18 (2.78)	4.29 (2.79)	4.57 (0.042)	0.99 (0.329)	2.17 (0.152)
Evening							
Urges	6.57 (2.67)	6.29 (3.00)	4.75 (3.22)	5.00 (3.50)	0.01 (0.935)	4.97 (0.034)	1.82 (0.188)
Irritability	5.43 (3.21)	5.29 (3.45)	3.43 (3.36)	3.54 (3.36)	0.02 (0.896)	6.54 (0.016)	1.42 (0.244)
Restlessness	4.89 (3.26)	4.96 (3.23)	3.43 (3.28)	3.61 (3.51)	1.34 (0.257)	4.91 (0.035)	0.35 (0.558)
Difficulty concentrating	4.36 (3.26)	4.36 (3.39)	2.93 (2.89)	3.14 (3.26)	0.81 (0.375)	3.92 (0.058)	1.13 (0.297)

Table 5.3: Mean ratings and summary of ANOVA analysis of urges and withdrawal symptoms pre and post cue-exposure (whole sample).

	Mean rating (SD)				F [1, 40] (p)		
N= 41	**EC baseline**	**EC post-cue**	**DNC baseline**	**DNC post-cue**	**Time**	**Product**	**Time x Product**
Morning							
Urges	6.80 (2.87)	7.41 (2.78)	6.85 (2.52)	7.05 (2.76)	3.32 (0.076)	0.19 (0.662)	1.33 (0.256)
Irritability	4.61 (3.08)	5.32 (3.16)	4.88 (2.70)	4.83 (2.85)	2.35 (0.134)	0.07 (0.796)	3.88 (0.056)
Restlessness	4.98 (3.11)	5.59 (2.95)	4.98 (2.78)	4.95 (2.77)	2.20 (0.146)	0.82 (0.371)	4.30 (0.045)
Difficulty concentrating	4.54 (2.81)	5.05 (3.06)	4.32 (2.91)	4.51 (2.79)	5.53 (0.024)	0.99 (0.326)	1.03 (0.317)
Evening							
Urges	6.41 (2.76)	6.49 (2.97)	4.98 (3.33)	5.07 (3.42)	0.16 (0.696)	7.09 (0.011)	0 (0.948)
Irritability	5.02 (3.09)	4.95 (3.29)	3.34 (3.24)	3.46 (3.16)	1.35 (0.812)	8.83 (0.005)	1.35 (0.253)
Restlessness	4.85 (3.05)	4.95 (3.10)	3.44 (3.06)	3.63 (3.35)	1.62 (0.210)	8.69 (0.005)	0.42 (0.523)
Difficulty concentrating	4.32 (3.17)	4.54 (3.26)	2.80 (2.74)	2.95 (3.05)	2.57 (0.117)	9.12 (0.004)	0.11 (0.746)

There was no evidence that the cue-exposure had a significant impact on any of the symptom ratings (i.e. no main effects of time were evident), following abstinence throughout the day. Ratings in general were of a moderate level, but somewhat lower for the DNC condition in comparison to the EC. Accordingly, the ANOVA revealed a main effect of product for urge to smoke ($F(1, 27) = 4.97$, $p= 0.034$), irritability ($F(1, 27) = 6.54$, $p= 0.016$) and restlessness ($F(1, 27) = 4.91$, $p= 0.035$), and a marginal effect for difficulty concentrating ($F(1, 27) = 3.92$, $p= 0.058$).

There was a similar pattern of results when all participants were included in the analysis; for all items there was a main effect of product in that urges ($F(1, 40) = 7.09$, $p= 0.011$), irritability ($F(1, 40) = 8.83$, $p= 0.005$), restlessness ($F(1, 40) = 8.69$, $p= 0.005$) and difficulty concentrating ($F(1, 40) = 9.12$, $p= 0.004$) were all significantly higher during the EC condition compared to the DNC.

5.2.6 **Urges to smoke and withdrawal symptoms over 1 hour**

Data were analysed with a repeated measures ANOVA to examine the effect of the products over the course of the hour, during the morning and evening session. Table 5.4 (abstainer sample) and Table 5.5 (whole sample) provide a summary of the ANOVA analyses. Mean ratings and standard deviations for each item by condition are shown in Appendices 16-20.

In the sample of participants who abstained throughout the study, there was a significant main effect of product for urge to smoke in the morning ($F(1, 27) = 4.54$, $p= 0.042$), and a marginal effect for composite withdrawal scores ($F(1, 27) = 4.11$, $p= 0.053$), whereby ratings were lower overall during the DNC condition. Irritability and difficulty concentrating also tended to be lower overall during the DNC condition, but did not reach significance ($F(1, 27) = 3.77$, $p= 0.063$; $F(1, 27) = 3.57$, $p= 0.070$, respectively). For both products, there were significant effects of time for all items (urge to smoke: $F(2.47, 66.76) = 21.36$, $p< 0.001$; irritability: $F(2.27, 61.22) = 11.35$, $p< 0.001$; restlessness: $F(2.25, 60.71) = 15.91$, $p< 0.001$; difficulty concentrating: $F(1.97, 52.81) = 6.95$, $p= 0.002$; and composite withdrawal: $F(2.07, 55.84) = 13.64$, $p< 0.001$). Mean ratings indicated both products alleviated all symptoms acutely (within 5-10 minutes), and these did not necessarily increase back to post-cue levels at 60 minutes, particularly with urge to smoke (see Figures 5.1- 5.5, top panel). The lack of interaction indicated these reductions occurred regardless of product.

A similar pattern emerged for the evening session, with both products alleviating symptoms acutely and to a similar extent, with the exception of difficulty concentrating which remained relatively stable over the hour (urge to smoke: $F(2.34, 63.30) = 18.76$, $p < 0.001$; irritability: $F(2.23, 60.17) = 4.68$, $p = 0.010$; restlessness: $F(1.50, 40.45) = 3.67$, $p = 0.046$; and composite withdrawal: $F(1.58, 42.62) = 4.01$, $p = 0.034$). For all items there were also significant main effects of product, with the DNC generating lower ratings overall compared to the EC (urge to smoke: $F(1, 27) = 5.73$, $p = 0.024$; irritability: $F(1, 27) = 5.25$, $p = 0.030$; restlessness: $F(1, 27) = 5.67$, $p = 0.025$; difficulty concentrating: $F(1, 27) = 4.35$, $p = 0.047$; and composite withdrawal: $F(1, 27) = 5.45$, $p = 0.027$). This is reflective of the fact that post-cue ratings were lower in the DNC condition to begin with (see Figures 5.1-5.5, top panel).

Table 5.4: Summary of ANOVA analysis for urges and withdrawal ratings over 1 hour in abstainers.

	Product	Time	Product x Time
N= 28		**F (df), p value**	
Morning			
Urge to smoke	4.54 (1,27) p= 0.042	21.36 (2.47, 66.76) p< 0.001	0.28 (2.03, 54.86) p= 0.763
Irritability	3.77 (1, 27) p= 0.063	11.35 (2.27, 61.22) p< 0.001	0.14 (1.95, 52.60) p= 0.861
Restlessness	2.18 (1, 27) p= 0.151	15.91 (2.25, 60.71) p< 0.001	0.67 (2.19, 59.24) p= 0.530
Difficulty concentrating	3.57 (1, 27) p= 0.070	6.95 (1.97, 52.81) p= 0.002	0.17 (2.82, 76.01) p= 0.907
Composite withdrawal	4.11 (1, 27) p= 0.053	13.64 (2.07, 55.84) p< 0.001	0.28 (2.17, 58.49) p= 0.778
Evening			
Urge to smoke	5.73 (1, 27) p= 0.024	18.76 (2.34, 63.30) p< 0.001	0.37 (2.98, 80.34) p= 0.772
Irritability	5.25 (1, 27) p= 0.030	4.68 (2.23, 60.17) p= 0.010	1.05 (2.73, 73.75) p= 0.373
Restlessness	5.67 (1, 27) p= 0.025	3.67 (1.50, 40.45) p= 0.046	0.75 (2.60, 70.20) p= 0.507
Difficulty Concentrating	4.35 (1, 27) p= 0.047	1.93 (1.70, 46.01) p= 0.162	0.435 (2.49, 67.09) p= 0.692
Composite withdrawal	5.45 (1, 27) p= 0.027	4.01 (1.58, 42.62) p= 0.034	0.72 (2.56, 69.14) p= 0.521

Table 5.5: Summary of ANOVA analysis for urges and withdrawal ratings over 1 hour (whole sample).

	Product	**Time**	**Product x Time**
N= 41		**F (df), p value**	
Morning			
Urge to smoke	3.60 (1, 40) p= 0.065	32.82 (2.50, 100.03) p< 0.001	0.48 (2.16, 86.25) p= 0.635
Irritability	2.07 (1, 40) p= 0.158	16.51 (2.46, 98.57) p< 0.001	0.21 (2.12, 84.84) p= 0.823
Restlessness	3.07 (1, 40) p= 0.088	22.44 (2.59, 103.64) p< 0.001	0.43 (2.21, 88.31) p= 0.675
Difficulty concentrating	4.65 (1, 40) p= 0.037	13.46 (2.25, 90.12) p< 0.001	0.13 (2.75, 109.94) p= 0.929
Composite withdrawal	3.96 (1, 40) p= 0.053	21.13 (2.39, 95.55) p< 0.001	0.21 (2.23, 88.99) p= 0.833
Evening			
Urge to smoke	6.41 (1, 40) p= 0.015	21.65 (2.54, 101.54) p< 0.001	0.711 (3.01, 120.31) p= 0.547
Irritability	4.83 (1, 40) p= 0.034	6.11 (2.27, 90.75) p= 0.002	1.58 (2.82, 112.96) p= 0.201
Restlessness	6.74 (1, 40) p= 0.013	5.73 (1.85, 74.00) p= 0.006)	1.60 (2.54, 101.56) p= 0.201
Difficulty Concentrating	7.78 (1, 40) p= 0.008	3.84 (1.85, 74.16) p= 0.029	1.64 (2.44, 97.77) p= 0.193
Composite withdrawal	7.36 (1, 40) p= 0.010	6.17 (1.74, 69.55) p= 0.005	1.96 (2.57, 102.77) p= 0.134

Figure 5.1: Mean urge to smoke ratings over 1 hour

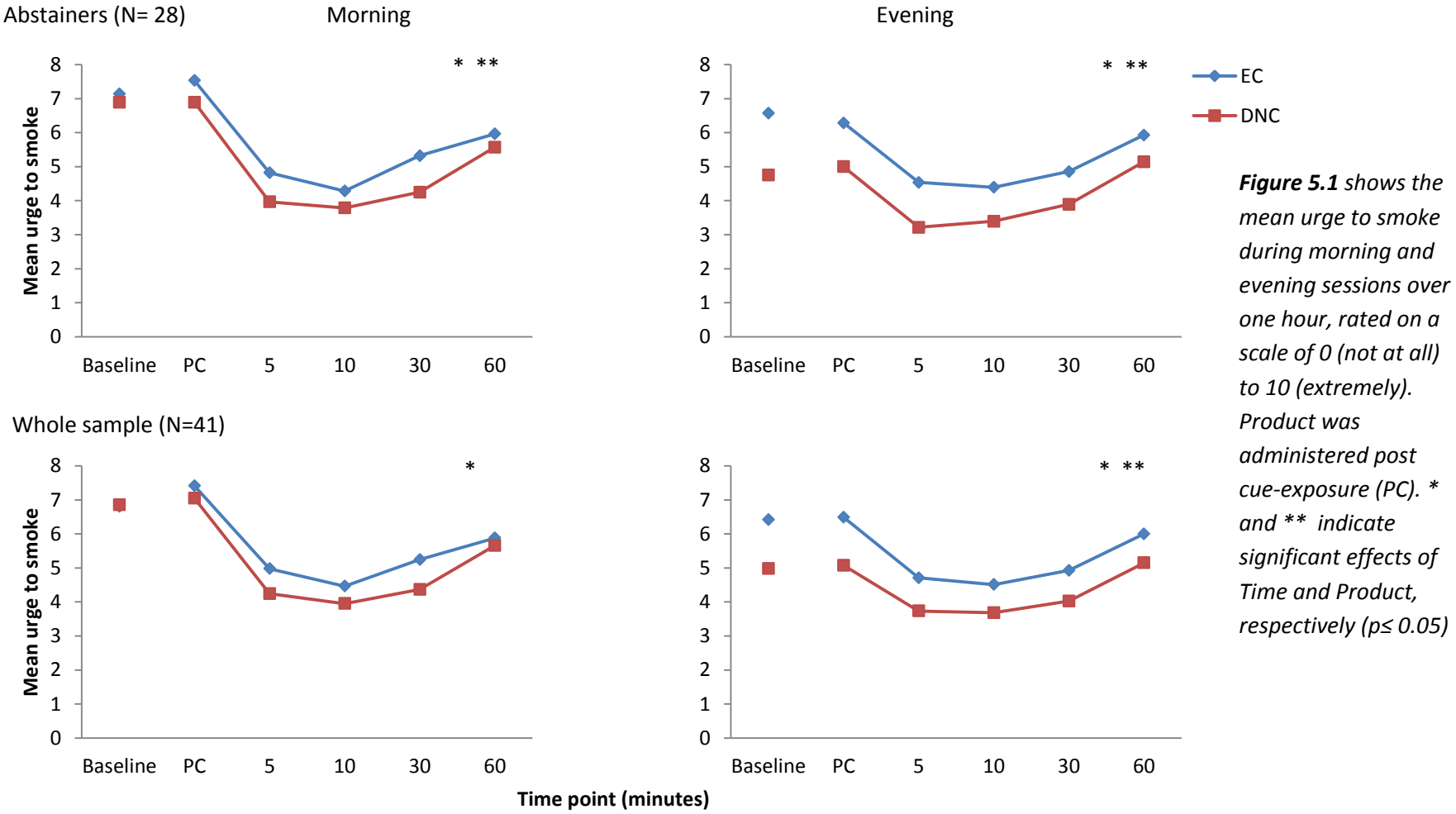


Figure 5.1 *shows the mean urge to smoke during morning and evening sessions over one hour, rated on a scale of 0 (not at all) to 10 (extremely). Product was administered post cue-exposure (PC). * and ** indicate significant effects of Time and Product, respectively (p≤ 0.05)*

Figure 5.2: Mean irritability ratings over 1 hour

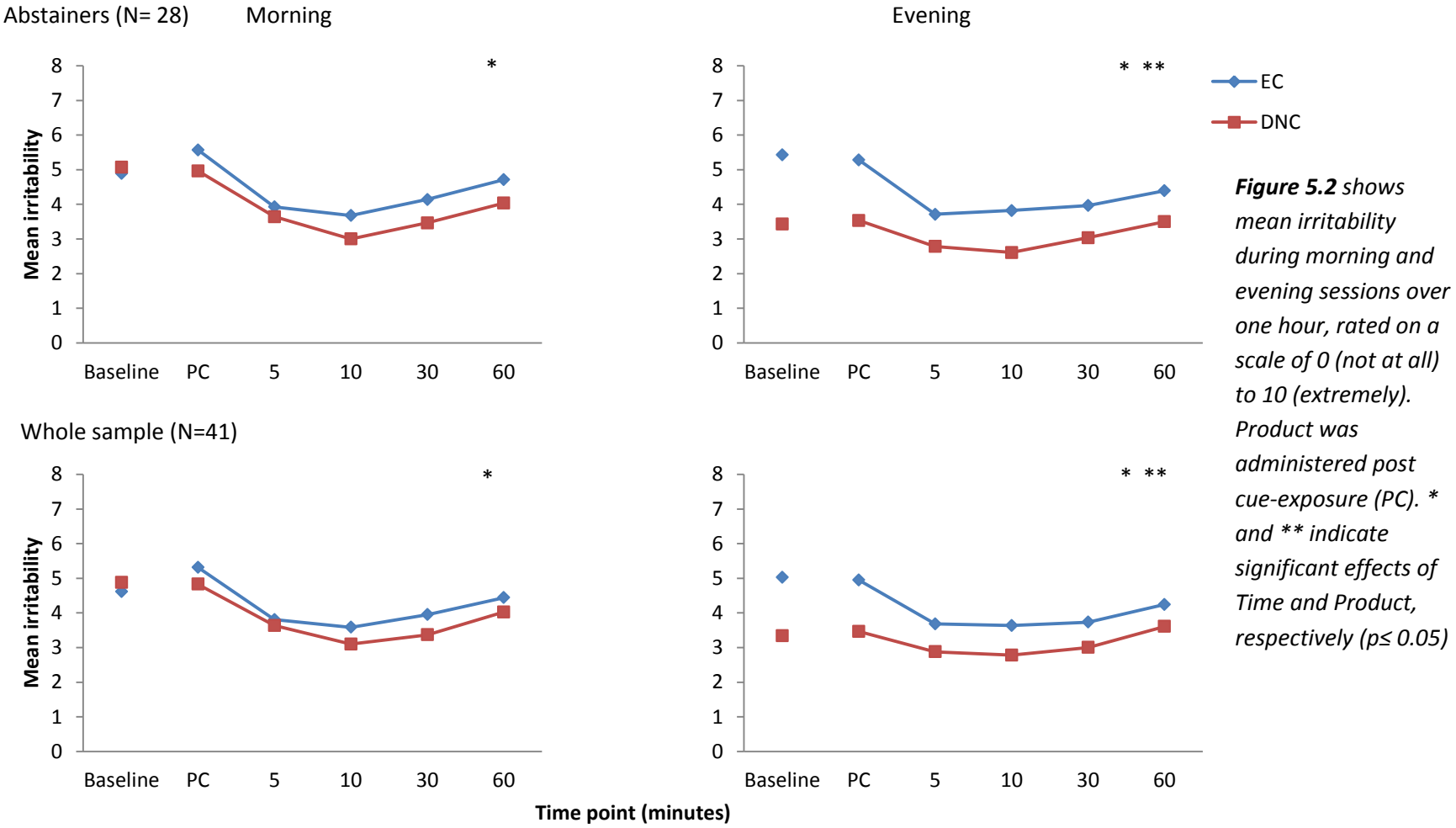


Figure 5.2 *shows mean irritability during morning and evening sessions over one hour, rated on a scale of 0 (not at all) to 10 (extremely). Product was administered post cue-exposure (PC). * and ** indicate significant effects of Time and Product, respectively (p≤ 0.05)*

Figure 5.3: Mean restlessness ratings over 1 hour

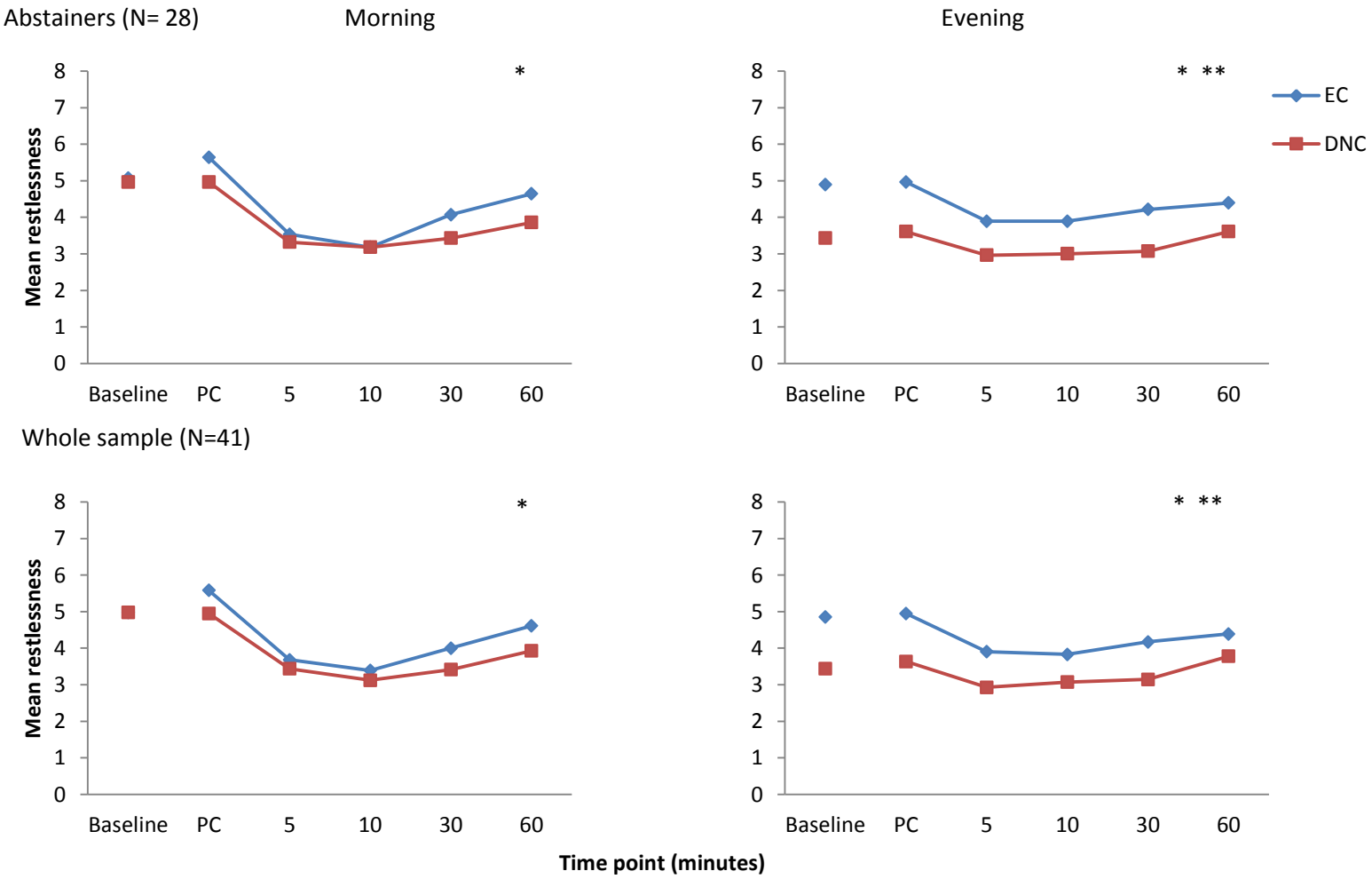


***Figure* 5.3** *shows mean restlessness during morning and evening sessions over one hour, rated on a scale of 0 (not at all) to 10 (extremely). Product was administered post cue-exposure (PC). * and ** indicate significant effects of Time and Product, respectively (p≤ 0.05)*

Figure 5.4: Mean ratings of difficulty concentrating over 1 hour

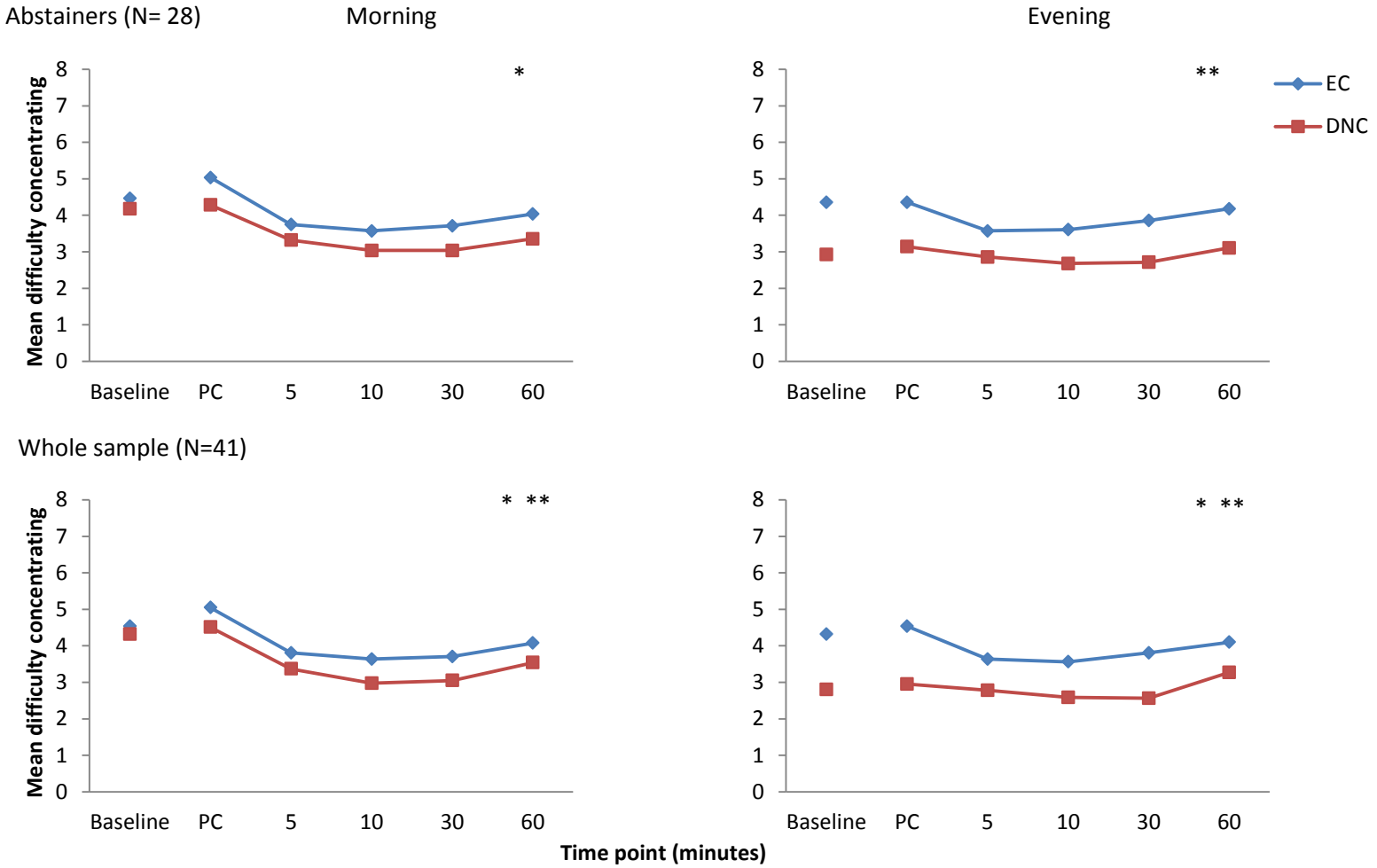


Figure 5.4 *shows mean difficulty concentrating during morning and evening sessions over one hour, rated on a scale of 0 (not at all) to 10 (extremely). Product was administered post cue-exposure (PC). * and ** indicate significant effects of Time and Product, respectively (p≤ 0.05)*

Figure 5.5: Mean composite withdrawal ratings over 1 hour

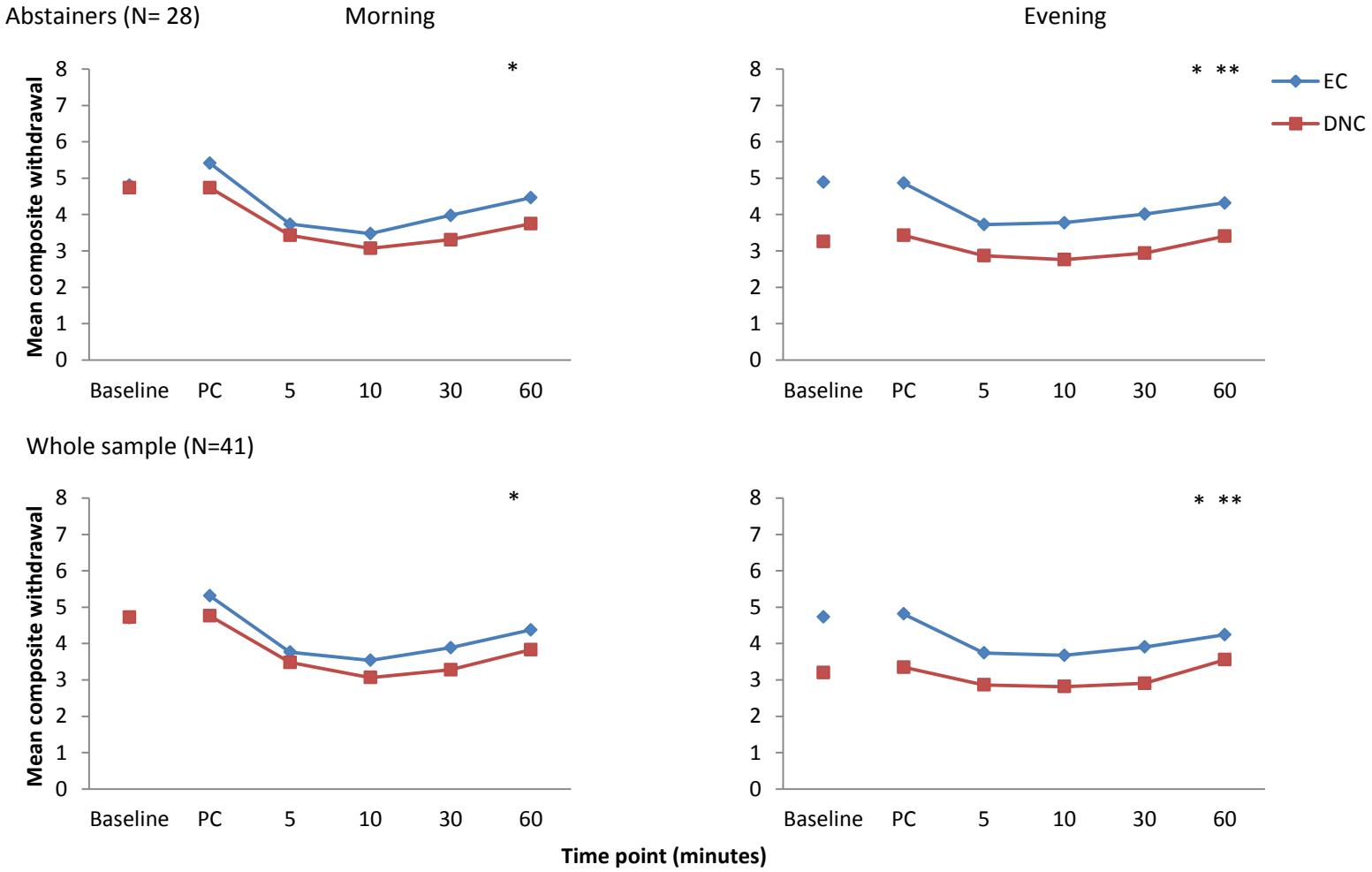


Figure 5.5 *shows mean composite withdrawal during morning and evening sessions over one hour, rated on a scale of 0 (not at all) to 10 (extremely). Product was administered post cue-exposure (PC). * and ** indicate significant effects of Time and Product, respectively (p≤ 0.05)*

When the analysis was conducted on the whole sample, an almost identical pattern of results emerged. Main effects of product in the morning were evident for difficulty concentrating in favour of the DNC, ($F(1, 40) = 4.65$, $p = 0.037$), and urge to smoke and composite withdrawal scores tended to be lower overall for the DNC condition ($F(1, 40) = 3.60$, $p = 0.065$; $F(1, 40) = 3.96$, $p = 0.053$, respectively). There were again significant effects of time for all items in the morning (urge to smoke: $F(2.50, 100.03) = 32.82$, $p < 0.001$; irritability: $F(2.46, 98.57) = 16.51$, $p < 0.001$; restlessness: $F(2.59, 103.64) = 22.44$, $p < 0.001$; difficulty concentrating: $F(2.25, 90.12)$, 13.46, $p < 0.001$; and composite withdrawal: $F(2.39, 95.55) = 21.13$, $p < 0.001$), but no interactions were evident (see Figures 5.1-5.5, bottom panel).

In the evening all items were overall significantly lower during the DNC condition (urge to smoke: $F(1, 40) = 6.41$, $p = 0.015$; irritability: $F(1, 40) = 4.83$, $p = 0.034$; restlessness: $F(1, 40) = 6.74$, $p = 0.013$; difficulty concentrating: $F(1, 40) = 7.78$, $p = 0.008$; and composite withdrawal: $F(1, 40) = 7.36$, $p = 0.010$), and there were again significant main effects of time for all items (urge to smoke: $F(2.54, 101.54) = 21.65$, $p < 0.001$; irritability: $F(2.27, 90.75) = 6.11$, $p = 0.002$; restlessness: $F(1.85, 74.00) = 5.73$, $p = 0.006$); difficulty concentrating: $F(1.85, 74.16) = 3.84$, $p = 0.029$; and composite withdrawal: $F(1.74, 69.55) = 6.17$, $p = 0.005$). There were no significant interactions (see Figures 5.1-5.5, bottom panel).

5.2.7 **Supplementary analyses: Acute effects on urges to smoke and withdrawal**

As with Study 1, a further set of analyses were conducted to examine the acute effects of the products more closely on urges to smoke and composite withdrawal. The same set of analyses in Study 1 were conducted here: comparisons (t-test/Wilcoxin) from post-cue to 10 minutes for each product separately in each session; repeated measures ANOVA to test for any interactional effects between time (post cue vs. 10 minutes) and products; and differences between products on area under the curve (AUC), maximum reduction (Rmax) and time to maximum reduction (Tmax) on data obtained over the first 10 minutes post product use.

Analyses were run on those who abstained throughout the study, and on the whole sample.

5.2.7.1 **Results: Abstainer sample**

Separate analysis for each product revealed that both the EC and DNC reduced urge to smoke at 10 minutes, during both the morning (EC: $z= -3.93$, $p< 0.001$; DNC: $z= -4.06$, $p< 0.001$) and evening sessions (EC: $t= 4.45$, $p< 0.001$; DNC: $z= -3.22$, $p= 0.001$; see Figure 5.6, top panel). The ANOVA revealed no interaction between time and product indicating a similar magnitude of reduction between products (see Table 5.6).

The comparable effects between products were confirmed with AUC analyses, which showed no differences between products on AUC values, Rmax or Tmax during both sessions (see Table 5.7). Figure 5.6, bottom panel, shows the mean reduction scores in urges to smoke over 10 minutes.

Figure 5.6: Acute effects of products on urge to smoke in abstainers

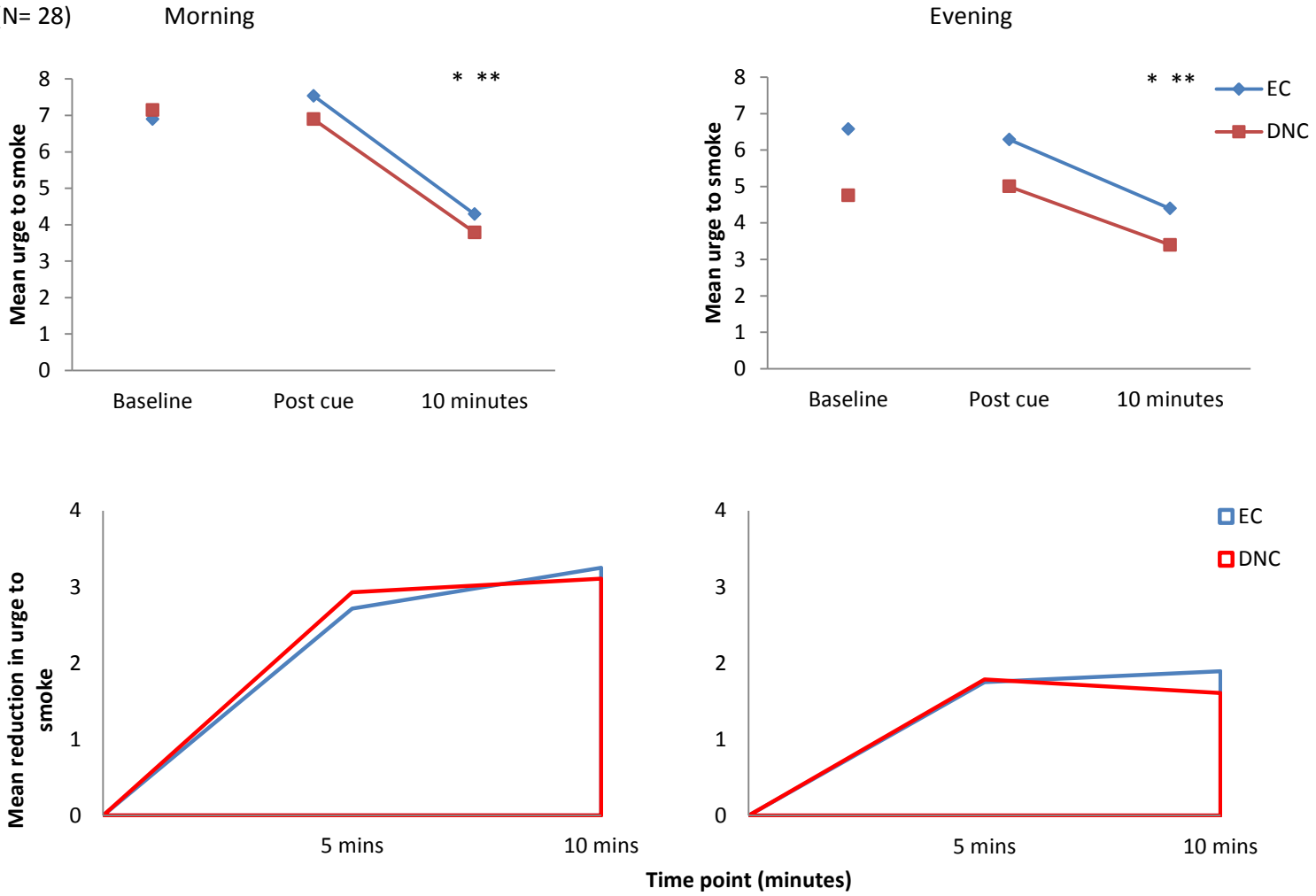


Figure 5.6 *Top panel shows the mean urge to smoke pre-product use and at 10-minutes post-product use. Product was administered post cue-exposure. * and ** indicate a significant change from post-cue to 10 minutes for EC and DNC respectively. Bottom panel shows reduction from post-cue in urge to smoke over 5 and 10 minutes post-product use. Analysis conducted on abstainers only; significance level $p \leq 0.05$.*

Table 5.6: Summary of ANOVA analysis on the acute effects of products on urges and withdrawal ratings in abstainers.

	Product	**Time**	**Product x Time**
N= 28		**F (df) p value**	
Morning			
Urge to smoke	2.66 (1, 27) p= 0.115	44.48 (1, 27) p< 0.001	0.051 (1, 27) p = 0.823
Composite withdrawal	3.07 (1, 27) p= 0.091	33.46 (1, 27) p< 0.001	0.31 (1, 27) p = 0.580
Evening			
Urges to smoke	4.39 (1, 27) p = 0.046	43.07 (1, 27) p< 0.001	0.21 (1, 27) p= 0.651
Composite withdrawal	5.61 (1, 27) p= 0.025	28.71 (1, 27) p< 0.001	0.92 (1, 27) p= 0.346

Composite withdrawal scores also reduced significantly at 10 minutes following use of both products in the morning (EC: t= 4.24, p< 0.001; DNC: t= 5.14, p< 0.001) and evening (EC: t= 3.77, p= 0.001; DNC: z= -2.21, p= 0.027; see Figure 5.7, top panel). As with urges, reductions between products were comparable in both sessions (see Table 5.6), and there were no differences between products with respects to AUC and Rmax, though time to maximum reduction tended to be longer with the DNC than EC in the morning (z= -1.93, p= 0.053; see Table 5.7). Figure 5.7, bottom panel, shows the mean reduction scores in composite withdrawal over 10 minutes.

Table 5.7: Mean area under the curve (AUC), reduction maximum (Rmax), and time to Rmax (Tmax) values and summary test statistics for acute urges and withdrawal ratings in abstainers.

N= 28	**EC**	**DNC**	**EC vs. DNC**	
Morning	Mean (SD)		Test statistic	Sig (p)
Urge to smoke				
AUC	21.70 (20.59)	22.41 (20.59)	t= -0.18	0.857
Rmax	3.61 (3.02)	3.43 (2.66)	z= -0.09	0.927
Tmax	5.36 (3.58)	5.71 (3.25)	z= -0.45	0.653
Composite withdrawal				
AUC	13.24 (16.70)	10.71 (12.73)	z= -0.31	0.755
Rmax	2.18 (2.26)	1.94 (1.63)	z= -0.38	0.706
Tmax	5.00 (3.85)	6.79 (3.39)	z= -1.93	0.053
Evening				
Urge to smoke				
AUC	13.48 (14.71)	12.95 (12.80)	z =-0.01	0.989
Rmax	2.21 (2.22)	2.07 (1.78)	z= -0.07	0.946
Tmax	4.82 (3.46)	4.46 (3.43)	z= -0.36	0.723
Composite withdrawal				
AUC	8.45 (10.26)	4.46 (9.30)	z= -1.17	0.244
Rmax	1.41 (1.51)	0.89 (1.22)	z= -1.13	0.257
Tmax	5.71 (3.53)	4.29 (4.24)	z= -1.29	0.198

5.2.7.2 **Results: Whole sample**

When the analysis was repeated on the whole sample, a similar picture emerged, with significant reductions in urge to smoke following both products in the morning (EC: z= -4.93, p< 0.001; DNC: z= -4.87, p< 0.001) and evening (EC: z= -4.70, p< 0.001; DNC: z= -3.62, p< 0.001; see Figure 5.8, top panel).

Figure 5.7: Acute effects of products on composite withdrawal in abstainers

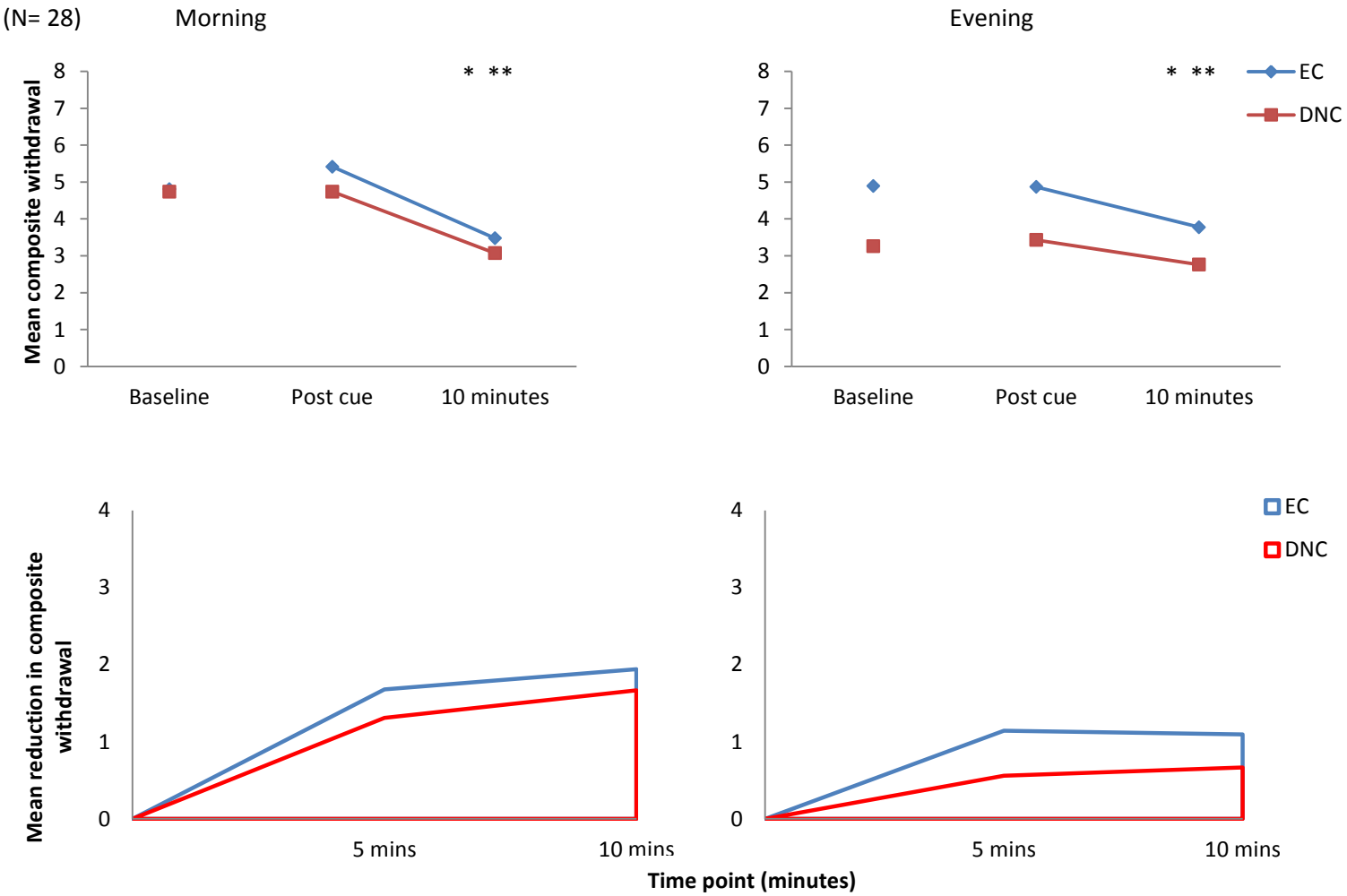


Figure 5.7 *Top panel shows the mean composite withdrawal pre-product use and at 10-minutes post-product use. Product was administered post cue-exposure. * and ** indicate a significant change from post-cue to 10 minutes for EC and DNC respectively. Bottom panel shows reduction from post-cue in composite withdrawal over 5 and 10 minutes post-product use. Analysis conducted on abstainers only; significance level p ≤ 0.05).*

Figure 5.8: Acute effects of products on urge to smoke (whole sample)

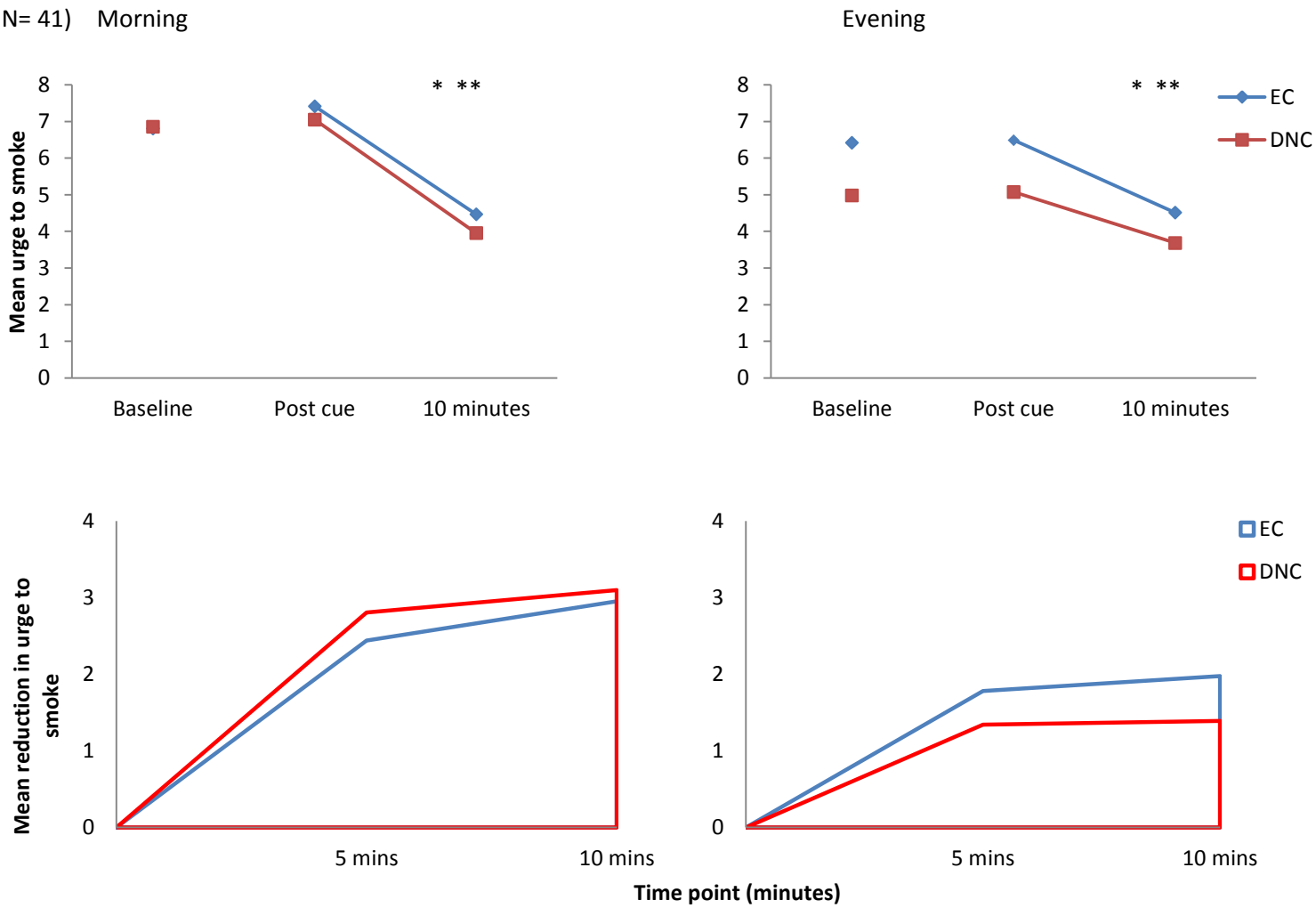


Figure 5.8 *Top panel shows the mean urge to smoke pre-product use and at 10-minutes post-product use. Product was administered post cue-exposure. * and ** indicate a significant change from post-cue to 10 minutes for EC and DNC respectively. Bottom panel shows reduction from post-cue in urge to smoke over 5 and 10 minutes post-product use. Analysis includes non-abstainers; significance level $p \leq 0.05$.*

There was no indication that the magnitude of reduction differed, from both the ANOVA analysis (see Table 5.8) and examination of AUC (see Table 5.9). Figure 5.8, bottom panel, shows the mean reduction scores in urges to smoke over 10 minutes.

For composite withdrawal, there were again significant reductions during both conditions in the morning (EC: z= -4.57, p< 0.001; DNC: z= -4.66, p< 0.001) and evening sessions (EC: t= 4.74, p< 0.001; DNC: z= -2.29, p= 0.022; see Figure 5.9, top panel). The ANOVA revealed no significant interaction for either session, though during the evening, withdrawal tended to decrease to a greater extent for the EC (F (1, 40) = 3.29, p= 0.077; see Table 5.8). This was also evident with AUC analysis, in that the maximum reduction was larger for the EC (z = -1.96, p= 0.05), and AUC values were marginally in favour of the EC (z= -1.89, p= 0.059; see Table 5.9). Given the fact that withdrawal ratings were lower at post-cue in the DNC condition, these findings likely reflect a floor effect with the DNC. Figure 5.9, bottom panel, shows the mean reduction scores in composite withdrawal over 10 minutes.

Table 5.8: Summary of ANOVA analysis on the acute effects of products on urges and withdrawal ratings in abstainers (whole sample).

	Product	**Time**	**Product x Time**
N= 41		**F (df) p value**	
Morning			
Urge to smoke	2.22 (1, 40) p= 0.144	71.61 (1, 40) p< 0.001	0.09 (1, 40) p= 0.765
Composite withdrawal	4.32 (1, 40) p= 0.044	51.92 (1, 40) p< 0.001	0.04 (1, 40) p= 0.836
Evening			
Urges to smoke	6.35 (1, 40) p= 0.016	52.56 (1, 40) p< 0.001	1.67 (1, 40) p= 0.203
Composite withdrawal	8.74 (1, 40) p= 0.005	30.42 (1, 40) p< 0.001	3.29 (1, 40) p= 0.077

Table 5.9: Mean area under the curve (AUC), reduction maximum (Rmax), and time to Rmax (Tmax) values and summary test statistics for acute urges and withdrawal ratings (whole sample).

N= 41	**EC**	**DNC**	**EC vs. DNC**	
Morning	Mean (SD)		Test statistic	Sig (p)
Urge to smoke				
AUC	19.57 (18.21)	21.77 (20.03)	t= -0.70	0.490
Rmax	3.22 (2.70)	3.37 (2.61)	z= -0.53	0.596
Tmax	5.85 (3.52)	5.85 (3.52)	z= -0.19	0.985
Composite withdrawal				
AUC	12.22 (14.62)	10.67 (13.82)	z= -0.21	0.834
Rmax	1.98 (1.99)	1.95 (1.72)	z= -0.02	0.982
Tmax	5.49 (3.84)	6.71 (3.47)	z= -1.67	0.094
Evening				
Urge to smoke				
AUC	13.84 (13.01)	10.18 (15.76)	z= -1.06	0.288
Rmax	2.22 (2.04)	1.80 (1.78)	z= -0.94	0.349
Tmax	5.12 (3.44)	4.15 (3.34)	z= -1.26	0.208
Composite withdrawal				
AUC	8.21 (10.25)	3.78 (9.38)	z= -1.89	0.059
Rmax	1.39 (1.51)	0.80 (1.11)	z= -1.96	0.050
Tmax	5.24 (3.87)	3.90 (3.79)	z= -1.58	0.114

Figure 5.9: Acute effects of products on composite withdrawal (whole sample)

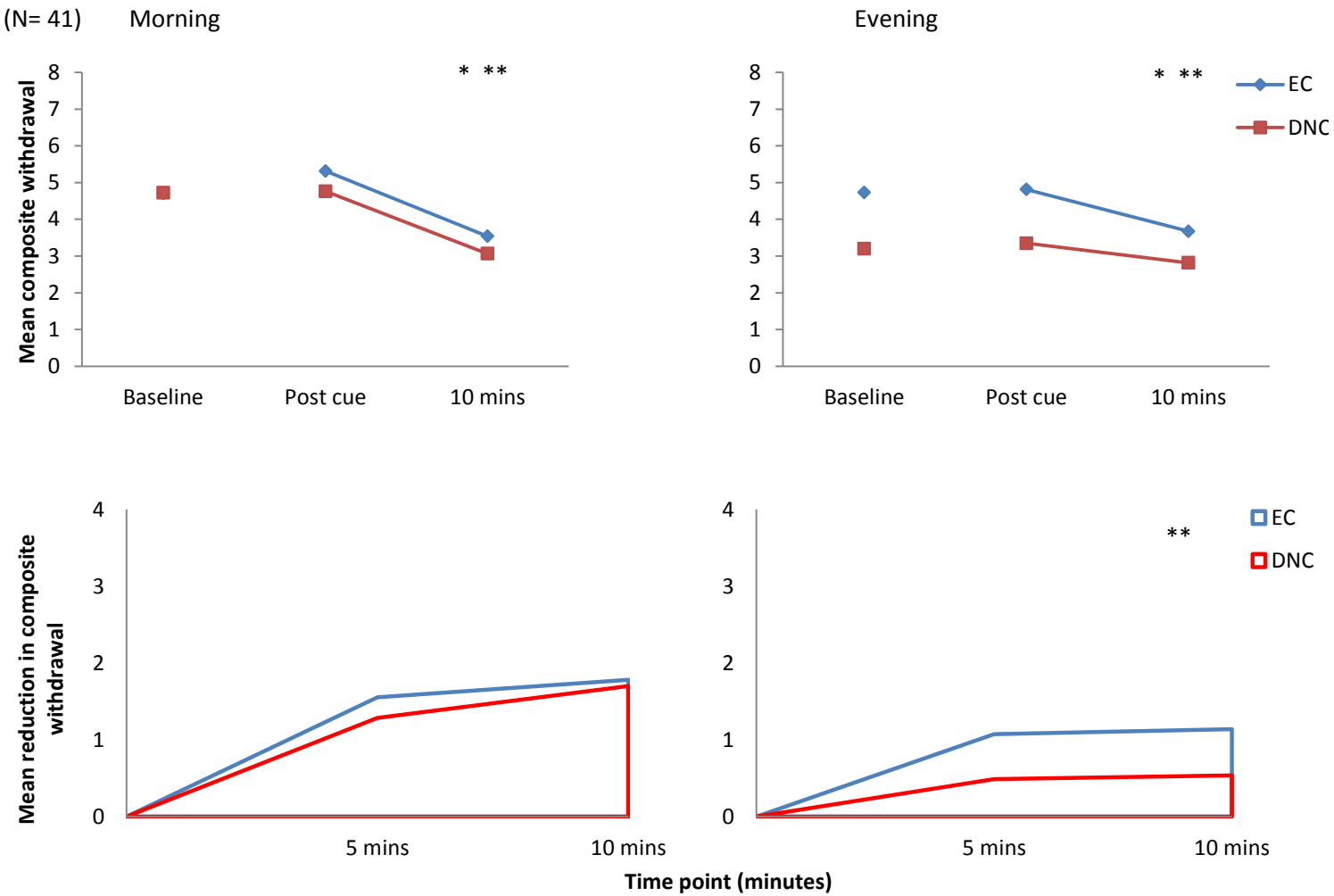


Figure 5.9 *Top panel shows the mean composite withdrawal pre-product use and at 10-minutes post-product use. Product was administered post cue-exposure. * and ** indicate a significant change from post-cue to 10 minutes for EC and DNC respectively. Bottom panel shows reduction from post-cue in composite withdrawal over 5 and 10 minutes post-product use. ** indicates a significant difference between products in Rmax. Analysis includes non-abstainers; significance level $p \leq 0.05$.*

5.2.8 **Urges to smoke and withdrawal symptoms during the day**

Table 5.10 shows the mean composite MPSS urge and withdrawal scores. As a whole, participants reported fairly moderate withdrawal symptoms and urges over the course of the day. Following abstinence over the day, withdrawal scores and urge scores were significantly lower during the DNC condition compared to the EC (z= -3.24, p= 0.001; t= 2.91, p= 0.007, respectively).

Individual items, depression (z= -2.22, p= 0.026), difficulty concentrating (z= -3.03, p= 0.002), urge frequency (z= -2.87, p= 0.004) and urge strength (z= -2.30, p= 0.021), were also significantly lower during the DNC condition, and restlessness was marginally lower (z= -1.93, p= 0.053). These findings suggest that the DNC may have been more effective than ECs in supressing urges and withdrawal symptoms over the day, though it should be noted that the magnitude of difference between the two was small. A summary of test results and mean scores for individual MPSS items is shown in Appendix 21.

Table 5.10: Mean scores and summary test statistics for composite MPSS and urges to smoke.

Product	**MPSS**	**Urge to smoke**	**Urge Frequency**	**Urge Strength**
Abstainers (N= 28)		**M (SD)**		
EC	2.47 (0.70)	3.46 (0.92)	3.57 (1.00)	3.36 (0.95)
DNC	2.01 (0.59)	2.88 (0.79)	2.86 (0.85)	2.89 (0.96)
Test statistic	z= -3.24	t= 2.91	z= -2.87	z= -2.30
Sig. (p)	0.001	0.007	0.004	0.021
Whole Sample (N= 41)				
EC	2.45 (0.69)	3.53 (0.90)	3.61 (0.97)	3.43 (0.93)
DNC	2.05 (0.58)	3.00 (0.86)	2.98 (0.92)	3.02 (1.00)
Test statistic	z= -3.50	z= -3.47	z= -3.66	z= -2.52
Sig. (p)	< 0.001	0.001	< 0.001	0.012

The same pattern of results was evident when the whole sample was analysed (z= -3.50, p< 0.001 for composite withdrawal; z= -3.47, p= 0.001 for composite urge), and a similar pattern was evident for individual items: depression (z = -2.40, p = 0.016), restlessness (z= -2.43, p= 0.015), difficulty concentrating (z= -3.30, p= 0.001), hunger (z= -2.02, p= 0.043), urge frequency (z= -3.66, p< 0.001) and urge strength (z= -2.52, p= 0.012) were all significantly lower during the DNC condition. A summary of test results and mean scores for individual MPSS items is shown in Appendix 21.

5.2.9 Supplementary analyses: baseline ratings during morning and evening sessions

As with Study 1, baseline ratings of urge to smoke and composite withdrawal scores completed during the 1 hour experimental sessions were compared from morning to evening. Mean baseline ratings in the evening appeared to be lower than in the morning but only for the DNC condition, indicating a potentially beneficial effect of DNCs over the course of the day in comparison to ECs. Scores from morning to evening were compared, for each condition individually, and a repeated measures ANOVA was used to examine this potential interaction.

5.2.9.1 Results: Abstainer sample

For the EC, there was no change in urge to smoke from morning to evening (z= -0.71, p= 0.481), but the DNC condition showed a significant reduction (z= -2.78, p= 0.005; see Figure 5.10, top left panel). The ANOVA revealed a marginal interaction between product and time (F (1, 27) = 3.85, p= 0.060; see Table 5.11). The same pattern of results emerged for composite withdrawal scores (see Figure 5.10, bottom left panel), with a reduction in withdrawal only evident for the DNC condition (DNC: t= 2.78, p= 0.010; EC: t= -0.18, p= 0.859), and an interaction which did not quite reach significance (F (1, 27) = 3.36, p= 0.078; see Table 5.11).

Figure 5.10: Mean baseline ratings of urge to smoke and composite withdrawal in the morning and evening

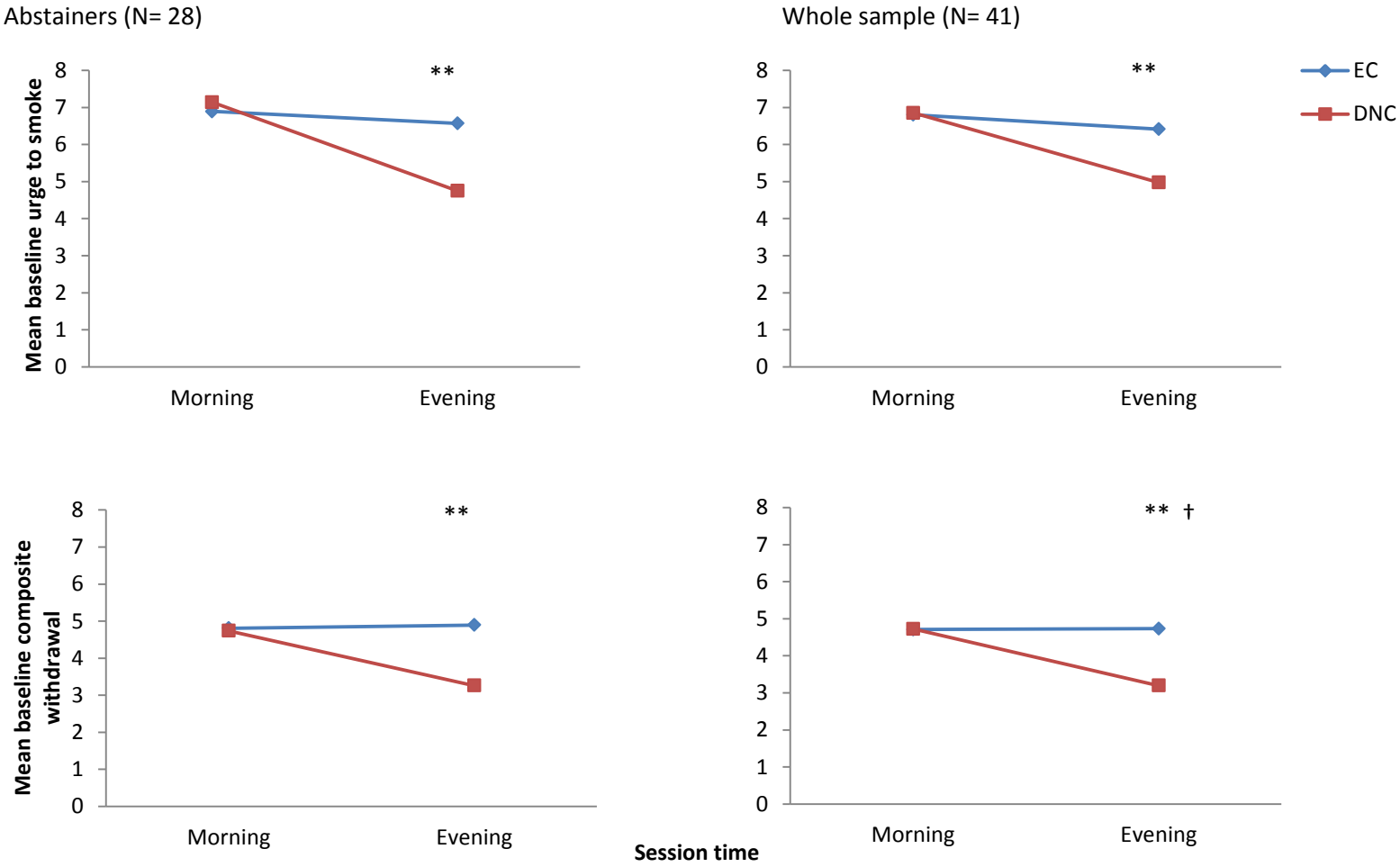


Figure 5.10 *shows the mean baseline ratings of urge to smoke (top panel) and composite withdrawal score (bottom panel) during morning and evening sessions, rated on a scale of 0 (not at all) to 10 (extremely), prior to commencing cue-exposure. ** indicates a significant reduction for DNC from morning to evening, and †, a significant interaction (p≤ 0.05)*

Table 5.11: Summary of ANOVA analysis on baseline urge and withdrawal ratings in the morning and evening.

	Product	Time	Product x Time
Abstainers (N= 28)		**F (df) p value**	
Urge to smoke	17. 29 (1, 27) p= 0.045	13.66 (, 27) p= 0.001	3.85 (1, 27) p= 0.060
Composite withdrawal	5.18 (1, 27) p= 0.031	7.16 (1, 27) p= 0.013	3.36 (1, 27) p= 0.078
Whole sample (N= 41)			
Urges to smoke	4.60 (1, 40) p= 0.038	12.09 (1, 40) p= 0.001	3.54 (1, 40) p= 0.067
Composite withdrawal	7.36 (1, 40) p= 0.010	7.54 (1, 40) p= 0.009	6.47 (1, 40) p= 0.015

5.2.9.2 **Results: Whole sample**

For the whole sample of participants, the findings were identical for urge to smoke (DNC: z= -3.08, p= 0.002; EC: z= -0.94, p= 0.345; see Figure 5.10, top right panel) and there was a trend for an interaction (F (1, 40) = 3.54, p= 0.067). This was also the case for composite withdrawal scores (DNC: z= -3.21, p= 0.001; EC: z= -0.52, p= 0.602; see Figure 5.10, bottom right panel), though here, the ANOVA revealed a significant interaction (F (1, 40) = 6.47, p= 0.015). Table 5.11 provides a summary of the analysis.

5.2.10 **Product perceptions, preferences and adverse effects**

Table 5.12 shows the mean product ratings and percentages of participants choosing each product.

Table 5.12: Mean product ratings and preferences.

Product ratings	**EC**	**DNC**	**Sig. (p)**
N= 41	**Mean (SD)**		
Satisfaction compared to usual cigarette	1.73 (1.07)	1.78 (0.94)	0.752
Helpful in keeping from smoking	2.76 (0.97)	3.07 (0.91)	0.070
Pleasantness	2.59 (1.07)	2.15 (1.11)	0.077
Embarrassing to use	1.66 (0.94)	1.22 (0.53)	0.007
Would use to quit smoking	3.15 (1.32)	3.17 (1.22)	0.897
Would recommend to others for quitting	3.39 (1.28)	3.39 (1.30)	0.876
Product preferences	**% of participants**		**x^2 (p)**
Liked more	36.6	63.4	2.95 (0.086)
Easier to use	48.8	51.2	0.02 (0.876)
More helpful in keeping from smoking*	42.5	57.5	0.90 (0.343)
More embarrassing to use**	91.2	8.8	23.06 (< 0.001)
More likely to use for quitting smoking**	45	55	0.40 (0.527)
More likely to recommend to others for quitting**	52.5	47.5	0.10 (0.752)

**N=7 and **N =1 did not choose between products.*

There were no differences between the two products in satisfaction ratings (z= -0.32, p= 0.752), how likely participants were to use them as an aid to quitting (z= -0.13, p= 0.897) and likelihood of recommending either product to someone who wanted to quit smoking (z= -0.16, p= 0.876). The EC was however rated as more embarrassing to use (z = -2.69, p= 0.007), but tended to be rated as more pleasant (z= -1.77, p= 0.077); the DNC though tended to be rated as more helpful than the EC in enabling participants to keep from smoking conventional cigarettes (z= -1.81, p= 0.070).

Overall, there were no differences in the number of participants choosing one product over the other, except that significantly more participants perceived the EC to be more embarrassing to use than the DNC (x^2 = 23.06, p< 0.001).

Thirteen participants reported adverse effects with the DNCs, and 9 participants reported adverse effects with the EC. For the DNC, these were moderate to strong nausea (N= 4); moderate cough/throat irritation (N= 4); moderate headache (N= 4); weak to moderate light headedness (N= 2); and one participant reported feeling moderately 'shaky'. For the EC, these were moderate headache (N= 4); moderate light headedness (N= 2); moderate cough/throat irritation (N= 3); and strong burning sensation on lips (N= 1). Additionally, one participant reported a mild rash, though this was deemed to be unrelated to the EC.

Table 5.13 shows the responses participants gave regarding what they liked most and least about the products. As in Study 1, participants reported liking most the sensorimotor replacement provided by the EC (N= 13). Again, taste was the least liked aspect of the EC (N= 16) and also the DNC (N= 22). The similarity to conventional cigarettes was the most liked aspect of the DNCs (N= 17).

Table 5.13: Open responses to questions "What did you like most/least about the product you used today?"

Liked Most		**Liked Least**	
EC	**N***		**N***
Sensorimotor replacement	13	Taste	16
Taste	9	Weight/size/shape	13
Similarity to real cigarettes	8	Too 'weak'/no 'throat 'hit'	6
Healthier/no smoke	6	No nicotine	5
Can be used anywhere/ around others	4	Technical problems	4
Weight/size/shape	2	Too dissimilar to cigarettes	3
Ease of use/Does not need lighting or putting out	2	Embarrassing	2
Could be used for cessation	1	Side effects (e.g. coughing, headache)	2
Everything	1	Difficult to puff/draw on	2
Nothing	9	No craving relief/satisfaction	1
		No start or finish	1
		Nothing	5
DNC			
Similarity to conventional cigarettes	17	Taste	22
Still able to smoke	9	Smell	7
Sensorimotor replacement	6	Too harsh/strong throat 'hit'	3
Taste	3	Increased cough	3
Reduced nicotine content	3	No satisfaction/enjoyment	3
Craving relief	2	Too dissimilar to smoking	
Could be used as a cessation aid	1	Still harmful to health	2
Smell	1	Weaker than conventional cigarettes/no 'hit'	2
Nothing	4	Appearance/design of cigarettes/packet	2
		Burnt down too quickly	1
		Still addictive	1
		Nothing	6

**N refers to the frequency of responses. Some participants gave more than one answer.*

5.2.11 **Supplementary analyses: Comparison of EC effects across studies**

Although the EC alleviated urge to smoke acutely in both studies, there was some indication that EC effects were less pronounced in Study 1 compared to Study 2. Mean change scores from post-cue to 10 minutes following overnight abstinence, for example, were greater in the second study than the first (3.25 vs. 1.82, respectively; abstainer only sample).

To examine whether EC effects differed across studies, a repeated measures ANOVA on urge to smoke was conducted for both sessions, where time had two levels (post-cue vs. 10 minutes) and study (1 vs. 2) was entered as a between-subjects factor. The sample comprised of those participants who had abstained throughout their respective study (N= 17 for Study 1; N= 28 for Study 2).

5.2.11.1 **Results**

Participant demographics and characteristics by Study are shown in Table 5.14. There were no differences between participants with respect to gender (x^2= 0.54, p= 0.463), age (F (1, 44) = 0.00, p= 0.973), ethnicity (x^2= 13.40, p= 0.374), employment status (x^2= 0.54, p= 0.307), qualifications (x^2= 4.35, p= 0.500), CPD (F (1, 44) = 0.12, p= 0.726), FTND scores (F (1, 44) = 0.65, p= 0.426) and EC use over the day (F (1, 44) = 0.20, p= 0.658).

Figure 5.11 shows the mean urge to smoke by Study during morning and evening sessions. For the morning session, the ANOVA confirmed previous findings of a significant reduction from post-cue to 10 minutes across both studies (F (1, 43) = 33.67, p< 0.001), but there was no significant main effect of Study (F (1, 43) = 0.14, p= 0.715) and no interaction between time and study, indicating that the EC reduced urge to smoke in both studies to a similar extent (F (1, 43) = 2.66, p= 0.110).

During the evening session, the pattern of results was similar with respect to main effects (Time: F (1, 43) = 19.17, p< 0.001; Study: F (1, 43) = 1.66, p= 0.204), except here, the interaction was marginal, with mean scores indicating that alleviation of urge tended to be greater in the second study compared to the first (F (1, 43) = 4.00, p= 0.052).

Table 5.14: Participant characteristics of 'abstainer' samples in Studies 1 and 2.

Demographics/baseline characteristics	**Study 1***	**Study 2***
	% (N= 17)	**% (N= 28)**
Gender		
Male	64.7	53.6
Ethnicity		
Caucasian	70.6	64.4
Mixed/other	23.5	35.6
Don't wish to answer	5.9	0
Employment status		
Employed	52.9	46.4
Unemployed	23.5	28.6
Student	5.9	7.1
Other (e.g. retired, sick/disabled)	17.7	17.9
Education		
Higher	53	57.1
Secondary or none	47	42.9
	Mean (SD)*	
Age	40.6 (15.5)	40.8 (15.0)
CPD	18.8 (6.5)	19.5 (6.1)
FTND	5.4 (1.9)	5.8 (1.4)
EC use during study day	12.7 (9.4)	14.6 (15.9)

**There were no significant differences between studies in any participant characteristics.*

Figure 5.11: Mean ratings of urge to smoke for EC in Studies 1 and 2 in abstainers

(N= 45)

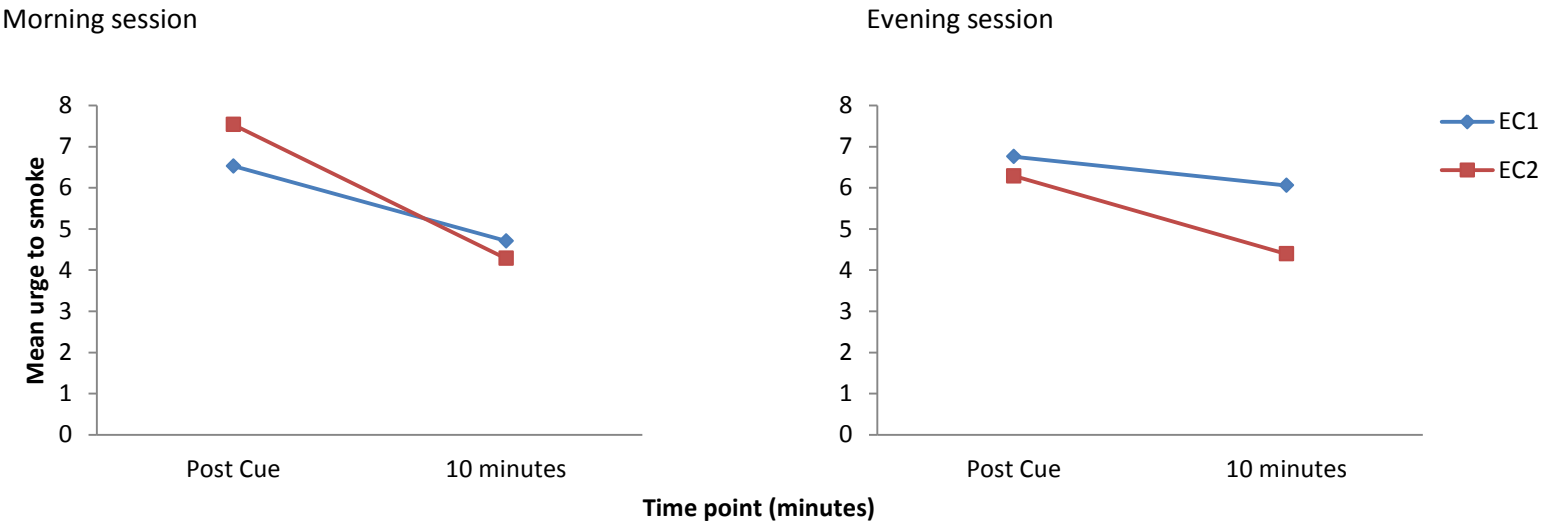


Figure 5.11 *shows the mean ratings of urge to smoke in the two studies (EC1= Study 1; EC2= Study 2), at post-cue and 10 minutes post-EC use (rated on a scale of 0 [not at all] to 10 [extremely]), in abstainers only. EC was administered post cue-exposure. Interactions between time and study were not significant at the p≤ 0.05 level, at either session.*

5.3 **Discussion**

This study aimed to examine whether sensorimotor effects were 'dose' dependent. Specifically, whether more proximal SMR from DNCs would better alleviate urges to smoke and withdrawal compared to ECs. Both the EC and DNC reduced urge to smoke and most withdrawal symptoms acutely (within 5-10 minutes) following overnight abstinence, with little indication of differences between products. Further analyses confirmed that acute alleviation of urges to smoke and composite withdrawal was similar for the two products during both sessions.

The comparable acute urge relief evident during the controlled experiments seems to suggest that proximity to real smoking may not necessarily be as important as previously hypothesised, at least for acute urge relief, so long as key elements of smoking behaviour (importantly the smoke - or vapour resembling smoke - puffing, inhaling/exhaling) are present.

One difference that did emerge from this study was the reduction in urges to smoke and withdrawal from the morning to the evening session, evident only in the DNC condition. This suggests that DNCs may have helped suppress withdrawal and urge to a greater extent than the EC over the course of the day. Data from MPSS scores collected at the evening session confirm this, as ratings following abstinence were significantly lower with the DNC than EC, though the difference was modest.

These findings point to the possibility that sensorimotor treatment effects may be sustained when the sensorimotor input is more proximal to conventional smoking. The DNC literature indicates that DNCs' reinforcing effects can extend over longer periods of time, (Baldinger et al., 1995b, Buchhalter et al., 2005, Donny and Jones, 2009, Hatsukami et al., 2013a). In this way, sensorimotor effects may still be 'dose-dependent'; a lower level of sensorimotor input may be sufficient to alleviate urge to smoke acutely (but perhaps only in the early treatment phase), so long as the key sensorimotor factors described above are present - to confirm this, a control condition would need to be included, such as a nicotine-free inhalator, which would offer some sensorimotor input, but not the key sensorimotor aspects (i.e. nothing resembling smoke, no inhaling/exhaling). With more proximal input however, these sensorimotor factors may remain reinforcing for longer, thus providing help for a more prolonged period; they may also impact on both 'background' and episodic withdrawal discomfort.

The cue-exposure procedure had very little impact on urges and withdrawal ratings during both the morning and evening sessions across conditions, but there was some evidence to suggest that product expectancies may have had an impact on the extent of cue reactivity. Some ratings such as restlessness, irritability and urges to smoke, remained relatively stable following cue exposure in the morning, when participants were told they would be using the DNC, but increased when told they would be using the EC. Thus participants may have held the expectation that the DNC would be of more help - given that it is still a tobacco cigarette - resulting in lowered reactivity to the cue-exposure procedure. There were few differences in product ratings and preferences, except that ECs were considered more embarrassing to use, though ratings of embarrassment were low in any case. Similarly to Study 1, taste was the least liked aspect of the EC, as well as with the DNC. Despite this, participants still reported that the provision of SMR (again having the vapour, being able to inhale/exhale etc.) was the most liked aspect of the EC, and that the similarity to normal cigarettes was most liked about the DNCs. Interestingly, few participants reported (in response to the open questions) that these products helped to alleviate their urges and/or withdrawal symptoms, across both studies.

This again raises the possibility that the alleviation of urge to smoke may not be the central mechanism involved in SMR. In this study, however, the effects of the EC on urge alleviation were not as small as those seen in Study 1, especially during the evening. Although the analysis across studies only revealed a marginal interaction, examination of mean scores shows quite marked differences in urge changes from post-cue to 10 minutes (Study 1: 6.76 to 6.06; Study 2: 6.29 to 4.39, respectively). Without a control condition in the second study, the contribution of conditioned sensorimotor input to these effects cannot be reliably interpreted. The difference in EC effects across studies is interesting to note and may reflect individual variability in responses to SMR. There is already some evidence of this in the literature, i.e. that effects may be moderated by characteristics such as gender and physical dependence (Brauer et al., 2001, Barrett, 2010, Dawkins et al., 2012, Dawkins et al., 2013b). A recent trial also reported a favourable treatment effect for SMR, but only in smokers who were categorised as highly 'behaviourally' dependent (Caponnetto et al., 2011a). It is logical to assume that such smokers, who place importance on the ritualistic/behavioural aspects of smoking, would find SMR of more benefit, but these findings were post-hoc and require replication. The final study therefore investigated the possibility that sensorimotor treatment effects may be moderated by behavioural dependence.

6 Study 3: Are sensorimotor replacement treatment effects moderated by 'behavioural' dependence?

6.1 Study synopsis

This study was part of a randomised controlled trial (RCT) investigating the effects of DNCs in combination with standard NHS-SSS treatment (i.e. behavioural and pharmacological support; DNC+ST) vs. standard NHS-SSS treatment (ST) alone (McRobbie et al., 2013).

The primary outcome of the main trial was the difference in urge to smoke between the two groups over the first week of abstinence. Secondary outcomes included (i) differences between the two groups on change in withdrawal symptoms (MPSS ratings) over four weeks of abstinence; (ii) abstinence rates over 12 weeks; (iii) predictors of abstinence at 4 and 12 weeks post-target quit day (TQD); (iv) effects of medication type (NRT vs. varenicline) on abstinence rates between DNC+ST and ST groups; and (v) DNC use, satisfaction and sensory ratings, and adverse effect.

6.2 Methodology

6.2.1 Aims

The aim of this study was to examine whether scores on the Glover-Nilsson Smoking Behavioural Questionnaire (GN-SBQ; Glover et al., 2005), which purports to measure behavioural dependence, would moderate any effect of SMR on smoking cessation outcomes. A secondary aim was to examine whether sensorimotor motives for smoking as measured by Sensorimotor subscale of the Motives for Smoking scale (SM-MFS; Russell et al., 1974) would also moderate treatment effects.

6.2.2 **Hypotheses**

It was hypothesised that behavioural dependence and/sensorimotor motives, would moderate treatment effects, in that abstinence rates would be greater in the DNC+ST vs. ST group for those reporting high scores on these measures at baseline, with a different pattern of results evident in the low dependence/motives sub-groups.

6.2.3 **Design**

This study was a RCT where participants were randomised (1:1) to one of two treatment groups: DNCs alongside standard NHS-SSS treatment (experimental condition), or to standard NHS-SSS treatment only (control condition).

6.2.4 **Participants**

6.2.4.1 **Recruitment**

Smokers seeking treatment were recruited from the Royal London Hospital Smokers Clinic and through advertisements in local London newspapers (see Appendix 1).

6.2.4.2 **Inclusion/exclusion**

Participants were included in the study if they were aged 18 or over and seeking smoking cessation treatment. Participants were excluded if they were pregnant/breastfeeding, or had an acute psychiatric illness.

6.2.5 **Procedures**

Participants interested in taking part were initially screened on the telephone, and if eligible, were posted study information (see Appendix 22), the baseline questionnaire and booked to attend the clinic. All participants received standard NHS-SSS treatment (i.e. weekly behavioural and pharmacological support).

At the first session, participants were consented (see Appendix 23) and baseline information was collected. Participants were also asked to choose which medication (NRT or varenicline, provided on prescription) they wished to use. The second session provided guidance on preparing for the TQD, scheduled for the following week. Those choosing varenicline were instructed to start taking the medication at the second session, and all participants were asked to smoke as normal up until the TQD (session 3).

On the TQD, participants were randomised to one of the two conditions. In order to examine interactional effects with medication type (a secondary outcome of the main trial), 100 participants using NRT and 100 using varenicline were randomised, resulting in a 50/50 split in medication type within each treatment group. The randomisation list was computer generated, and participants were sequentially allocated to either use the DNCs or continue with standard treatment only. Study staff and participants were not blinded to treatment allocation. The DNCs used in Study 2 were also used in the present study. Participants were given an initial supply of 140 DNCs on the TQD, though anyone reporting baseline cigarette consumption greater than 20/day were given extra. Participants could request a further supply of DNCs the following week. Those randomised to the DNC+ST group were asked to smoke their first DNC, and rate its sensory effects, satisfaction and other user ratings at the session. They were instructed to smoke the cigarettes ad-libitum over the following two weeks. Those using NRT were instructed to start using their products from the TQD.

All participants were telephoned 24 hours post-TQD, to assess smoking status, withdrawal symptoms and urges, and for the DNC+ST group, to rate the DNCs. Following this, participants attended a further 6 sessions for weekly behavioural support. At each session, participants completed questionnaires assessing smoking status (with CO validation), withdrawal and urges, DNC use and ratings (sessions 4 and 5 only), and adverse effects. All participants were followed up at 3 months post-TQD to assess smoking status. Participants were paid £20 at session 9 and £10 at the follow up, for travel expenses pertaining to the 3 extra visits on top of standard treatment (usually only 7 sessions).

Table 6.1 gives a summary of the study assessment procedures for the whole trial.

The study was approved by the National Research Ethics Service Committee (Clinical Trials registration Number: NCT01250301 [www.clinicaltrials.gov]) and ran from July 2011 until July 2012.

Table 6.1: Summary of Study 3 Procedures.

Measures/ procedures	**Weeks Post-TQD**										
	-2	**-1**	**0 TQD**	**24 hr – post TQD phone call**	**1**	**2**	**3**	**4**	**5**	**6**	**12**
Screening + consent	X										
Baseline questionnaire (including GN-SBQ and SM-MFS)	X										
Randomisation			X								
CO	X	X	X		X	X	X	X	X	X	X
MPSS	X	X	X		X	X	X	X	X	X	X
Smoking status	X	X	X	X	X	X	X	X	X	X	X
Adverse effects		X	X	X	X	X	X	X	X	X	X
DNC ratings			X	X	X	X					
DNC urges							X	X	X	X	
Medication/ DNC use		← Varenicline →									
			← NRT →								
			← DNC →								

6.2.6 **Measures and Outcomes**

6.2.6.1 **Behavioural dependence and sensorimotor motives**

Participants completed the standard Royal London Hospital Smokers Clinic Baseline questionnaire (see Appendix 3), which included demographic details, smoking history and the FTND, as in Study 1 and 2 (details provided in Study 1 methodology). This also included the Glover-Nilsson Smoking Behavioural Questionnaire (GN-SBQ) which purports to measure the construct of behavioural dependence to smoking (Glover et al., 2005). This questionnaire was used in a previous study to examine the potential moderating effect of behavioural dependence on treatment effects of a non-nicotine inhalator (Caponnetto et al., 2011a).

Two items from this questionnaire asked participants how much they value their cigarette habit and the handling/manipulating ritual of smoking, on a 5-point scale ("not at all", "somewhat", "moderately so", "very much so" or "extremely so"). The remaining 9 items required participants to rate the frequency of behaviours associated with smoking on a 5-point scale ("never", "seldom", "sometimes", "often", or "always"). The behaviours, for example, include smoking routinely without craving and using smoking as a reward. The GN-SBQ classifies smokers into 4 dependence categories based on total scores: mild (<12), moderate (12-22), strong (23-33) and very strong (>33), with a maximum score of 44 possible.

The GN-SBQ has a strong focus on the ritual of smoking and behaviours associated with it, but little attention is paid to the sensory aspects. Thus, in addition, participants also completed the Sensorimotor subscale of the Motives for Smoking scale (SM-MFS; Russell et al., 1974). This 5-item questionnaire measured the extent to which participants were motivated to smoke by sensorimotor aspects. Questions were rated on a 4-point scale ("uncertain or not at all", "a little", "quite a bit", "very much so"). Other questionnaires with sensorimotor sub-scales exist, such as the Occasions for Smoking scale (Ikard et al., 1969, Horn and Waingrow, 1966) and Reasons for Smoking scale (McKennell, 1973, McKennell, 1970), but there is considerable overlap, and the measure chosen, the SM-MFS, combines these two previous scales (Shiffman, 1993).

6.2.6.2 **Abstinence**

Smoking status over the past week was recorded at every visit ("not a single puff"; "a few puffs"; "1-5 cigarettes"; "more than 5 cigarettes"). Self-reported abstinence was verified with a CO reading (cut off <10ppm). During DNC use, abstinence (from conventional cigarettes) was self-report only.

6.2.6.3 **Outcomes**

The outcomes of interest were the differences between the treatment groups in abstinence rates at 4 and 12 weeks post-TQD, within high and low GN-SBQ sub-groups, as per the previous study by Caponnetto *et al* (2011a); specifically, whether DNC treatment effects were more apparent in the high vs. low sub-groups. Abstinence was defined as CO-validated continuous abstinence from 2 weeks post-TQD, and reflected standard NHS-SSS outcome criteria at 4 weeks.

Secondary outcomes included differences in abstinence rates at 4 and 12 weeks post-TQD between treatment groups, within the high/low SM-MFS sub-groups; and GN-SBQ and SM-MFS as predictors of abstinence at 4 and 12 weeks post-TQD.

6.2.7 **Sample size**

A total of 200 participants were randomised into the trial as it was powered to detect a difference in the primary outcome of the main study (i.e. urge to smoke at one-week post-TQD, measured by the MPSS) of 0.5 ($p \leq 0.05$, 2-tailed test, 90% power), and thus required 69 participants in each group. In order to account for an estimated 30% attrition rate between the TQD and one week post-quit, the sample size was increased to one hundred participants in each condition. This also allowed detection of a 20% difference in 4-week validated abstinence rates between groups ($p \leq 0.05$, 2-tailed test, 80% power).

In the Caponnetto *et al* (2011a) study, abstinence rates in the high GN-SBQ sub-group at 4-weeks were 67% and 35% in the experimental and control conditions, respectively. To

detect a similar difference, a total of 38 participants would be needed in each treatment group at a two-sided significance level of 0.05, with 80% power.

6.2.8 **Data analysis**

Participants were categorised into high or low dependence groups. For the GN-SBQ, high dependence was defined as a total score of more than 22, and low dependence as a score of 22 or below (Caponnetto et al., 2011a). Similarly, for the SM-MFS sub-scale, a score of 8 or more was categorised as high and 7 or less as low. Differences in abstinence rates over 4 and 12 weeks between the DNC+ST and ST groups were examined with chi-square tests, within each behavioural dependence/SM-MFS sub-group. In addition, logistic regression was used to examine whether GN-SBQ dependence category (mild [<12], moderate [12-22], strong [23-33] and very strong [>33]), as per the original questionnaire, and total GN-SBQ and SM-MFS scores, predicted abstinence at 4 and 12 weeks within the DNC group only. Finally, to explore the general predictive utility of these measures on abstinence, the logistic regression was repeated on the whole sample.

In all analyses, participants lost to follow-up were considered to still be smoking.

6.3 **Results**

6.3.1 **Participant characteristics**

A total of 251 participants consented to take part in the study, and 200 were randomised (100 in each group). Figure 6.1 shows the flow of participants throughout the study, and Table 6.2 reports the baseline characteristics and demographics of the sample. There were no significant differences between groups in participant characteristics (all p's> 0.05; a summary of test results is shown in Appendix 24).

Figure 6.1: Study 3 Participant flow diagram

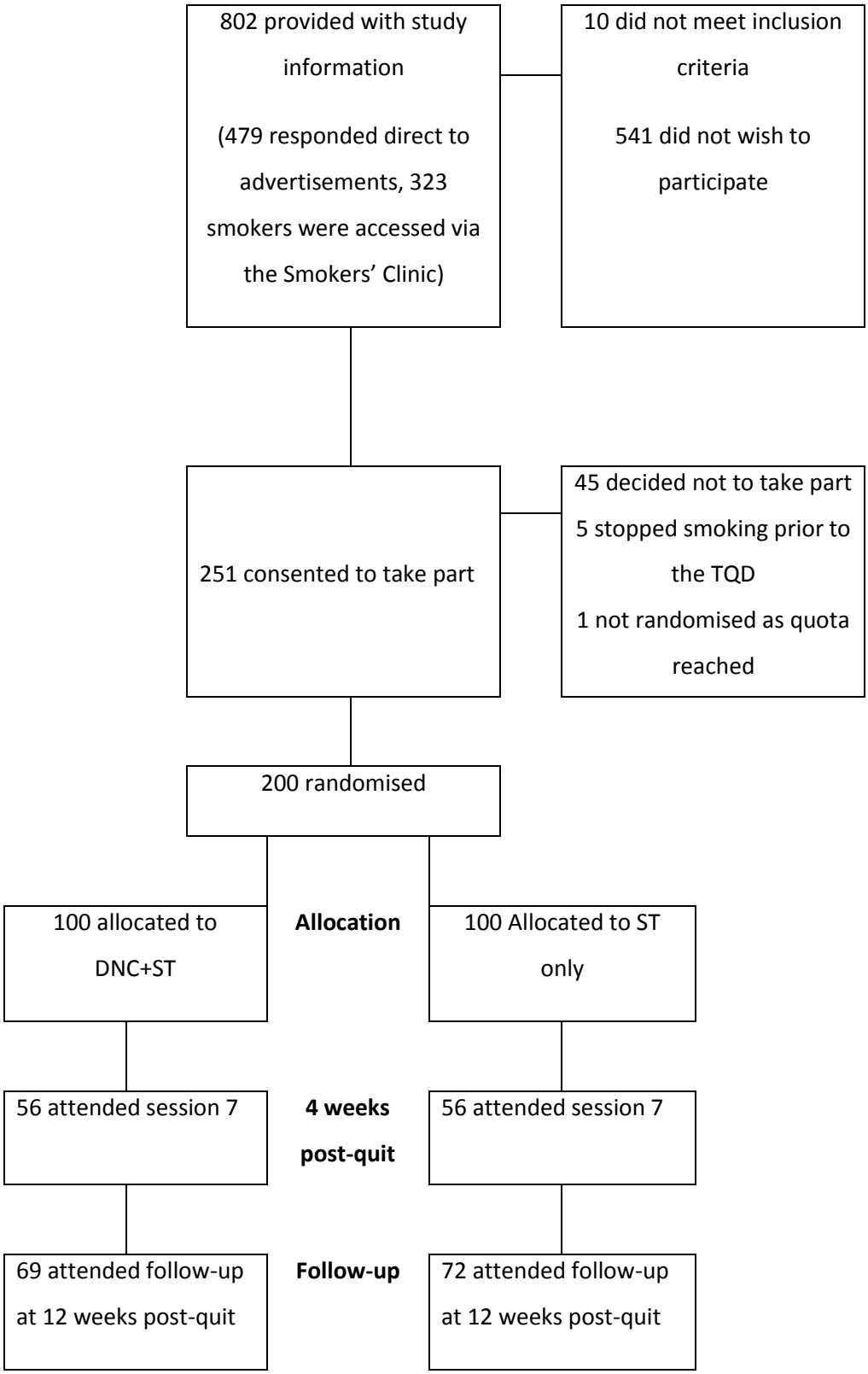


Table 6.2: Study 3 Participant Characteristics

Baseline demographics/characteristics	**% (N= 194- 200)***	
	DNC+ST (N= 96-100)*	**ST (N= 97-100)***
Gender		
Male	56	56
Ethnicity		
Caucasian	82	75
Mixed/other	17	24
Don't wish to answer	1	1
Employment status		
Employed	56	48
Unemployed	13	13
Student	1	4
Other (e.g. retired, sick/disabled)	30	35
Education		
Higher	57	60
Secondary or none	43	40
Behavioural Dependence/ Sensorimotor Motives**		
High GN-SBQ (N= 67)	49.3	50.7
Low GN-SBQ (N= 128)	50.8	49.2
High SM-MFS (N= 26)	42.3	57.7
Low SM-MFS (N= 173)	50.9	49.1
	Mean (SD)	
Age	45.64 (10.53)	47.20 (13.24)
CPD	19.11 (9.56)	18.82 (8.79)
FTND	5.23 (2.36)	4.99 (2.47)
GN-SBQ	19.16 (7.27)	20.31 (6.94)
SM-MFS	3.70 (2.95)	4.19 (3.26)

**Ns vary due to missing data*
***Data missing for 6 participants (N= 5 for GN-SBQ; N= 1 for SM-MFS)*

6.3.2 De-nicotinised cigarette use

Participants in the DNC+ST arm were provided with DNCs for up to 2 weeks post-quit day. On average, participants smoked 8.9 (SD= 7.76) DNCs per day in the first week, and 6.4 (SD= 6.26) per day in the second week.

6.3.3 Smoking cessation

Table 6.3 and Table 6.4 give a summary of abstinence rates at 4 and 12 weeks by GN-SBQ and SM-MFS sub-groups, respectively. Overall, 4-week abstinence rates were higher for the DNC group compared to controls (58% vs. 43%, respectively; p= 0.034; McRobbie et al., 2013). When the analysis was separated by behavioural dependence group, both sub-groups revealed the same pattern of results (i.e. higher abstinence in the DNC+ST vs. ST group), though differences did not reach significance in either sub-group (59% vs. 44%, respectively, for low dependence; 54% vs. 41%, respectively, for high dependence). For the SM-MFS measure, the majority of participants were categorised into the low motives group, and only 26 participants fell into the high category. As a result of this, data from the high motives group are difficult to interpret. The pattern of results within the low motives group was understandably consistent with the pattern of overall abstinence rates, as this sub-group made up almost the whole sample. Accordingly, at 4-weeks, abstinence rates were marginally higher for the DNC group vs. controls (57% vs. 42%, respectively, p= 0.057).

At 12 weeks post-TQD, there were no differences in overall abstinence rates, though rates in the DNC+ST group were slightly higher than ST (39% vs. 31%, respectively; p= 0.237; McRobbie et al., 2013). A similar pattern of results was found within the respective sub-groups (see Table 6.3 and Table 6.4). There is therefore little indication that any SMR effects are moderated by these baseline characteristics.

Table 6.3: Abstinence rates within high and low GN-SBQ sub-groups.

	High GN-SBQ (N= 67)			Low GN-SBQ (N= 128)		
Time since TQD	**DNC+ST % (N)**	**ST**	**Chi-square (p)**	**DNC+ST % (N)**	**ST**	**Chi-square (p)**
4 weeks	54.4 (18)	41.2 (14)	1.20 (0.273)	58.5 (38)	44.4 (28)	2.12 (0.113)
12 weeks	33.3 (11)	23.5 (8)	0.79 (0.373)	41.5 (27)	34.9 (22)	0.59 (0.441)

Table 6.4: Abstinence rates within high and low SM-MFS sub-groups.

	High SM-MFS (N= 26)			Low SM-MFS (N= 173)		
Time since TQD	**DNC+ST % (N)**	**ST**	**Chi-square (p)**	**DNC+ST % (N)**	**ST**	**Chi-square (p)**
4 weeks	63.6 (7)	46.7 (7)	0.74 (0.391)	56.8 (50)	42.4 (36)	3.52 (0.057)
12 weeks	36.4 (4)	33.3 (5)	0.03 (0.873)	38.6 (34)	30.6 (26)	1.24 (0.266)

6.3.4 **Predictors of abstinence**

Regression analysis revealed that at 4-weeks post-TQD, neither GN-SBQ or SM-MFS total scores, nor GN-SBQ category, were significant predictors of abstinence within the DNC condition, or for the whole sample. This was also the case for abstinence at 12 weeks post-TQD. Table 6.5 provides a summary of the analysis.

Table 6.5: Summary of logistic regression analyses for GN-SBQ and SM-MFS as predictors of abstinence.

	4 weeks post-TQD	**12 weeks post-TQD**
DNC condition (N= 97)*	**Wald (p)**	
GN-SBQ total	0.13 (0.719)	2.67 (0.102)
GN-SBQ category**	0.15 (0.694)	1.88 (0.170)
SM-MFS total	0.26 (0.608)	1.35 (0.246)
Whole sample (N= 194)*		
GN-SBQ total	0.05 (0.828)	0 (0.953)
GN-SBQ category**	0.04 (0.842)	0.14 (0.711)
SM-MFS total	0.30 (0.586)	0.07 (0.787)

**Data missing for GN-SBQ and SM-MFS measures*

***Category scores: mild (<12), moderate (12-22), strong (23-33) and very strong (>33).*

6.4 **Discussion**

The present study examined the possibility that sensorimotor treatment effects may be moderated by the GN-SBQ (Glover et al., 2005), which was proposed as a measure of behavioural dependence. A recent study reported greater quit rates at 4 and 24-weeks post-quit in the experimental group (non-nicotine inhalator and standard treatment) vs. controls (standard treatment only) but only in a sub-group of smokers with high GN-SBQ scores; in the low scoring group, the pattern was reversed indicating an unfavourable effect of SMR for this sub-group (Caponnetto et al., 2011a). This sub-group comparison was however post-hoc, and required replication. The results of the present study do not support these findings. At four weeks post-TQD, there was a small benefit for those participants treated with standard NHS-SSS treatment and DNCs (McRobbie et al., 2013), but there was no indication that this outcome was moderated by GN-SBQ scores: both sub-groups followed a similar pattern to overall abstinence rates. At 12 weeks, effects of DNCs in general were diminished, and again this pattern was reflected in both GN-SBQ sub-groups.

The different findings could reflect the different sensorimotor products used (i.e. non-nicotine inhalator vs. DNCs). Caponnetto *et al* (2011a), speculate that the apparent unfavourable effects of the inhalator in the low-dependence group could be a result of participants' expectations (i.e. that the inhalator would help them in quitting) not being met. This could then lead to added stress and frustration, which in turn could undermine the quit attempt. If this were true, participants in the present study may not have encountered this problem because of the more adequate SMR provided by the DNCs, compared to the limited input of an inhalator. Indeed, a previous study reported more effective craving relief with DNCs vs. a placebo inhalator (Barrett, 2010).

There were other notable differences between the two studies aside from the treatment offered. Firstly, baseline daily cigarette smoking was slightly higher in the Caponnetto study (on average ~5 CPD more than the sample in the present study), and participants scored somewhat higher on the FTND. This difference reflects the fact that Caponnetto *et al* only included participants who smoked ≥20 CPD for at least 10 years, with a minimum CO reading of 10ppm; in the present study, no such restrictions were set. In addition, their sample was two thirds male, compared to a more equal gender split in the present study.

The distribution of high and low GN-SBQ scores were also more equal, with 58% reporting low behavioural dependence and, 42% high dependence; in the current study, the

distribution was more skewed towards the low dependence category (66%). These differences in sample characteristics, i.e. a predominantly male and more physically and behaviourally dependent sample in the Caponnetto study, may have contributed to the disparate findings between studies.

In addition to the GN-SBQ, a second measure, the SM-MFS (Russell et al., 1974), was also included. The two measures overlapped slightly, and scores were correlated to a moderate extent ($r= 0.61$, $p< 0.001$), but the SM-MFS was included as it focused more on the sensory aspects and behaviour of smoking per se as opposed to other behaviours associated with smoking. As with the GN-SBQ, it was hypothesised that those smokers, who were motivated by, and enjoyed the sensorimotor aspects of smoking, would benefit more from SMR. Unfortunately, as almost the entire sample was categorised into the low motives group, it is difficult to draw any strong conclusions with respect to this. The same pattern of results (i.e. higher abstinence rates in the DNC+ST group vs. ST) within the two sub-groups again seems to suggest no moderating effects, but this needs to be considered with caution.

In addition to examining quit rates amongst these sub-groups, further analysis revealed that total scores on either of these measures, did not predict abstinence rates at 4 or 12 weeks. This was also true when participants were categorised into the four original behavioural dependence groups of the GN-SBQ (mild, moderate, strong, very strong), suggesting that abstinence did not vary as a function of these baseline characteristics.

The notion that smoking cessation treatment can be tailored to the individual based on their motivation for smoking or type of dependence, is appealing but not necessarily effective. This idea stems back over 40 years, when the concept of smoking typologies, for example, was introduced. Questionnaires such as the Motives for Smoking Scale (MFS; Russell et al., 1974) were developed in order to categorise smokers by their main motivation or reason for smoking, which could then potentially be used to tailor treatment. This was also the rationale behind the GN-SBQ (Glover et al., 2005). Although this seems like a logical concept, Russell *et al* (1974), concluded that it would be of more utility to classify with regards to level of physical addiction on a single dimension, rather than by smoker type. Accordingly, a review of the typology literature at least, revealed little evidence that these typologies helped to inform treatment or that matching typology to treatment improved cessation (Shiffman, 1993). The results here would seem to be in accordance with this.

Alternatively, the possibility that the GN-SBQ is not an adequate measure needs to be considered. Behavioural dependence reflects patterns of use, and according to the authors, includes the rituals of smoking, the relationship between cigarettes and the smoker, and perceived benefits that smoking provides with regards to confidence and/feelings of security (Glover et al., 2005). There has been little research utilising the GN-SBQ, and only recently has its validity and reliability been examined (Rath et al., 2013). In a sample of smokers not seeking treatment, the measure showed good consistency and reliability. It was not correlated with the FTND; this would suggest that if GN-SBQ were to show a relationship to smoking cessation outcome, it may indicate independent contributions of physical and behavioural dependence. However, one study of treatment-seeking smokers did find a positive relationship between the two measures (Nerín et al., 2005). Moreover, the findings reported here, and in a recent trial with the EC (Bullen et al., 2013), found no relationship between scores on the GN-SBQ and smoking cessation outcomes, questioning its clinical utility.

The measure could also benefit from some refinement and clarification. For example, the statement "I handle and manipulate my cigarette as part of the ritual of smoking" was, at least in this sample of participants, difficult to grasp and answer. Handling/manipulating a cigarette is an integral part of smoking behaviour (e.g. holding it, flicking ash) for every smoker, and may not necessarily reflect 'behavioural dependence'. Other items also now require updating, given Smokefree legislation.

Some limitations were inherent with the study. Firstly, the cut-offs used to classify participants into high and low dependence/motives sub-groups may make it difficult to detect differences between smokers at the extreme ends of the scale; removing those with moderate-strong scores would reflect 'high' and 'low' sub-groups more accurately, but would substantially diminish the sample size of each sub-group in the present study. Alternatively, in another study, smokers were classified into three GN-SBQ groups on the basis of the distribution of total scores. Those in the lower (0-16) and upper (23-33) thirds were then classified as 'low' and 'high' dependence groups, respectively, and the middle third (17-22) omitted (Rath et al., 2013). This may have been a more appropriate approach, but would have compromised comparisons to the Caponnetto *et al* (2011a) study.

For the SM-MFS, scores were highly skewed towards the lower end of the scale, meaning that the majority of participants were considered to have low sensorimotor motives. The distribution of scores seen here was in fact similar to that of the original samples on which the questionnaire was developed from (Russell et al., 1974), whereby very few participants

responded to items with the “quite a bit” or “very much so” options. It may be that only a very small proportion of the population feel motivated to smoke for these reasons. Another explanation is that participants were uncertain about their motivations. Russell *et al* instructed participants to select “not at all” if uncertain about their answer, and this was also mirrored in the present study with “Uncertain or not at all” presented together as one option. It has been proposed previously that smokers may be unaware or misguided about their motives and smoking patterns (Shiffman, 1993). In hindsight, it may have been worth separating these responses to distinguish between the two.

In conclusion, SMR combined with standard NHS-SSS treatment may help improve short-term cessation rates, providing some support for the notion of addressing primary and secondary reinforcers of smoking in tandem. This effect, however, does not seem to be moderated by baseline levels of GN-SBQ, and it is likely that this is also true with regards to levels of sensorimotor motives for smoking.

7 General Discussion and Conclusions

Although there is a range of smoking cessation medicines available to assist smokers to quit, their efficacy is low and there remains substantial room for improvement. One potential problem with current treatments is that they do not address all of the factors which contribute to tobacco dependence (Rose, 2006). The aim of the present research was to examine more closely the non-nicotine sensorimotor factors which likely play some role in the reinforcing effects of smoking, and in particular, whether different types of 'sensorimotor replacement' (SMR) have potential to improve on existing treatments.

In Chapter 2, the thesis provided an overview of theories and mechanisms which underlie the 'SMR hypothesis'. It is widely believed that sensorimotor stimuli become conditioned reinforcers as a result of classical conditioning processes; a neutral stimulus (in this case sensorimotor stimuli) may become rewarding if it is closely followed by a real reward (i.e nicotine; Rose and Levin, 1991). It follows that a cigarette substitute, which adequately replaces the sensory and behavioural aspects of smoking, should theoretically help to alleviate urges to smoke and withdrawal, and may additionally offer some enjoyment. If combined with current medications, SMR may help enhance treatment by offering a way of addressing both primary and secondary reinforcers of tobacco dependence - something missing with current smoking cessation treatments.

In Chapter 3, a review of the literature was presented concerning three types of SMR products that had previously been evaluated for their effects on cigarette withdrawal symptoms and smoking cessation. These were flavoured non-nicotine inhalators/aerosols, de-nicotinised cigarettes (DNCs) and electronic cigarettes (ECs). The review concluded that there is some evidence in support of the SMR hypothesis, particularly with DNCs, but there were important theoretical questions requiring clarification.

Firstly, no prior studies had compared SMR to a 'distraction' control condition where no conditioned sensorimotor stimuli were present. In most cases, products were compared to placebo devices (e.g. unflavoured inhalators) or other control conditions such as puffing on unlit cigarettes/air etc., which could offer some, albeit limited, sensorimotor input; or they were compared to no intervention at all.

Secondly, whether or not SMR is 'dose dependent' had not been examined. In particular, how proximal to conventional smoking does sensorimotor input need to be to provide any withdrawal relief?

The final question concerned 'behavioural dependence', which was proposed as an individual propensity that may moderate sensorimotor effects. A recent study suggested that the Glover-Nilsson Smoking Behavioural Questionnaire (GN-SBQ) measures this construct and relates to individual reactivity to sensorimotor stimulation, but the findings were post-hoc (Caponnetto et al., 2011a). The review identified a need to replicate and clarify this result.

Aside from theoretical considerations, there were also potential clinical implications of the research questions posed. If sensorimotor input does not surpass simple distraction, there would be little justification for using SMR products in treatment; other tools are available that offer a means of distracting away from urges to smoke (e.g. 'tangles' or squeeze/stress balls often provided with NHS Quit Kits) and cost less than DNCs/ECs. If SMR does enhance treatment effects, the next clinical question concerns the type of product to use, i.e. how do any DNC and EC effects compare? Finally, identifying smokers who would particularly benefit from this approach would have practical implications for tailoring treatments to individual needs.

Following the literature review, three separate studies addressed the three issues discussed above. The first two studies used an experimental approach to examine the effects of the products on short-term urge and withdrawal relief. In Study 1, a nicotine-free EC was compared to a stress ball (SB) to assess the importance of sensorimotor input per se. In Study 2, the nicotine-free EC and DNC were compared to examine potential 'dose' effects. Finally, Study 3 was a RCT comparing the combination of DNCs with standard smoking cessation treatment (DNC+ST), vs. standard treatment (ST) alone, and sought to examine potential moderating effects of behavioural dependence on abstinence rates.

The key findings can be summarised as follows, and are discussed in further detail below:

(i) SMR can surpass behavioural distraction but this effect may be short-lived.
(ii) SMR more proximal to conventional smoking appears to offer more sustained urge and withdrawal alleviation.
(iii) SMR seems to be of benefit to some but not all smokers, but behavioural dependence, as measured by the GN-SBQ, is not a moderator of these effects.
(iv) SMR may have a more modest effect on acute urge to smoke and withdrawal alleviation than previously hypothesised.

7.1 Sensorimotor replacement vs. behavioural distraction

Given the sensorimotor stimuli present with the EC, it was hypothesised that the EC would alleviate urges to smoke and withdrawal to a greater extent than the SB, and that the EC would be rated higher in terms of user acceptability and generally preferred over the SB. Overall, there appeared to be a slight benefit for the EC in urge alleviation, acutely and over the course of the day, but differences between products were not as large as expected. The most pronounced differences between products were evident during the morning session following overnight abstinence, in those participants who had complied with the study protocol and abstained throughout the study; here, urge reduction from post-cue to 10 minutes was significantly larger for the EC (mean reduction of 1.82) vs. SB (mean reduction of 0.82), despite participants reporting slightly lower baseline urge scores during the EC condition. By the evening, these differences diminished, notably due to reduced effectiveness of the EC as opposed to an improvement in the effects of the SB. Thus, although SMR appeared to surpass distraction, the effects were smaller than expected and short-lived.

It is somewhat surprising that the EC did not generate a greater effect compared to the SB. Demand characteristics, especially given a controlled experimental environment, may go some way to explaining SB effects, although the same could be expected for the EC. In addition, a comparison across the two studies in EC effects indicated that EC effects were more pronounced in the second study compared to the first. It may be that the sample of participants in Study 1 did not find SMR as beneficial for urges/withdrawal alleviation as those in Study 2. This was particularly evident in the evening session where the interaction almost reached significance, though even in the morning mean reduction scores from post-cue to 10 minutes favoured the EC in Study 2 compared to Study 1 (3.25 vs. 1.82, respectively). The magnitude of reduction seen in Study 2 was also more in line with data from an earlier study, where the nicotine-free EC reduced urge to smoke by 2.8 units (on the same scale used here) from baseline to post-cue (Bullen et al., 2010). These findings highlight the potential individual variability in SMR effects, as reported previously by others (Brauer et al., 2001, Barrett, 2010, Dawkins et al., 2012, Dawkins et al., 2013b). But, since there was no behavioural-distraction control condition in Study 2, how this second sample would have responded to a SB is unknown.

EC effects were found to diminish somewhat by the evening in Study 2 also, though to a markedly lesser extent than in Study 1. The reduced efficacy cannot be attributed to

differences in baseline ratings of urges and withdrawal as these did not appear to change from morning to evening in either study. Alternatively, the findings could reflect novelty effects, though it is possible that some participants had tried ECs previously, as only current EC users were excluded from the study (as opposed to ever-users). Furthermore, given that ratings of urge to smoke are extremely subjective, the EC may simply have been perceived by participants as more effective in the morning.

Another possible explanation is that conditioned sensorimotor input per se, at least from the EC, remains reinforcing only for a short period time, thus helping to alleviate urge when used initially, above and beyond behavioural distraction. Once conditioned sensorimotor effects have dissipated, the EC may still offer some help, albeit limited, by providing a behavioural distraction or way of coping. This would have some implication for the notion of 'behavioural' withdrawal proposed by Baker *et al* (2006). This model posits that when smokers quit they will experience both pharmacological and behavioural withdrawal (i.e. the absence of the self-administration ritual, that is, smoking) and as a result, withdrawal symptoms would be exacerbated because individuals cannot revert to their usual means of coping. This would imply that SMR would be the most effective way of dealing with behavioural withdrawal and in turn, nicotine withdrawal symptoms. Indeed, it was suggested that pharmacological nicotine withdrawal symptoms should be eased even if the self-administration ritual is performed without the delivery of nicotine, and the findings from both Study 1 and 2 seem to provide some support for this, albeit it modest.

However, the model also posits that behavioural withdrawal is what accounts for ex-smokers experiencing (i) prolonged withdrawal symptoms (namely urges and negative affect) long after physical withdrawal has dissipated, and (ii) exacerbated reactions to environmental events or smoking-related cues. This therefore suggests that even after a prolonged period of abstinence, when an ex-smoker does experience an urge to smoke, SMR should help to ease this. However, the model does not consider for how long engaging in the self-administration ritual, or as in this case using a SMR product, can be effective for, and if we assume that SMR effects are short-lived, this may limit the practical utility of the effect.

The model does assert that these prolonged symptoms can be overcome if either smoking-related cues/triggers extinguish, and/or if the individual finds a new effective coping strategy. It may be then, as suggested above, a SMR product could still be of help after conditioned sensorimotor effects dissipate, because of the behavioural distraction/coping elements it provides. Coping strategies, distraction techniques and other cognitive-

behavioural tools have been shown to help ease cue-induced cravings acutely (Ferguson and Shiffman, 2009), and as was seen in Study 1, the SB still generated some symptom alleviation.

It could be argued that the EC does not fully replicate the self-administration ritual, and that only DNCs - which still involve the actual ritual of smoking - would be effective long-term. The authors themselves make direct reference to the use of DNCs as a means of alleviating behavioural and physical withdrawal (Baker et al., 2006), and the findings of Study 2 would appear to lend some support for this (discussed further below).

Regarding product preferences and user ratings, this part of the hypothesis was supported. Most participants preferred the EC over the SB, and rated the EC more highly on user acceptability items. In particular, the provision of cigarette-like sensorimotor input (i.e. smoke like vapour, the ability to inhale/exhale) and its overall similarity to conventional cigarettes, gave the EC an advantage over a product which did not provide this type of sensorimotor stimulation, adding weight to the notion that the sensorimotor input is perceived as helpful, or at least desirable. This is consistent with a recent qualitative study of EC users investigating the perceived efficacy of ECs in smoking cessation, which identified sensorimotor input - in particular the feeling of inhaling, the throat 'hit', and seeing the 'vapour cloud' upon exhaling - as an important factor (Barbeau et al., 2013). Even if the EC does not give much more in the way of urge alleviation above and beyond simple behavioural distraction, the fact that it is similar to conventional smoking gives it added appeal. From a practical point of view it is unlikely that the SB would be adhered to if recommended to smokers as a coping/distraction strategy; the EC has more potential in this respect.

7.2 Proximity of sensorimotor replacement to smoking

It was hypothesised that the DNC would alleviate urge to smoke and withdrawal symptoms to a greater extent than the EC, would be rated higher in terms of user acceptability, and preferred over the EC. This was supported to some degree; compared to ECs, DNCs reduced baseline ratings of urge to smoke from the morning to the evening session to a greater extent, and MPSS ratings were lower over the course of the day. This would suggest that with more proximal SMR, conditioned sensorimotor factors may remain reinforcing for a longer period of time, helping to supress general or 'background' urges to smoke and

withdrawal when used regularly throughout the day. There was however, comparable urge relief during the controlled experiments, and very few differences between the two products in terms of product preferences and ratings.

Consequently, proximity to real smoking may not necessarily be as important as previously hypothesised with regards to acute urge relief. Since both the EC and DNC provide key elements of smoking behaviour - namely the presence of smoke (or vapour in the case of the EC), inhalation/exhalation, airway sensations - this would imply that so long as these aspects are present, they are sufficient to alleviate symptoms acutely, without the need for more 'realistic' sensorimotor input. Exactly how long this would remain reinforcing for until more proximal input is needed is a key question.

It should be considered that as DNCs do contain tobacco, some of these effects may be attributed to other tobacco smoke constituents which may themselves be reinforcing (Rose, 2006). It may be that some of these chemicals, such as MAO inhibitors, help to reduce general withdrawal and urges to smoke, along with some effects of conditioned sensorimotor input, but that sensorimotor input itself only provides some acute relief. This may help explain why both the EC and DNC were comparable during the controlled experimental sessions, but the DNC showed a benefit over the course of the whole day.

The findings have some implications for treatment. DNCs may be a more effective product to use given that they may help supress 'background' urges and withdrawal, and potentially episodic symptoms as and when they arise; the EC on the other hand may only provide some acute relief in times of need, and potentially only during the initial treatment phase. If DNCs remain reinforcing for a longer period of time, they may also be of help as a relapse prevention tool. If behavioural withdrawal (described above) persists long after physical withdrawal subsides, and is eased by engaging in the self-administration ritual (Baker et al., 2006), then DNCs may offer a way of alleviating these symptoms and preventing a lapse back to smoking.

7.3 Moderators of sensorimotor replacement effects

Behavioural dependence (measured with the GN-SBQ) was proposed by Caponnetto *et al* (2011a) as one possible moderator of sensorimotor effects in treatment. Based on their previous findings, it was therefore hypothesised that participants who were considered highly behaviourally dependent by this measure, and/or motivated by the sensorimotor

aspects of smoking - measured with the Sensorimotor subscale of the Motives for Smoking scale (SM-MFS;Russell et al., 1974) - would benefit more from SMR in treatment. This hypothesis was not supported. The addition of SMR with DNCs to current stop-smoking treatment, had a small benefit on short-term cessation outcomes (McRobbie et al., 2013) - providing some support for the rationale of addressing both primary and secondary reinforcers - but there was no evidence to suggest that behavioural dependence moderated these effects. The pattern of results was the same in both high and low GN-SBQ sub-groups. Data for the SM-MFS were more difficult to interpret (due to extremely unequal size of sub-groups), but followed a similar pattern of results. In addition, there was no evidence of a relationship between the total scores on these baseline measures and cessation outcomes. These findings are in contrast to those reported by Caponnetto *et al* (2011a), but it should be noted that their findings were post-hoc. The present results appear to be in line with the general smoking-typology literature, which found little evidence that matching smoker typology to treatment would improve cessation outcomes (Shiffman, 1993).

This is not to say that sensorimotor effects are not moderated by other variables, and indeed could still be moderated by behavioural dependence, but the GN-SBQ may simply be an inadequate measure of this construct. The lack of predictive relationship between the GN-SBQ and abstinence rates reported here and in another recent trial with ECs (Bullen et al., 2013), also calls into question its clinical utility. The marked variability in responses to the EC seen across the two experimental studies may imply that SMR is helpful for a particular sub-group not identified by the questionnaires used. Although there is no doubt that nicotine is the primary reinforcer in tobacco smoking, smokers may differ in their responsiveness to secondary reinforcers. Gender is one variable which has been identified as a potential moderator of responsiveness to conditioned reinforcement (Perkins, 1996). Research with SMR suggests that women may be more susceptible to the sensorimotor aspects of smoking, whereas for men, nicotine may be a more powerful reinforcer (Barrett, 2010, Dawkins et al., 2013b, Dawkins et al., 2012). The literature is somewhat mixed though, with other studies reporting the opposite (Brauer et al., 2001).

Another factor identified in previous work was level of physical dependence, whereby more dependent smokers may place more value on the sensorimotor aspects than those less dependent, presumably because the association between nicotine and sensorimotor aspects are stronger given more frequent and intensive pairings (Behm et al., 1993, Brauer et al., 2001). Participants across the two EC studies were similar in key demographics and characteristics such as age, gender, ethnicity, employment status, qualifications, CPD and

FTND scores as well as EC use over the day, and as such these factors perhaps may not moderate the findings here. It is unlikely that study procedures influenced these results as these were kept constant across both studies.

The variability in responses could, of course, be specific to the EC only, though given previous research suggesting individual differences with DNCs (Brauer et al., 2001), it is likely that a variety of factors play a role in how smokers respond to SMR in general. For some individuals, engaging in a behaviour so similar to conventional smoking may have a negative effect; if proximal smoking-related cues such as lighters, cigarettes, seeing others smoke etc., can act as conditioned stimuli and trigger urges to smoke or smoking behaviour, the SMR product itself may have the same effect, particularly in the case of DNCs, and in individuals who are especially reactive to such cues. Furthermore, if the replacement is not deemed to be adequate or satisfactory, this may lead to feelings of frustration and exacerbate withdrawal. For others, SMR may be perceived positively and as a step towards quitting or way of bridging the gap; and although the replacement may not be as satisfactory as a real cigarette, it is considered better than nothing at all, particularly in high-risk situations where there is a danger of relapse to conventional smoking.

7.4 Effects of sensorimotor replacement on urges to smoke: Implications for the central SMR hypothesis.

The central mechanism of action proposed for SMR was the alleviation of acute urge to smoke via conditioned sensorimotor input. It is important to consider that although statistically significant reductions in urge were evident, the effects were modest, especially in Study 1, and could be reflective of a Type 1 statistical error. In Study 2, effects were more apparent, but without a control condition this is difficult to interpret. This calls into question whether or not sensorimotor factors have as much of an impact on reducing urges to smoke as previously hypothesised. A lack of an effect on urge to smoke however, does not necessarily relate to a lack of effect on cessation. Indeed, previous smoking cessation trials with DNCs have not consistently reported beneficial effects on craving and withdrawal, despite some benefits for cessation (Hatsukami et al., 2010, McRobbie et al., 2013, Walker et al., 2012). This is in line with the general smoking-cessation literature; a recent review reported inconsistent findings regarding the relationship of craving (either measured pre-quit or post-quit) to smoking-cessation outcomes (Wray et al., 2013).

Thus, SMR products may exert their effects in ways other than directly alleviating urge to smoke. For example, SMR products may work well as a coping tool, providing engagement in a concrete behavioural task during high-risk relapse situations. This could help to alleviate the *distress* experienced during an urge/craving, something which has been put forward as a potential clinical target (Tiffany and Wray, 2012). In the case of DNCs specifically, as discussed previously, other tobacco smoke constituents may play a role (Rose, 2006). It is also theoretically plausible that over an extended period of time, SMR could help to extinguish the associations formed between smoking and other stimuli which provoke urges to smoke and/or smoking behaviour (Walker et al., 2009).

Another possible mechanism not previously considered in the sensorimotor literature concerns the aversiveness of sensorimotor input. Despite participants reporting that they liked that the DNCs and ECs provided sensorimotor input, taste was frequently reported as the main disliked aspect of both products. Additionally, across both studies, ratings of pleasantness were modest and typically in the range of 'slightly-somewhat'. This raises the possibility that the unpleasantness of the taste/flavour itself may help to deter away from thoughts of smoking, and potentially form or reinforce a negative perception of cigarettes. Since the flavour of ECs can be manipulated and users can 'shop around' for flavours they prefer, aversive processes may only be pertinent to DNCs. Previous research with DNCs has not examined the potential aversive properties of DNCs, but in our trial (McRobbie et al., 2013), when participants were asked what they liked/disliked about the DNCs, 44 participants listed taste as the main disliked aspect (as seen in Study 2 also), but two participants reported that although the DNCs were unpleasant, this actually helped deter them away from smoking conventional cigarettes. Such reports were not evident in Study 2 though.

The unpleasant taste/flavour of the products does not necessarily negate the SMR hypothesis; taste is only one aspect of SMR, and as other factors are still present (e.g. puffing, holding, inhaling/exhaling) they may still confer conditioned reinforcement. Instead, aversive properties for some individuals may provide an additional deterrent from smoking. Unpleasant taste/flavour could of course have negative consequences. If deemed too unpleasant, the product may not be adhered to at all, when it could confer some benefit. Despite negative comments regarding taste, across studies 1 and 2, most participants reported that they would at least consider using an EC or DNC in smoking cessation, or recommend to others for quitting. Improving the sensory input would likely enhance satisfaction and enjoyment and in turn adherence, potentially improving efficacy.

7.5 **Cue-exposure effects**

The present findings also have some implications for cue-exposure research. A cue-exposure procedure was used in the experimental studies to amplify urges to smoke and withdrawal in order to avoid potential floor effects, as well as to expose participants to a proximal smoking cue that they would typically encounter outside of the study setting. In this way, potential effects of the products on cue-induced urges, as opposed to just background withdrawal and urges to smoke, could also potentially be assessed, as per other interventions/medications (Ferguson and Shiffman, 2009). The impact of the cue-exposure procedure across the two studies was inconsistent, and where there was an effect, change from baseline was quite modest. This resonates with recent literature questioning the relevance and utility of cue exposure research (Wray et al., 2013, Perkins, 2012, Sayette and Tiffany, 2012, Perkins, 2009).

Despite this, there were some interesting patterns of results that emerged. In Study 1, the cue-exposure increased urge to smoke during morning and evening sessions but only in the sample of participants who were able to comply with study procedures and abstain throughout both study sessions. Abstinence length may explain the finding that in the evening session, those who abstained showed an increase in urges following cue-exposure since previous cue-reactivity research has proposed this as a potential moderator.

Most research with respect to this has in fact reported weaker reactions following longer deprivation as opposed to stronger reactivity (Bidwell et al., 2013, Payne et al., 1996, Heishman et al., 2010, Drobes and Tiffany, 1997, Sayette and Hufford, 1994, Tidey et al., 2008). Some of these reports could be a reflection of ceiling effects or potential habituation to cues in repeated measures designs (though see below regarding habituation). One study did report increased cue-reactivity as abstinence length increased (Bedi et al., 2011). In this study however, participants were randomised to relatively long periods of abstinence (7, 14, or 35 days) as opposed to overnight/12 hour's abstinence, common in other designs. In addition, reactions to smoking cues were relatively stable over time when a within-subjects analysis was conducted in a fourth group, who remained abstinent for 35 days, and cue-reactivity was measured at 7, 14 and 35 days (Bedi et al., 2011). Others have also reported no moderating effect of abstinence on cue-reactivity (Shiffman et al., 2013, Carter et al., 2006, McDonough and Warren, 2001).

Even if abstinence length does play a role, it does not explain why only the abstainer sample was affected by the cue-exposure in the morning, as all participants were overnight-abstinent at this point. The findings could be reflective of an acquiescence tendency in this sub-group of participants.

In study 2, this pattern was not evident, and the cue-exposure appeared to have little effect overall (i.e. there were few main effects of time). But, there was some evidence to suggest that participants' product expectancies moderated the extent of cue-reactivity in the morning. There was a marginal interaction between time and product for urge to smoke in the morning in the sample of abstainers. Urge increased after cue-exposure but only when participants were told they would be using the EC ; , when told they would be using the DNC, urge reduced slightly. This pattern was also reflected in ratings of irritability and restlessness. For example, in the whole sample, there was a marginal and significant interaction for ratings of irritability and restlessness, respectively; this wasn't however evident in the abstainer sample, possibly due to the smaller sample size. These patterns were only evident in the morning when participants were naïve to the products.

It may be then that participants had the expectation that the DNC - which at least is still a tobacco cigarette - would be more helpful. Together with the knowledge that they would be able to smoke this cigarette after the cue-exposure, this may have helped to supress their urge and feelings of irritability/restlessness, compared to when they were told they would be using the EC, where their expectations of its helpfulness were maybe more ambiguous.

Research regarding the role of perceived cigarette availability suggests that when participants believe they can smoke soon after cue-exposure, cravings actually increase compared to when they believe they are not able to smoke (Wertz and Sayette, 2001), and generally, craving is believed to increase when smokers have the opportunity or know that the opportunity to smoke is imminent (Jędras et al., 2014), though some inconsistencies were highlighted in this review. Jędras *et al* (2014), speculate that although imminent drug expectancy may well increase craving, cue-exposure, together with the knowledge that drug/drug self-administration procedure will not be available, could give rise to negative mood and/or frustration, potentially amplifying craving.

This, of course, pertains to perceived (conventional) cigarette availability, as opposed to the expectancies of novel products. It may be that when participants have positive expectations that an imminent intervention will be helpful, this may moderate the impact of cue-

exposure. In Study 1, there was also a significant interaction between time and product for restlessness ratings in the morning (in abstainers) where the cue-exposure had no impact when participants were told they would be using the EC, but increased restlessness when told SB.. Moreover, analyses also revealed significant main effects of product for urges to smoke, and trends for the other ratings, whereby baseline and post-cue ratings in the morning were overall lower prior to EC use vs. SB use. This again could reflect these expectations regarding product efficacy, and/or as noted, increased frustration/negative mood due to a lack of drug self-administration in the SB condition.

Despite previous research suggesting that smoking-related cues generally increase craving in comparison to neutral cues (Carter and Tiffany, 1999), the inconsistent findings presented here raise questions for the cue-exposure paradigm. There are undoubtedly a number of methodological factors which may moderate reactions to smoking-related cues, including type of cues, such as proximal vs. distal cues (Shiffman et al., 2013, Conklin et al., 2008), modality of cue-exposure (Wray et al., 2011, Niaura et al., 1998, Heishman et al., 2010), and as discussed previously, abstinence length (Bidwell et al., 2013, Payne et al., 1996, Heishman et al., 2010, Drobes and Tiffany, 1997, Sayette and Hufford, 1994, Tidey et al., 2008). The modest impact of the procedure in the present studies could potentially reflect the type of cue used. Although a commonly used in-vivo cue was chosen (lighting and holding a cigarette for 1 minute), in previous work, this has usually been conducted with the participants' own brand of cigarette (Ferguson and Shiffman, 2009). This was not implemented in the current studies due to logistical reasons, but use of own brand cigarettes could help bolster the impact of the cue exposure.

Individual differences will likely also play a role and there will no doubt be some individuals for whom cue-exposure (at least cue-exposure examined in the laboratory) will have no impact, and others who are highly reactive. In some studies, this has been acknowledged and outcomes have been examined in 'reactor' sub-groups, though definitions of 'reactors' have varied from simply change scores greater than zero (Weinberger et al., 2012), to an increase of at least one unit in average craving (Shiffman et al., 2003). Differences in cue-reactivity could therefore relate to the possibility that some individuals are particularly responsive to secondary or conditioned reinforcers of smoking behaviour (discussed above). Some authors have proposed the notion of a 'cue-reactive' phenotype, which generalises across stimuli (Styn et al., 2013). For example, Styn *et al* reported a significant positive relationship between cue-induced cigarette cravings and cue-induced chocolate cravings in a sample of non-deprived (chocolate and cigarettes) smokers. Alternatively, as

was seen in one study (Shiffman et al., 2003), these differences could be attributed to other characteristics such as age, years smoked and baseline CO (all lower in 'reactors' vs. 'non-reactors').

7.6 Strengths and Limitations

The current research extends upon the sensorimotor literature in several ways. Firstly, it adds to the limited data on the acute effects of nicotine-free ECs specifically as SMR products, and confirms that sensorimotor input from the EC can help reduce urge acutely to a certain extent, at least early on. As seen with other SMR products (e.g. flavoured non-nicotine inhalators/aerosols) that provide limited input, conditioned sensorimotor effects per se may be short-lived.

The research also provides the first comparison between different sensorimotor products. There was some speculation that the more consistent and robust effects seen with DNCs in the literature were due to the proximal sensorimotor input that this product provides, and the findings here provide some evidence for this, but only in relation to long-term effects. The research also contributes to the evidence base of DNCs in treatment, with the first trial to investigate the combination of DNCs not only with varenicline but with all types of NRT, within an intensive behavioural support context (McRobbie et al., 2013). There has been very little examination of potential moderators in treatment with SMR, and the final study here provides the first set of data (for this type of intervention), on the role (or lack of it as the case may be) of behavioural dependence and sensorimotor motives, on smoking-cessation outcomes.

There are some limitations with the current research that should be considered. Firstly, the use of controlled experimental sessions as in Study 1 and 2 can be highly artificial, hence findings may be difficult to generalise to 'real world' situations. Individuals are not in their typical environment, surrounded by the plethora of psycho-social factors which can influence smoking behaviour. One of the key strengths of the present studies however, was the use of products outside of the study setting to improve generalisability. The cue-exposure procedure was also intended to provide a smoking cue that smokers may typically encounter in a 'real-world' context.

With regards to the cue-exposure procedure, participants could have habituated to the procedure over the course of the study, since it was repeated 4 times in total. Evidence suggests cue-reactivity effects can remain stable following repeated trials (Miranda et al., 2008, Morissette et al., 2012, Bidwell et al., 2013, Conklin and Tiffany, 2001), though one study reported some decreases in reactions to both neutral and smoking cues (presented weekly with approximately one hour of abstinence beforehand), from session one to three, but no change at the fourth session, suggesting some novelty effects (LaRowe et al., 2007). In the present studies, the impact of the cue-exposure on urges within each condition at least, seemed to be fairly similar in the morning and evening. For example, in the abstainer sample in Study 1, across both products, urge increased by 0.50 and 0.56 units in the morning and evening respectively; and in Study 2, urge increased by 0.19 units across both products in the morning, and barely changed in the evening. These scores in the evening could have been confounded by abstinence over the day. To fully examine any habituation effects per se, an analysis of pre to post-cue exposure scores, with session number (1 to 4) as a repeated factor, would need to be conducted.

It should be noted that although cue-exposure was used here in part to increase external validity, cue-exposure in the laboratory itself is still artificial and again may not reflect what occurs outside of the study setting. Cue-reactivity research could be applied clinically in several ways such as indexing addiction severity, identifying cues which may interfere with treatment, as a treatment itself (e.g. cue-exposure therapy), and in identifying those prone to relapse (Carter and Tiffany, 1999). But, its clinical utility has recently been questioned. Several reviews found that the relationship between cue-reactivity to relapse and other indicators of nicotine dependence (Perkins, 2009) and a variety of other treatment outcomes (e.g. abstinence, time to first lapse, likelihood of quitting; Wray et al., 2013, Perkins, 2012) was generally quite weak and inconsistent. Another common application of the cue-exposure paradigm concerns the efficacy of medications/interventions in alleviating cue-induced cravings (Ferguson and Shiffman, 2009). Given the inconsistency in cue-exposure effects and interactions with products (discussed above), it is difficult to draw any conclusions on whether or not SMR may impact on cue-induced urges specifically. If anything, the cue-exposure may have confounded the subsequent analyses where post-cue was used as ‘baseline’, though the modest impact of cue-exposure (where there was an effect) may mitigate these concerns.

One limitation of the first study was that there was no control condition in which participants had no intervention at all. It is difficult then to ascertain how much behavioural

distraction itself added to any effects as opposed to just the procedural aspects of the study. There may have also been several confounding factors across both studies 1 and 2. Firstly, some participants were recruited from the Smokers' Clinic and as such were actively seeking smoking-cessation treatment; others responded to advertisements and were not necessarily interested in quitting smoking. It is unlikely that motivation level impacted in any way on symptom ratings, since the experience of physical withdrawal would not be expected to vary with motivation; it may however impact on product preferences and user ratings.

Although the study sessions were kept as consistent as possible throughout the two experimental studies, ensuring a consistent rest-period between study sessions (i.e. time between the first study day to the next) was problematic, and as such there was only a minimum rest-period implemented (of at least two days). The majority of participants completed the study within 7 days, but the inconsistency may have introduced some bias. In relation to this, some flexibility in the timings of morning and evening sessions was also allowed (up to 30 minutes either side), again introducing potential bias.

The sample size calculated in Study 1 did not account for an attrition rate. This was however considered in Study 2, and overall attrition was fairly minimal. But in both studies, the sample size did not account for those participants who would not comply with study procedures and remain abstinent over the course of the day. Since the main outcomes of the study were urges and withdrawal symptoms, the effect of the products could only reliably be interpreted in those who abstained. This was not problematic for the primary outcomes since this specifically concerned acute relief of urges to smoke in the morning where everyone was abstinent overnight. For all other analyses of symptom ratings in abstainers, the analysed sample was reduced, especially in Study 1. With regard to abstinence verification itself, during the DNC condition in Study 2, abstinence was self-report only due to the likelihood of increased CO from smoking DNCs.

Another limitation of the first two studies concerns the measurement of product use over the course of the day. This was not a concern for the DNCs since quantifying DNC use was based on how many were smoked throughout the day. But for the EC and SB conditions, participants were instructed that taking at least 5 puffs of the EC and squeezing the SB at least 15 times constituted one 'use' of each product. Defining use in this way meant that for any participants who were using their products continuously over a prolonged period of time, this could be construed as just one use of the product, or if used for less than the defined amount (i.e. just a few puffs every now and again) would be considered as no use.

It is also likely that participants may not have been attentive at times to how many puffs they took or amount of times they squeezed the SB in order to quantify use as instructed. Most participants were able to quantify their product use and provide a record, but whether or not this was consistent with the instructions and thus consistent across participants is unknown.

This approach was used because alternative methods may also have proved just as problematic or not particularly useful. For example, for the EC, the number of cartridges used could have provided an objective measure of use, but given that product use was measured only over several hours, all participants would have used between 1 and 2 cartridges, providing no useful information. Recording each puff/squeeze would have been unrealistic and probably inaccurate if inevitably completed retrospectively. However, use of a manual counter for each puff/squeeze, as in a recent study (Nides et al., 2014), may have been appropriate for this and perhaps more 'user friendly'.

As discussed previously, one of the major limitations of the third study pertains to the measurement of 'behavioural' dependence with the GN-SBQ, which may not be adequately captured by this questionnaire. Sub-group analysis can also often be problematic in terms of statistical power to detect differences between groups, since sample sizes inevitably reduce. In Study 3, the trial was powered to detect a difference in urges to smoke (the primary outcome of the main trial), and it is likely that the analysis of abstinence rates among sub-groups was underpowered. This was particularly evident in the 'high' SM-MFS sub-group, where the sample size was substantially diminished.

7.7 **Future research**

The present findings raise several questions for future research. Recent developments in SMR have centred on the use of DNCs in treatment, and indeed the findings here would suggest that DNCs may have the most clinical utility. Until the arrival of ECs, no other SMR products had been developed that could have a decent chance of rivalling DNCs. Given the primacy of nicotine in tobacco addiction, it would be advisable for patients to use nicotine ECs over nicotine-free ECs, and research suggests that very few EC users who have successfully quit are using nicotine-free versions (Farsalinos et al., 2013). In terms of research priority then, a comparison of the effects of *nicotine* ECs and DNCs would have important theoretical and clinical implications, and help to extend the present findings.

Addressing both primary and secondary reinforcers should theoretically be most effective for treatment, and therefore should favour the nicotine EC, yet it is not known whether the almost complete sensory and behavioural replacement offered by DNCs, together with potential reinforcing effects of smoke constituents, would be enough to surpass nicotine EC effects. Assuming adequate nicotine delivery with the EC, if the DNC was superior, or even comparable, this would give a strong case in support of proximal SMR. There was some suggestion of this in comparison to the nicotine inhalator in a previous study (Barrett, 2010), though this may not present a fair comparison, as nicotine delivery from the inhalator can be inadequate. In further support of the reinforcing efficacy of DNCs, some studies have reported comparable acute craving relief to even conventional nicotine cigarettes (Hasenfratz et al., 1993, Butschky et al., 1995, Rose et al., 1994, Baldinger et al., 1995c, Baldinger et al., 1995b, Westman et al., 1996b, Gross et al., 1997, Pickworth et al., 1999, Breland et al., 2002, Buchhalter et al., 2001, Dallery et al., 2003, Rose and Behm, 2004, Eid et al., 2005, Buchhalter et al., 2005, Juliano et al., 2006, Donny et al., 2007, Brody et al., 2009, Cobb et al., 2010, Perkins et al., 2010, Barrett, 2010, Attwood et al., 2009, Domino et al., 2013). Clinically, a comparison of DNCs and nicotine ECs would also offer some insight as to which product may be preferable if SMR was implemented in treatment.

A second priority concerns the mechanisms of action and potential mediators of SMR. There is some indication from the data that SMR may not necessarily be involved primarily in the alleviation of urges to smoke; that is, the measurement of urges and other symptoms perhaps does not adequately capture sensorimotor 'treatment' effects. Individuals may still find these products useful despite not reporting much urge alleviation per se. This is highlighted by the results of Study 1 in particular, whereby a vast majority of participants preferred the EC to the SB, and would consider using it as an aid in cessation, despite there being only modest symptom alleviation and not much difference between the two products in this respect.

Thus, SMR may impact upon constructs yet to be examined other than urge alleviation, such as coping skills, and extinction of associations between smoking and other cues/triggers. A recent qualitative study with ECs also highlighted the impact of ECs on wider domains such as personal and social identity, and the perception of ECs (particularly third generation EC devices) as a 'hobby' (Barbeau et al., 2013). Establishing mechanisms would help guide the best way for SMR to be utilised in treatment. DNCs, for example, have so far been used prior to quitting as an extinction tool (Becker et al., 2008, Rezaishiraz et al., 2007, Rose et al., 2006); or post-quit in the early stages of abstinence (McRobbie et al.,

2013, Walker et al., 2012, Hatsukami et al., 2010, Hatsukami et al., 2013b). One approach yet to be tested is the use of DNCs as a relapse prevention tool in recent quitters, used during 'emergency' situations when a lapse to smoking is likely. In Study 3, the way in which DNCs were used varied across participants for example, with some smoking DNCs regularly throughout the day (though less so vs. baseline cigarette consumption) and others only in high-risk situations. This was driven by individual preference, but one approach could be more useful than the other, and shed light on potential mediators.

Other questions still remain regarding SMR. Firstly, for whom SMR may be of benefit for remains unknown. Secondly, the finding that the EC generated comparable symptom alleviation to the DNC during the experimental sessions raises a question as to whether or not there are key sensorimotor aspects that are more crucial for urge alleviation than others. Both products provide smoke/vapour and actions of puffing, inhaling/exhaling, and these may be more pertinent than, for example, other aspects such as the taste/flavour and possibly even strength of airway sensations. These latter sensorimotor aspects may be of more relevance for user acceptability and adherence, and the positive reinforcing effects of sensorimotor factors (i.e. enjoyment, satisfaction etc.), as opposed to negative reinforcement (urge to smoke/withdrawal alleviation).

Previous research in the SMR literature resonates with this hypothesis. Rose and colleagues in their early work with citric acid, ascorbic acid, and black pepper extract inhalators/aerosols, maintained that strength of airway sensations (most notably the 'scratch' or hit at the back of the throat) was particularly important with regards to reinforcing efficacy. In some studies, their hypothesis was supported in that there were associations reported between the perception of strength and satisfaction and liking (Levin et al., 1990), craving relief, help in refraining from smoking and even abstinence rates (Westman et al., 1995); in others though, the relationship between airway sensations and outcomes were inconclusive (Levin et al., 1993). One study examining the effect of sensory blockade on DNCs (Baldinger et al., 1995c), reported no impact of the blocking of olfactory cues on reductions in craving, yet ratings of taste and enjoyment were reduced. It is important to note however that strength ratings also did not differ as a result of sensory blockade, and it is still possible that there were no differences in craving reduction between blockade/no blockade, because the strength was similar.

Theoretically, we would expect the throat scratch to be particularly reinforcing as it is the main sensory stimulus which is experienced just prior to nicotine delivery. Although the present studies did not examine the sensory impact of the products, the throat 'hit' or

scratch was mentioned by some participants in Study 2: 6 participants reported disliking the EC due to a 'weak' or lack of throat hit, but with the DNCs, 3 participants felt the hit was too harsh or strong, whereas 2 felt it was too weak. Given the variability in responses, it is likely that there are individual preferences regarding sensations, taste, etc. and that there is no 'one size fits all' SMR; but, so long as key elements of smoking behaviour are present this is sufficient to have some treatment effect. Future work could therefore try to establish the relative reinforcing efficacy of different aspects of sensorimotor input.

7.8 Conclusions

In conclusion, the findings of the present series of studies suggest that sensorimotor factors are perceived as important to smokers and the provision of a SMR product may help them to cope during abstinence, but this may not necessarily translate to urge alleviation. SMR likely has some scope in treatment but how best to utilise it, and for whom this may be beneficial for remains unclear. One approach yet to be tested is the use of SMR as a relapse prevention tool, or at least as a 'last resort' coping tool in the early treatment phase. This would most likely best be tested with DNCs, given that the findings here suggest more proximal input may exert more sustained effects, though a comparison of DNCs with nicotine ECs would be useful both from a theoretical and clinical perspective.

8 References

ADKISON, S. E., O'CONNOR, R. J., BANSAL-TRAVERS, M., HYLAND, A., BORLAND, R., YONG, H. H., CUMMINGS, K. M., MCNEILL, A., THRASHER, J. F., HAMMOND, D. & FONG, G. T. 2013. Electronic nicotine delivery systems: international tobacco control four-country survey. *American Journal of Preventive Medicine,* 44, 207-215.

ATTWOOD, A. S., PENTON-VOAK, I. S. & MUNAFÒ, M. R. 2009. Effects of acute nicotine administration on ratings of attractiveness of facial cues. *Nicotine & Tobacco Research,* 11, 44-48.

BAKER, T. B., JAPUNTICH, S. J., HOGLE, J. M., MCCARTHY, D. E. & CURTIN, J. J. 2006. Pharmacologic and Behavioral Withdrawal From Addictive Drugs. *Current Directions in Psychological Science,* 15, 232-236.

BALDINGER, B., HASENFRATZ, M. & BÄTTIG, K. 1995a. Comparison of the effects of nicotine on a fixed rate and a subject-paced version of the rapid information processing task. *Psychopharmacology,* 121, 396-400.

BALDINGER, B., HASENFRATZ, M. & BÄTTIG, K. 1995b. Effects of smoking abstinence and nicotine abstinence on heart rate, activity and cigarette craving under field conditions. *Human Psychopharmacology: Clinical and Experimental,* 10, 127-136.

BALDINGER, B., HASENFRATZ, M. & BÄTTIG, K. 1995c. Switching to ultralow nicotine cigarettes: Effects of different tar yields and blocking of olfactory cues. *Pharmacology Biochemistry and Behavior,* 50, 233-239.

BALFOUR, D. J. K. 2004. The neurobiology of tobacco dependence: a preclinical perspective on the role of the dopamine projections to the nucleus accumbens [corrected]. *Nicotine & Tobacco Research,* 6, 899-912.

BALFOUR, D. J. K. 2008. The psychobiology of nicotine dependence. *European Respiratory Review,* 17, 172-181.

BARBEAU, A. M., BURDA, J. & SIEGEL, M. 2013. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach. *Addiction Science & Clinical Practice* [Online], 8. Available: http://www.ncbi.nlm.nih.gov/pubmed/23497603 [Accessed 23 Oct 2013].

BARRETT, S. P. 2010. The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. *Behavioural Pharmacology,* 21, 144-52.

BARRETT, S. P. & DARREDEAU, C. 2012. The acute effects of nicotine on the subjective and behavioural responses to denicotinized tobacco in dependent smokers. *Behavioural Pharmacology,* 23, 221-7.

BECKER, K. M., ROSE, J. E. & ALBINO, A. P. 2008. A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation. *Nicotine & Tobacco Research,* 10, 1139-48.

BEDI, G., PRESTON, K. L., EPSTEIN, D. H., HEISHMAN, S. J., MARRONE, G. F., SHAHAM, Y. & DE WIT, H. 2011. Incubation of cue-induced cigarette craving during abstinence in human smokers. *Biological Psychiatry,* 69, 708-11.

BEHM, F. M., LEVIN, E. D., LEE, Y. K. & ROSE, J. E. 1990. Low-nicotine regenerated smoke aerosol reduces desire for cigarettes. *Journal of Substance Abuse,* 2, 237-247.

BEHM, F. M., SCHUR, C., LEVIN, E. D., TASHKIN, D. P. & ROSE, J. E. 1993. Clinical evaluation of a citric acid inhaler for smoking cessation. *Drug and Alcohol Dependence,* 31, 131-138.

BIDWELL, L. C., LEVENTHAL, A. M., TIDEY, J. W., BRAZIL, L., NIAURA, R. S. & COLBY, S. M. 2013. Effects of abstinence in adolescent tobacco smokers: withdrawal symptoms, urge, affect, and cue reactivity. *Nicotine & Tobacco Research* 15, 457-64.

BRAUER, L. H., BEHM, F. M., LANE, J. D., WESTMAN, E. C., PERKINS, C. & ROSE, J. E. 2001. Individual differences in smoking reward from de-nicotinized cigarettes. *Nicotine & Tobacco Research,* 3, 101-109.

BRAUER, L. H., BEHM, F. M., WESTMAN, E. C., PATEL, P. & ROSE, J. E. 1999. Naltrexone blockade of nicotine effects in cigarette smokers. *Psychopharmacology (Berl),* 143, 339-46.

BRELAND, A. B., BUCHHALTER, A. R., EVANS, S. E. & EISSENBERG, T. 2002. Evaluating acute effects of potential reduced-exposure products for smokers: clinical laboratory methodology. *Nicotine & Tobacco Research,* 4 Suppl 2, S131-40.

BRODY, A. L., MANDELKERN, M. A., OLMSTEAD, R. E., ALLEN-MARTINEZ, Z., SCHEIBAL, D., ABRAMS, A. L., COSTELLO, M. R., FARAHI, J., SAXENA, S., MONTEROSSO, J. & LONDON, E. D. 2009. Ventral striatal dopamine release in response to smoking a regular vs a denicotinized cigarette. *Neuropsychopharmacology,* 34, 282-9.

BUCHHALTER, A. R., ACOSTA, M. C., EVANS, S. E., BRELAND, A. B. & EISSENBERG, T. 2005. Tobacco abstinence symptom suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. *Addiction,* 100, 550-9.

BUCHHALTER, A. R., SCHRINEL, L. & EISSENBERG, T. 2001. Withdrawal-suppressing effects of a novel smoking system: comparison with own brand, not own brand, and de-nicotinized cigarettes. *Nicotine & Tobacco Research,* 3, 111-118.

BULLEN, C., HOWE, C., LAUGESEN, M., MCROBBIE, H., PARAG, V., WILLIMAN, J. & WALKER, N. 2013. Electronic cigarettes for smoking cessation: a randomised controlled trial. *The Lancet,* 382, 1629-1637.

BULLEN, C., MCROBBIE, H., THORNLEY, S., GLOVER, M., LIN, R. & LAUGESEN, M. 2010. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tobacco Control,* 19, 98-103.

BUTSCHKY, M. F., BAILEY, D., HENNINGFIELD, J. E. & PICKWORTH, W. B. 1995. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. *Pharmacology Biochemistry and Behavior,* 50, 91-96.

CAGGIULA, A. R., DONNY, E. C., CHAUDHRI, N., PERKINS, K. A., EVANS-MARTIN, F. F. & SVED, A. F. 2002. Importance of nonpharmacological factors in nicotine self-administration. *Physiology & behavior,* 77, 683-687.

CAGGIULA, A. R., DONNY, E. C., WHITE, A. R., CHAUDHRI, N., BOOTH, S., GHARIB, M. A., HOFFMAN, A., PERKINS, K. A. & SVED, A. F. 2001. Cue dependency of nicotine self-administration and smoking. *Pharmacology Biochemistry and Behavior,* 70, 515-530.

CAPONNETTO, P., AUDITORE, R., RUSSO, C., CAPPELLO, G. C. & POLOSA, R. 2013a. Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *International Journal of Environmental Research and Public Health,* 10, 446-61.

CAPONNETTO, P., CAMPAGNA, D., CIBELLA, F., MORJARIA, J. B., CARUSO, M., RUSSO, C. & POLOSA, R. 2013b. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as Tobacco Cigarettes Substitute: A Prospective 12-Month Randomized Control Design Study. *PLoS One,* 8, e66317.

CAPONNETTO, P., CIBELLA, F., MANCUSO, S., CAMPAGNA, D., ARCIDIACONO, G. & POLOSA, R. 2011a. Effect of a nicotine free inhalator as part of a smoking cessation program. *European Respiratory Journal,* 38, 1005-1011.

CAPONNETTO, P., POLOSA, R., AUDITORE, R., RUSSO, C. & CAMPAGNA, D. 2011b. Smoking cessation with E-cigarettes in smokers with a documented history of depression and recurring relapses. *International Journal of Clinical Medicine,* 2, 281-284.

CAPONNETTO, P., POLOSA, R., RUSSO, C., LEOTTA, C. & CAMPAGNA, D. 2011c. Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses: a case series. *Journal of Medical Case Reports,* 5, 1-6.

CARTER, B. L., ROBINSON, J. D., LAM, C. Y., WETTER, D. W., TSAN, J. Y., DAY, S. X. & CINCIRIPINI, P. M. 2006. A psychometric evaluation of cigarette stimuli used in a cue reactivity study. *Nicotine & Tobacco Research,* 8, 361-9.

CARTER, B. L. & TIFFANY, S. T. 1999. Meta-analysis of cue-reactivity in addiction research. *Addiction,* 94, 327-340.

CHAUDHRI, N., CAGGIULA, A., DONNY, E., PALMATIER, M., LIU, X. & SVED, A. 2006. Complex interactions between nicotine and nonpharmacological stimuli reveal multiple roles for nicotine in reinforcement. *Psychopharmacology,* 184, 353-366.

COBB, C. O., WEAVER, M. F. & EISSENBERG, T. 2010. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. *Tobacco Control,* 19, 367-373.

CONKLIN, C. A., ROBIN, N., PERKINS, K. A., SALKELD, R. P. & MCCLERNON, F. J. 2008. Proximal versus distal cues to smoke: the effects of environments on smokers' cue-reactivity. *Experimental and clinical psychopharmacology,* 16, 207-14.

CONKLIN, C. A. & TIFFANY, S. T. 2001. The impact of imagining personalized versus standardized urge scenarios on cigarette craving and autonomic reactivity. *Experimental and clinical psychopharmacology,* 9, 399-408.

CONKLIN, C. A. & TIFFANY, S. T. 2002. Applying extinction research and theory to cue-exposure addiction treatments. *Addiction,* 97, 155-67.

DALLERY, J., HOUTSMULLER, E., PICKWORTH, W. & STITZER, M. 2003. Effects of cigarette nicotine content and smoking pace on subsequent craving and smoking. *Psychopharmacology,* 165, 172-180.

DARREDEAU, C., STEWART, S. H. & BARRETT, S. P. 2013. The effects of nicotine content information on subjective and behavioural responses to nicotine-containing and denicotinized cigarettes. *Behavioural Pharmacology,* 24, 291-7.

DAWKINS, L. & CORCORAN, O. 2013. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology* [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/23978909 [Accessed Aug 27].

DAWKINS, L., TURNER, J. & CROWE, E. 2013a. Nicotine derived from the electronic cigarette improves time-based prospective memory in abstinent smokers. *Psychopharmacology (Berl),* 227, 377-84.

DAWKINS, L., TURNER, J., HASNA, S. & SOAR, K. 2012. The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. *Addictive Behaviors,* 37, 970-3.

DAWKINS, L., TURNER, J., ROBERTS, A. & SOAR, K. 2013b. 'Vaping' profiles and preferences: an online survey of electronic cigarette users. *Addiction,* 108, 1115-25.

DOCKRELL, M., MORRISON, R., BAULD, L. & MCNEILL, A. 2013. E-cigarettes: prevalence and attitudes in Great Britain. *Nicotine &Tobacco Research,* 15, 1737-44.

DOMINO, E. F., NI, L., DOMINO, J. S., YANG, W., EVANS, C., GUTHRIE, S., WANG, H., KOEPPE, R. A. & ZUBIETA, J. K. 2013. Denicotinized versus average nicotine tobacco cigarette smoking differentially releases striatal dopamine. *Nicotine & Tobacco Research,* 15, 11-21.

DONNY, E. C., HOUTSMULLER, E. & STITZER, M. L. 2007. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. *Addiction,* 102, 324-34.

DONNY, E. C. & JONES, M. 2009. Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. *Drug and Alcohol Dependence,* 104, 23-33.

DROBES, D. J. & TIFFANY, S. T. 1997. Induction of smoking urge through imaginal and in vivo procedures: physiological and self-report manifestations. *Journal of Abnormal Psychology,* 106, 15-25.

EID, N. C., FANT, R. V., MOOLCHAN, E. T. & PICKWORTH, W. B. 2005. Placebo cigarettes in a spaced smoking paradigm. *Pharmacology Biochemistry and Behavior,* 81, 158-64.

EISSENBERG, T. 2010. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tobacco Control,* 19, 87-88.

ETTER, J. F. 2010. Electronic cigarettes: a survey of users. *BMC Public Health,* 10, 231.

ETTER, J. F. & BULLEN, C. 2011. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction,* 106, 2017-2028.

ETTER, J. F. & BULLEN, C. 2014. A longitudinal study of electronic cigarette users. *Addictive Behaviors,* 39, 491-4.

FARSALINOS, K. E., ROMAGNA, G., TSIAPRAS, D., KYRZOPOULOS, S. & VOUDRIS, V. 2013. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. *Substance Abuse: Research and Treatment,* 7, 139-46.

FERGUSON, S. G. & SHIFFMAN, S. 2009. The relevance and treatment of cue-induced cravings in tobacco dependence. *Journal of Substance Abuse Treatment,* 36, 235-43.

FOULDS, J., VELDHEER, S. & BERG, A. 2011. Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives. *International Journal of Clinical Practice,* 65, 1037-1042.

GLOVER, E. D., NILSSON, F., WESTIN, A., GLOVER, P. N., LAFLIN, M. T. & PERSSON, B. 2005. Developmental history of the Glover-Nilsson smoking behavioral questionnaire. *American Journal of Health Behavior,* 29, 443-55.

GONIEWICZ, M. L., LINGAS, E. O. & HAJEK, P. 2012. Patterns of electronic cigarette use and user beliefs about their safety and benefits: An Internet survey. *Drug and Alcohol Review,* 32, 133-140.

GROSS, J., LEE, J. & STITZER, M. L. 1997. Nicotine-Containing Versus De-Nicotinized Cigarettes: Effects on Craving and Withdrawal. *Pharmacology Biochemistry and Behavior,* 57, 159-165.

HAJEK, P., JARVIS, M. J., BELCHER, M., SUTHERLAND, G. & FEYERABEND, C. 1989. Effect of smoke-free cigarettes on 24 h cigarette withdrawal: a double-blind placebo-controlled study. *Psychopharmacology,* 97, 99-102.

HAJEK, P., WEST, R., FOULDS, J., NILSSON, F., BURROWS, S. & MEADOW, A. 1999. Randomized Comparative Trial of Nicotine Polacrilex, a Transdermal Patch, Nasal Spray, and an Inhaler. *Archives of Internal Medicine,* 159, 2033-2038.

HASENFRATZ, M., BALDINGER, B. & BÄTTIG, K. 1993. Nicotine or tar titration in cigarette smoking behavior? *Psychopharmacology,* 112, 253-258.

HATSUKAMI, D. K., HEISHMAN, S. J., VOGEL, R. I., DENLINGER, R. L., ROPER-BATKER, A. N., MACKOWICK, K. M., JENSEN, J., MURPHY, S. E., THOMAS, B. F. & DONNY, E. 2013a. Dose-

response effects of spectrum research cigarettes. *Nicotine & Tobacco Research,* 15, 1113-1121.

HATSUKAMI, D. K., HERTSGAARD, L. A., VOGEL, R. I., JENSEN, J. A., MURPHY, S. E., HECHT, S. S., CARMELLA, S. G., AL'ABSI, M., JOSEPH, A. M. & ALLEN, S. S. 2013b. Reduced nicotine content cigarettes and nicotine patch. *Cancer Epidemiology Biomarkers & Prevention,* 22, 1015-24.

HATSUKAMI, D. K., KOTLYAR, M., HERTSGAARD, L. A., ZHANG, Y., CARMELLA, S. G., JENSEN, J. A., ALLEN, S. S., SHIELDS, P. G., MURPHY, S. E., STEPANOV, I. & HECHT, S. S. 2010. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction,* 105, 343-55.

HEATHERTON, T., KOZLOWSKI, L., FRECKER, R. & FAGERSTROM, K. 1991. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *British Journal of Addiction,* 86, 1119 - 1127.

HEAVNER, K. K., DUNWORTH, J., BERGEN, P. L., NISSEN, C. M. & PHILLIPS, C. V. 2009. *Electronic cigarettes (e-cigarettes) as potential tobacco harm reduction products: Results of an online survey of e-cigarette user* [Online]. Available: http://www.tobaccoharmreduction.org/wpapers.htm [Accessed 22 October 2010].

HEISHMAN, S. J., LEE, D. C., TAYLOR, R. C. & SINGLETON, E. G. 2010. Prolonged duration of craving, mood, and autonomic responses elicited by cues and imagery in smokers: Effects of tobacco deprivation and sex. *Experimental and clinical psychopharmacology,* 18, 245-56.

HENNINGFIELD, J. E. & GOLDBERG, S. R. 1983. Nicotine as a reinforcer in human subjects and laboratory animals. *Pharmacology Biochemistry and Behavior,* 19, 989-992.

HENNINGFIELD, J. E., MIYASATO, K. & JASINSKI, D. R. 1985. Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine. *Journal of Pharmacology and Experimental Theraputics,* 234, 1-12.

HORN, D. & WAINGROW, S. 1966. Some dimensions of a model for smoking behavior change. *American journal of public health and the nation's health,* 56, Suppl 56:21-6.

HUGHES, J. R. & HATSUKAMI, D. 1986. Signs and Symptoms of Tobacco Withdrawal. *Archives of General Psychiatry,* 43, 289-294.

HUTCHISON, K. E., RUTTER, M. C., NIAURA, R., SWIFT, R. M., PICKWORTH, W. B. & SOBIK, L. 2004. Olanzapine attenuates cue-elicited craving for tobacco. *Psychopharmacology (Berl),* 175, 407-13.

IKARD, F. F., GREEN, D. E. & HORN, D. 1969. A scale to differentiate between types of smoking as related to the management of affect. *Substance Use & Misuse,* 4, 649-659.

JĘDRAS, P., JONES, A. & FIELD, M. 2014. The role of anticipation in drug addiction and reward. *Neuroscience and Neuroeconomics,* 3, 1-10.

JULIANO, L. M. & BRANDON, T. H. 2002. Effects of nicotine dose, instructional set, and outcome expectancies on the subjective effects of smoking in the presence of a stressor. *Journal of Abnormal Psychology,* 111, 88-97.

JULIANO, L. M., DONNY, E. C., HOUTSMULLER, E. J. & STITZER, M. L. 2006. Experimental evidence for a causal relationship between smoking lapse and relapse. *Journal of Abnormal Psychology,* 115, 166-73.

JULIANO, L. M., FUCITO, L. M. & HARRELL, P. T. 2011. The influence of nicotine dose and nicotine dose expectancy on the cognitive and subjective effects of cigarette smoking. *Experimental and Clinical Psychopharmacology,* 19, 105-15.

KASSEL, J. D., EVATT, D. P., GREENSTEIN, J. E., WARDLE, M. C., YATES, M. C. & VEILLEUX, J. C. 2007. The acute effects of nicotine on positive and negative affect in adolescent smokers. *Journal of Abnormal Psychology,* 116, 543-53.

KELEMEN, W. L. & KAIGHOBADI, F. 2007. Expectancy and pharmacology influence the subjective effects of nicotine in a balanced-placebo design. *Experimental and Clinical Psychopharmacology,* 15, 93-101.

KING, A., MCNAMARA, P., CONRAD, M. & CAO, D. 2009. Alcohol-induced increases in smoking behavior for nicotinized and denicotinized cigarettes in men and women. *Psychopharmacology,* 207, 107-117.

KOZLOWSKI, L. T., MEHTA, N. Y., SWEENEY, C. T., SCHWARTZ, S. S., VOGLER, G. P., JARVIS, M. J. & WEST, R. J. 1998. Filter ventilation and nicotine content of tobacco in cigarettes from Canada, the United Kingdom, and the United States. *Tobacco Control,* 7, 369-75.

KRALIKOVA, E., KUBATOVA, S., TRUNECKOVA, K., KMETOVA, A. & HAJEK, P. 2012. The electronic cigarette: what proportion of smokers have tried it and how many use it regularly? *Addiction,* 107, 1528-9.

KRALIKOVA, E., NOVAK, J., WEST, O., KMETOVA, A. & HAJEK, P. 2013. Do e-Cigarettes Have the Potential to Compete With Conventional Cigarettes?: A Survey of Conventional Cigarette Smokers' Experiences With e-Cigarettes. *Chest,* 144, 1609-14.

LANE, J. D., LEFEBVRE, J. C., ROSE, J. E. & KEEFE, F. J. 1995. Effects of cigarette smoking on perception of thermal pain. *Experimental and Clinical Psychopharmacology,* 3, 140-147.

LAROWE, S. D., SALADIN, M. E., CARPENTER, M. J. & UPADHYAYA, H. P. 2007. Reactivity to nicotine cues over repeated cue reactivity sessions. *Addictive Behaviors,* 32, 2888-99.

LEVIN, E. D., BEHM, F., CARNAHAN, E., LECLAIR, R., SHIPLEY, R. & ROSE, J. E. 1993. Clinical trials using ascorbic acid aerosol to aid smoking cessation. *Drug and Alcohol Dependence,* 33, 211-23.

LEVIN, E. D., ROSE, J. E. & BEHM, F. 1990. Development of a citric acid aerosol as a smoking cessation aid. *Drug and Alcohol Dependence,* 25, 273-279.

LINDSEY, K. P., BRACKEN, B. K., MACLEAN, R. R., RYAN, E. T., LUKAS, S. E. & FREDERICK, B. D. 2013. Nicotine content and abstinence state have different effects on subjective ratings of

positive versus negative reinforcement from smoking. *Pharmacology Biochemistry & Behavior,* 103, 710-6.

MACQUEEN, D. A., HECKMAN, B. W., BLANK, M. D., JANSE VAN RENSBURG, K., EVANS, D. E. & DROBES, D. J. 2012. Transient compensatory smoking in response to placebo cigarettes. *Psychopharmacology (Berl),* 223, 47-54.

MCDONOUGH, B. E. & WARREN, C. A. 2001. Effects of 12-h tobacco deprivation on event-related potentials elicited by visual smoking cues. *Psychopharmacology,* 154, 282-91.

MCKENNELL, A. C. 1970. Smoking motivation factors. *British Journal of Social and Clinical Psychology,* 9, 8-22.

MCKENNELL, A. C. 1973. Is addictive smoking an independent trait? *Substance Use & Misuse,* 8, 505-509.

MCROBBIE, H., PRZULJ, D., SMITH, K., CORNWALL, D. & HAJEK, P. 2013. Complementing current NHS Stop Smoking Service Treatment for smokers with behavioural replacement: the role of de-nicotinised cigarettes. [Oral Presentation PA 18-3]. *19th Annual Conference, Society for Research on Nicotine and Tobacco.* Boston: Society for Research on Nicotine and Tobacco.

MCROBBIE, H., THORNLEY, S., BULLEN, C., LIN, R. B., SENIOR, H., LAUGESEN, M., WHITTAKER, R. & HAJEK, P. 2010. A randomized trial of the effects of two novel nicotine replacement therapies on tobacco withdrawal symptoms and user satisfaction. *Addiction,* 105, 1290-8.

MIRANDA, R., JR., ROHSENOW, D. J., MONTI, P. M., TIDEY, J. & RAY, L. 2008. Effects of repeated days of smoking cue exposure on urge to smoke and physiological reactivity. *Addictive behaviors,* 33, 347-53.

MORISSETTE, S. B., GULLIVER, S. B., KAMHOLZ, B. W., SPIEGEL, D. A., TIFFANY, S. T. & BARLOW, D. H. 2012. Transdermal nicotine during cue reactivity in adult smokers with and without anxiety disorders. *Psychology of Addictive Behaviors* 26, 507-18.

NAQVI, N. H. & BECHARA, A. 2005. The airway sensory impact of nicotine contributes to the conditioned reinforcing effects of individual puffs from cigarettes. *Pharmacology Biochemistry & Behavior,* 81, 821-9.

NAQVI, N. H. & BECHARA, A. 2006. Skin conductance responses are elicited by the airway sensory effects of puffs from cigarettes. *International Journal of Psychophysiology,* 61, 77-86.

NERÍN, I., CRUCELAEGUI, A., NOVELLA, P., BEAMONTE, A., SOBRADIEL, N., BERNAL, V. & GARGALLO, P. 2005. Assessment of Behavioral Dependence With the Glover-Nilsson Test in Smoking Cessation Treatment. *Archivos de Bronconeumología (English Edition),* 41, 493-498.

NIAURA, R., SHADEL, W. G., ABRAMS, D. B., MONTI, P. M., ROHSENOW, D. J. & SIROTA, A. 1998. Individual differences in cue reactivity among smokers trying to quit: effects of gender and cue type. *Addictive Behaviors,* 23, 209-24.

NIDES, M. A., LEISCHOW, S. J., BHATTER, M. & SIMMONS, M. 2014. Nicotine Blood Levels and Short-term Smoking Reduction with an Electronic Nicotine Delivery System. *American Journal of Health Behavior,* 38, 265-274.

PAYNE, T. J., SMITH, P. O., STURGES, L. V. & HOLLERAN, S. A. 1996. Reactivity to smoking cues: Mediating roles of nicotine dependence and duration of deprivation. *Addictive Behaviors,* 21, 139-154.

PERKINS, K. A. 1996. Sex differences in nicotine versus nonnicotine reinforcement as determinants of tobacco smoking. *Experimental and Clinical Psychopharmacology,* 4, 166-177.

PERKINS, K. A. 2009. Does smoking cue-induced craving tell us anything important about nicotine dependence? *Addiction* 104, 1610-6.

PERKINS, K. A. 2012. Subjective reactivity to smoking cues as a predictor of quitting success. *Nicotine & Tobacco Research* 14, 383-7.

PERKINS, K. A., CICCOCIOPPO, M., CONKLIN, C. A., MILANAK, M. E., GROTTENTHALER, A. & SAYETTE, M. A. 2008. Mood influences on acute smoking responses are independent of nicotine intake and dose expectancy. *Journal of Abnormal Psychology,* 117, 79-93.

PERKINS, K. A., GERLACH, D., VENDER, J., GROBE, J., MEEKER, J. & HUTCHISON, S. 2001. Sex differences in the subjective and reinforcing effects of visual and olfactory cigarette smoke stimuli. *Nicotine & Tobacco Research,* 3, 141-50.

PERKINS, K. A., JACOBS, L., CICCOCIOPPO, M., CONKLIN, C., SAYETTE, M. & CAGGIULA, A. 2004. The Influence of Instructions and Nicotine Dose on the Subjective and Reinforcing Effects of Smoking. *Experimental and Clinical Psychopharmacology,* 12, 91-101.

PERKINS, K. A., KARELITZ, J. L., CONKLIN, C. A., SAYETTE, M. A. & GIEDGOWD, G. E. 2010. Acute negative affect relief from smoking depends on the affect situation and measure but not on nicotine. *Biological Psychiatry,* 67, 707-14.

PERKINS, K. A., SAYETTE, M., CONKLIN, C. & CAGGIULA, A. 2003. Placebo effects of tobacco smoking and other nicotine intake. *Nicotine & Tobacco Research,* 5, 695-709.

PICKWORTH, W. B., NELSON, R. A., ROHRER, M. S., FANT, R. V. & HENNINGFIELD, J. E. 1999. Pharmacodynamic effects of new de-nicotinized cigarettes. *Nicotine & Tobacco Research,* 1, 357-364.

POLOSA, R., CAPONNETTO, P., MORJARIA, J. B., PAPALE, G., CAMPAGNA, D. & RUSSO, C. 2011. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. *BMC Public Health,* 11, 786.

POLOSA, R., MORJARIA, J. B., CAPONNETTO, P., CAMPAGNA, D., RUSSO, C., ALAMO, A., AMARADIO, M. & FISICHELLA, A. 2013. Effectiveness and tolerability of electronic cigarette

in real-life: a 24-month prospective observational study. *Internal and Emergency Medicine* [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/23873169 [Accessed Jul 20].

PRITCHARD, W., ROBINSON, J., GUY, T., DAVIS, R. & STILES, M. 1996. Assessing the sensory role of nicotine in cigarette smoking. *Psychopharmacology,* 127, 55-62.

RATH, J. M., SHARMA, E. & BECK, K. H. 2013. Reliability and Validity of the Glover-Nilsson Smoking Behavioral Questionnaire. *American Journal of Health Behavior,* 37, 310-317.

REZAISHIRAZ, H., HYLAND, A., MAHONEY, M. C., O'CONNOR, R. J. & CUMMINGS, K. M. 2007. Treating smokers before the quit date: can nicotine patches and denicotinized cigarettes reduce cravings? *Nicotine & Tobacco Research,* 9, 1139-46.

ROBINSON, M. L., HOUTSMULLER, E. J., MOOLCHAN, E. T. & PICKWORTH, W. B. 2000. Placebo cigarettes in smoking research. *Experimental & Clinical Psychopharmacology,* 8, 326-32.

ROHSENOW, D. J. & MARLATT, G. A. 1981. The balanced placebo design: methodological considerations. *Addictive Behaviors,* 6, 107-22.

ROSE, J. 2006. Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology,* 184, 274-285.

ROSE, J. E. 1988. The role of upper airway stimulation in smoking. *In:* POMERLEAU, O. F. & POMERLEAN, C. S. (eds.) *Nicotine Replacement: A Critical Evaluation.* New York: Alan R. Liss.

ROSE, J. E. & BEHM, F. 1987. Refined cigarette smoke as a method for reducing nicotine intake. *Pharmacology Biochemistry and Behavior,* 28, 305-310.

ROSE, J. E. & BEHM, F. M. 1994. Inhalation of vapor from black pepper extract reduces smoking withdrawal symptoms. *Drug and Alcohol Dependence,* 34, 225-9.

ROSE, J. E. & BEHM, F. M. 2004. Effects of low nicotine content cigarettes on smoke intake. *Nicotine & Tobacco Research,* 6, 309-319.

ROSE, J. E., BEHM, F. M. & LEVIN, E. D. 1993. Role of nicotine dose and sensory cues in the regulation of smoke intake. *Pharmacology Biochemistry & Behavior,* 44, 891-900.

ROSE, J. E., BEHM, F. M., SALLEY, A. N., BATES, J. E., COLEMAN, R. E., HAWK, T. C. & TURKINGTON, T. G. 2007. Regional brain activity correlates of nicotine dependence. *Neuropsychopharmacology,* 32, 2441-52.

ROSE, J. E., BEHM, F. M., WESTMAN, E. C., BATES, J. E. & SALLEY, A. 2003. Pharmacologic and sensorimotor components of satiation in cigarette smoking. *Pharmacology Biochemistry and Behavior,* 76, 243-50.

ROSE, J. E., BEHM, F. M., WESTMAN, E. C. & JOHNSON, M. 2000. Dissociating nicotine and nonnicotine components of cigarette smoking. *Pharmacology Biochemistry and Behavior,* 67, 71-81.

ROSE, J. E., BEHM, F. M., WESTMAN, E. C. & KUKOVICH, P. 2006. Precessation treatment with nicotine skin patch facilitates smoking cessation. *Nicotine & Tobacco Research,* 8, 89-101.

ROSE, J. E., BEHM, F. M., WESTMAN, E. C., LEVIN, E. D., STEIN, R. M., LANE, J. D. & RIPKA, G. V. 1994. Combined effects of nicotine and mecamylamine in attenuating smoking satisfaction. *Experimental and Clinical Psychopharmacology,* 2, 328-344.

ROSE, J. E. & HICKMAN, C. S. 1987. Citric acid aerosol as a potential smoking cessation aid. *Chest,* 92, 1005-1008.

ROSE, J. E. & LEVIN, E. D. 1991. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. *British Journal of Addiction,* 86, 605-609.

ROSE, J. E., SALLEY, A., BEHM, F. M., BATES, J. E. & WESTMAN, E. C. 2010. Reinforcing effects of nicotine and non-nicotine components of cigarette smoke. *Psychopharmacology (Berl),* 210, 1-12.

ROSE, J. E., TASHKIN, D. P., ERTLE, A., ZINSER, M. C. & LAFER, R. 1985. Sensory blockade of smoking satisfaction. *Pharmacology Biochemistry and Behavior,* 23, 289-293.

ROSE, J. E., ZINSER, M. C., TASHKIN, D. P., NEWCOMB, R. & ERTLE, A. 1984. Subjective response to cigarette smoking following airway anesthetization. *Addictive Behaviors,* 9, 211-215.

RUSSELL, M. A. 1971. Cigarette dependence. I. Nature and classification. *British Medical Journal,* 2, 330-1.

RUSSELL, M. A., JARVIS, M. J., SUTHERLAND, G. & FEYERABEND, C. 1987. Nicotine replacement in smoking cessation. Absorption of nicotine vapor from smoke-free cigarettes. *JAMA,* 257, 3262-5.

RUSSELL, M. A. H., PETO, J. & PATEL, U. A. 1974. The Classification of Smoking by Factorial Structure of Motives. *Journal of the Royal Statistical Society. Series A (General),* 137, 313-346.

SAYETTE, M. A. & HUFFORD, M. R. 1994. Effects of cue exposure and deprivation on cognitive resources in smokers. *Journal of Abnormal Psychology,* 103, 812-8.

SAYETTE, M. A., SHIFFMAN, S., TIFFANY, S. T., NIAURA, R. S., MARTIN, C. S. & SHADEL, W. G. 2000. The measurement of drug craving. *Addiction,* 95 Suppl 2, S189-210.

SAYETTE, M. A. & TIFFANY, S. T. 2012. Peak provoked craving: an alternative to smoking cue-reactivity. *Addiction,* 108, 1019-1025.

SHADEL, W. G., NIAURA, R. A. & ABRAMS, D. B. 2001. Does completing a craving questionnaire promote increased smoking craving? An experimental investigation. *Psychology of Addictive Behaviors,* 15, 265-7.

SHAHAN, T. A., BICKEL, W. K., BADGER, G. J. & GIORDANO, L. A. 2001. Sensitivity of nicotine-containing and de-nicotinized cigarette consumption to alternative non-drug reinforcement: a behavioral economic analysis. *Behavioral Pharmacology,* 12, 277-84.

SHAHAN, T. A., BICKEL, W. K., MADDEN, G. J. & BADGER, G. J. 1999. Comparing the reinforcing efficacy of nicotine containing and de-nicotinized cigarettes: a behavioral economic analysis. *Psychopharmacology (Berl),* 147, 210-6.

SHIFFMAN, S. 1993. Assessing smoking patterns and motives. *Journal of Consulting and Clinical Psychology,* 61, 732-42.

SHIFFMAN, S., DUNBAR, M., KIRCHNER, T., LI, X., TINDLE, H., ANDERSON, S. & SCHOLL, S. 2013. Smoker reactivity to cues: Effects on craving and on smoking behavior. *Journal of Abnormal Psychology,* 122, 264-80.

SHIFFMAN, S., SHADEL, W. G., NIAURA, R., KHAYRALLAH, M. A., JORENBY, D. E., RYAN, C. F. & FERGUSON, C. L. 2003. Efficacy of acute administration of nicotine gum in relief of cue-provoked cigarette craving. *Psychopharmacology,* 166, 343-350.

SHIFFMAN, S. M. & JARVIK, M. E. 1976. Smoking withdrawal symptoms in two weeks of abstinence. *Psychopharmacology (Berl),* 50, 35-9.

SPEALMAN, R. & GOLDBERG, D. 1981. Persistent behavior at high rates maintained by intravenous self-administration of nicotine. *Science,* 214, 573-575.

STEAD, L. F., PERERA, R., BULLEN, C., MANT, D. & LANCASTER, T. 2008. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews*, CD000146.

STEWART-WILLIAMS, S. & PODD, J. 2004. The Placebo Effect: Dissolving the Expectancy Versus Conditioning Debate. *Psychological Bulletin,* 130, 324-340.

STRASSER, A. A., LERMAN, C., SANBORN, P. M., PICKWORTH, W. B. & FELDMAN, E. A. 2007. New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. *Drug and Alcohol Dependence,* 86, 294-300.

STYN, M. A., BOVBJERG, D. H., LIPSKY, S. & ERBLICH, J. 2013. Cue-induced cigarette and food craving: a common effect? *Addictive Behaviors,* 38, 1840-3.

THE HEALTH AND SOCIAL CARE INFORMATION CENTRE 2012. Statistics on NHS Stop Smoking Services: England, April 2011 – March 2012. London: The Information Centre, Lifestyle Statistics.

THE HEALTH AND SOCIAL CARE INFORMATION CENTRE 2013. Statistics on Smoking, England 2013. London: The Information Cente, Lifestyles Statistics.

TIDEY, J. W., COLBY, S. M. & XAVIER, E. M. 2013. Effects of Smoking Abstinence on Cigarette Craving, Nicotine Withdrawal, and Nicotine Reinforcement in Smokers With and Without Schizophrenia. *Nicotine & Tobacco Research* [Online]. Available: http://www.ncbi.nlm.nih.gov/pubmed/24113929 [Accessed 10 Oct 2013].

TIDEY, J. W., ROHSENOW, D. J., KAPLAN, G. B., SWIFT, R. M. & ADOLFO, A. B. 2008. Effects of smoking abstinence, smoking cues and nicotine replacement in smokers with schizophrenia and controls. *Nicotine & Tobacco Research* 10, 1047-56.

TIDEY, J. W., ROHSENOW, D. J., KAPLAN, G. B., SWIFT, R. M. & AHNALLEN, C. G. 2012. Separate and Combined Effects of Very Low Nicotine Cigarettes and Nicotine Replacement in Smokers with Schizophrenia and Controls. *Nicotine & Tobacco Research,* 15, 121-129.

TIFFANY, S. T. & DROBES, D. J. 1991. The development and initial validation of a questionnaire on smoking urges. *British Journal of Addiction,* 86, 1467-76.

TIFFANY, S. T. & WRAY, J. M. 2012. The clinical significance of drug craving. *Annals of the New York Academy of Sciences,* 1248, 1-17.

VANSICKEL, A. R., COBB, C. O., WEAVER, M. F. & EISSENBERG, T. E. 2010. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiology Biomarkers and Prevention,* 19, 1945-53.

VANSICKEL, A. R. & EISSENBERG, T. 2012. Electronic Cigarettes: Effective Nicotine Delivery After Acute Administration. *Nicotine & Tobacco Research,* 15, 267-270.

VANSICKEL, A. R., WEAVER, M. F. & EISSENBERG, T. 2012. Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction,* 107, 1493-1500.

VICKERMAN, K. A., CARPENTER, K. M., ALTMAN, T., NASH, C. M. & ZBIKOWSKI, S. M. 2013. Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine & Tobacco Research* 15, 1787-1791.

WALKER, BULLEN & MCROBBIE 2009. Reduced – nicotine content cigarettes: Is there potential to aid smoking cessation? *Nicotine & Tobacco Research,* 11, 1274-1279.

WALKER, N., HOWE, C., BULLEN, C., GRIGG, M., GLOVER, M., MCROBBIE, H., LAUGESEN, M., PARAG, V. & WHITTAKER, R. 2012. The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation: a randomized controlled trial. *Addiction,* 107, 1857-1867.

WEINBERGER, A. H., MCKEE, S. A. & GEORGE, T. P. 2012. Smoking cue reactivity in adult smokers with and without depression: a pilot study. *The American journal on addictions / American Academy of Psychiatrists in Alcoholism and Addictions,* 21, 136-44.

WERTZ, J. M. & SAYETTE, M. A. 2001. A review of the effects of perceived drug use opportunity of self-reported urge. *Experimental and clinical psychopharmacology,* 9, 3-13.

WEST, R. & HAJEK, P. 2004. Evaluation of the mood and physical symptoms scale (MPSS) to assess cigarette withdrawal. *Psychopharmacology (Berl),* 177, 195-9.

WEST, R., HAJEK, P., STEAD, L. & STAPLETON, J. 2005. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction,* 100, 299-303.

WEST, R. & HARDY, A. 2006. *Theory of addiction,* Oxford, Blackwell.

WEST, R. & USSHER, M. 2010. Is the ten-item Questionnaire of Smoking Urges (QSU-brief) more sensitive to abstinence than shorter craving measures? *Psychopharmacology (Berl),* 208, 427-32.

WESTMAN, E. C., BEHM, F. M. & ROSE, J. E. 1995. Airway sensory replacement combined with nicotine replacement for smoking cessation. A randomized placebo-controlled trial using a citric acid inhaler. *Chest,* 107, 1358-1364.

WESTMAN, E. C., BEHM, F. M. & ROSE, J. E. 1996a. Airway sensory replacement as a treatment for smoking cessation. *Drug Development Research,* 38, 257-262.

WESTMAN, E. C., BEHM, F. M. & ROSE, J. E. 1996b. Dissociating the nicotine and airway sensory effects of smoking. *Pharmacology Biochemistry and Behavior,* 53, 309-315.

WRAY, J. M., GASS, J. C. & TIFFANY, S. T. 2013. A Systematic Review of the Relationships Between Craving and Smoking Cessation. *Nicotine & Tobacco Research* 15, 1167-1182.

WRAY, J. M., GODLESKI, S. A. & TIFFANY, S. T. 2011. Cue-reactivity in the natural environment of cigarette smokers: the impact of photographic and in vivo smoking stimuli. *Psychology of Addictive Behaviors* 25, 733-7.

XIE, J., SONG, W., MAKSYMOWICZ, W., JIN, W., CHEAH, K., CHEN, W., CARNES, C., KE, J. & CONKLING, M. A. 2004. Biotechnology: A Tool for Reduced Risk Tobacco Products – The Nicotine Experience From Test Tube to Cigarette Pack. *Recent Advances in Tobacco Science,* 30, 17-37.

ZHU, S.-H., GAMST, A., LEE, M., CUMMINS, S., YIN, L. & ZOREF, L. 2013. The use and perception of electronic cigarettes and snus among the US population. *PLoS One,* 8, e79332.

9 Appendix

1 Study Advertisements

Studies 1 and 2:

Smokers Wanted

Barts and The London School of Medicine is testing new products to help smokers quit.

If you would like to take part call:

0207 882 5949

At the end of the study, help will be available to assist you to stop smoking if you wish to do so.

Study 3:

Smokers Wanted

Barts and The London School of Medicine is testing a new approach to help smokers quit.

If you would like to take part call:

0207 882 8230

2 Clinical records form (Studies 1 and 2)[2]

Barts and The London
School of Medicine and Dentistry

CLINICAL RECORD FORM

Sensorimotor Replacement of Cigarettes
(SeROC Study)

Participant no: | | |

Participant initials: | | |

STUDY STAFF USE ONLY

1. Date | | | | | | | | |

2. Participant number | | | |

3. Check inclusion criteria Excluded if answer YES to any of the below questions	YES	NO
Under 18	☐	☐
Pregnant/breastfeeding	☐	☐
Acute psychiatric illness	☐	☐
Enrolment in other research	☐	☐
Smoke after 1 hour of waking	☐	☐
Smoke less than 10cpd	☐	☐
Current use of E-cigs	☐	☐
Current use of De-nics*	☐	☐
Current use of NRT	☐	☐
Eligible for study	☐	☐
4. Consent form completed	☐	☐

5. Clinicians initials | | | |

[2] Note: forms were identical for both studies except where shown: * indicates this item was removed in Study 1; **indicates item was amended for 'stress ball' condition in Study 1.

TEST SESSION 1: MORNING

STUDY STAFF USE ONLY

1. Date

2. CO reading

3. Overnight abstinence verified YES ☐ NO☐

If no, alternative date arranged: _____

4. Allocated product Denic** ☐

E-cig ☐

TEST SESSION 1: MORNING

Please respond to the following questions by ticking the appropriate box (tick **ONLY ONE** box on each line).

Right now, how strong is your urge to smoke?

	Not at all										Extremely
	0	1	2	3	4	5	6	7	8	9	10
Baseline	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Post cue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
30 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
60 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Right now, how irritable do you feel?

	Not at all										Extremely
	0	1	2	3	4	5	6	7	8	9	10
Baseline	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Post cue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
30 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
60 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Right now, how restless do you feel?

	Not at all										Extremely
Baseline	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Post cue	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
5 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
10 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
30 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
60 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Right now, how difficult are you finding it to concentrate?

	Not at all										Extremely
Baseline	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Post cue	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
5 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
10 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
30 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
60 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

TEST SESSION 1: RECORDING FORM

We would like you to record how often you are using your product throughout the day.

Please write the number of times you use your product within each hour after leaving the study centre. <u>One use</u> means taking <u>5 or more puffs</u> from either the de-nicotinised cigarette or E-cigarette.**

Please remember to <u>stop using your product one hour before returning</u> to the study centre this evening.

TIME	Number of times used (e.g. 0x, 1x, 3x, etc.)
9am-10am	
10am-11am	
12pm-1pm	
1pm-2pm	
2pm-3pm	
3pm- 4pm	
4pm-5pm	

TEST SESSION 1: EVENING

1. **Please show for each of the items how you have been feeling <u>today</u>** (tick the **ONE** box which best applies to you on each line)

	Not at all	Slightly	Somewhat	Very	Extremely
Depressed	☐	☐	☐	☐	☐
Irritable	☐	☐	☐	☐	☐
Restless	☐	☐	☐	☐	☐
Hungry	☐	☐	☐	☐	☐
Poor concentration	☐	☐	☐	☐	☐

2. **How much of the time have you felt the urge to smoke today** (tick one box)
   - ☐ Not at all
   - ☐ A little of the time
   - ☐ Some of the time
   - ☐ A lot of the time
   - ☐ Almost all of the time
   - ☐ All of the time

3. **How strong have these urges been?** (tick one box)
   - ☐ No urges
   - ☐ Slight
   - ☐ Moderate
   - ☐ Strong
   - ☐ Very strong
   - ☐ Extremely strong

4. **Write your carbon monoxide breath test reading in the box** ☐

5. **Have you smoked any of your <u>usual cigarettes</u> today?** (tick ONE box)

No	A few puffs	1-5 cigarettes	More than 5 cigarettes
☐	☐	☐	☐

TEST SESSION 1: EVENING

Please answer the following questions, thinking about the product that you have used today (tick **ONLY ONE** box on each line)

1. **<u>Compared to your usual cigarette</u> how satisfying was the product?**

Much less than usual	A little less than usual	The same as usual	A little more than usual	Much more than usual
☐	☐	☐	☐	☐

2. **How helpful did you find the product in enabling you to keep from smoking?**

Not at all helpful	Slightly helpful	Somewhat helpful	Very Helpful	Extremely helpful
☐	☐	☐	☐	☐

3. **How pleasant was the product to use?**

Not at all pleasant	Slightly pleasant	Somewhat pleasant	Very Pleasant	Extremely pleasant
☐	☐	☐	☐	☐

4. **How embarrassing was the product to use in the company of others?**

Not at all embarrassing	Slightly embarrassing	Somewhat embarrassing	Very embarrassing	Extremely embarrassing
☐	☐	☐	☐	☐

5. **Would you use this product to help you to stop smoking?**

Definitely not	Probably not	Maybe	Probably	Definitely
☐	☐	☐	☐	☐

6. **Would you recommend this product to a friend who wanted to stop smoking?**

Definitely not	Probably not	Maybe	Probably	Definitely
☐	☐	☐	☐	☐

7. **What did you <u>like most</u> about the product you used today?**

---

8. What did you <u>like least</u> about the product you used today?

---

9. Please describe any unpleasant effects that you may have experienced when using the product, and rate how strong this effect was.

Unpleasant effect	Strength *(tick one box)*		
1.	Weak ☐	Moderate ☐	Strong ☐
2.	Weak ☐	Moderate ☐	Strong ☐
3.	Weak ☐	Moderate ☐	Strong ☐
4.	Weak ☐	Moderate ☐	Strong ☐
5.	Weak ☐	Moderate ☐	Strong ☐
6.	Weak ☐	Moderate ☐	Strong ☐

TEST SESSION 1: EVENING

Please respond to the following questions by ticking the appropriate box (tick **ONLY ONE** box on each line).

<u>Right now</u>, how strong is your urge to smoke?

	Not at all										Extremely
Baseline	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Post cue	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
5 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
10 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
30 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
60 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

<u>Right now</u>, how irritable do you feel?

	Not at all										Extremely
Baseline	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Post cue	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
5 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
10 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
30 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
60 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Right now, how restless do you feel?

	Not at all										Extremely
Baseline	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Post cue	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
5 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
10 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
30 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
60 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Right now, how difficult are you finding it to concentrate?

	Not at all										Extremely
Baseline	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Post cue	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
5 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
10 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
30 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
60 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

TEST SESSION 2: MORNING

STUDY STAFF USE ONLY

1. Date ☐

2. CO reading ☐

3. Overnight abstinence verified YES ☐ NO ☐

   If no, alternative date arranged: _____

4. Allocated product Denic** ☐

   E-cig ☐

TEST SESSION 2: MORNING

Please respond to the following questions by ticking the appropriate box (tick **ONLY ONE** box on each line).

Right now, how strong is your urge to smoke?

	Not at all										Extremely
	0	1	2	3	4	5	6	7	8	9	10
Baseline	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Post cue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
30 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
60 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Right now, how irritable do you feel?

	Not at all										Extremely
	0	1	2	3	4	5	6	7	8	9	10
Baseline	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Post cue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
30 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
60 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Right now, how restless do you feel?

	Not at all										Extremely
	0	1	2	3	4	5	6	7	8	9	10
Baseline	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Post cue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
30 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
60 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Right now, how difficult are you finding it to concentrate?

	Not at all										Extremely
	0	1	2	3	4	5	6	7	8	9	10
Baseline	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Post cue	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
5 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
10 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
30 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
60 mins	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

TEST SESSION 2: RECORDING FORM

We would like you to record how often you are using your product throughout the day.

Please write the number of times you use your product within each hour after leaving the study centre. <u>One use</u> means taking <u>5 or more puffs</u> from either the de-nicotinised cigarette or E-cigarette.**

Please remember to <u>stop using your product one hour before returning</u> to the study centre this evening.

TIME	Number of times used (e.g. 0x, 1x, 3x, etc.)
9am-10am	
10am-11am	
12pm-1pm	
1pm-2pm	
2pm-3pm	
3pm- 4pm	
4pm-5pm	

TEST SESSION 2: EVENING

1. **Please show for each of the items how you have been feeling <u>today</u>** (tick the **ONE** box which best applies to you on each line)

	Not at all	Slightly	Somewhat	Very	Extremely
Depressed	☐	☐	☐	☐	☐
Irritable	☐	☐	☐	☐	☐
Restless	☐	☐	☐	☐	☐
Hungry	☐	☐	☐	☐	☐
Poor concentration	☐	☐	☐	☐	☐

2. **How much of the time have you felt the urge to smoke today** (tick one box)
   - ☐ Not at all
   - ☐ A little of the time
   - ☐ Some of the time
   - ☐ A lot of the time
   - ☐ Almost all of the time
   - ☐ All of the time

3. **How strong have these urges been?** (tick one box)
   - ☐ No urges
   - ☐ Slight
   - ☐ Moderate
   - ☐ Strong
   - ☐ Very strong
   - ☐ Extremely strong

4. **Write your carbon monoxide breath test reading in the box** ☐

5. **Have you smoked any of your <u>usual cigarettes</u> today?** (tick ONE box)

No	A few puffs	1-5 cigarettes	More than 5 cigarettes
☐	☐	☐	☐

TEST SESSION 2: EVENING

Please answer the following questions, thinking about the product that you have used today (tick **ONLY ONE** box on each line)

1. Compared to your usual cigarette how satisfying was the product?

Much less than usual	A little less than usual	The same as usual	A little more than usual	Much more than usual
☐	☐	☐	☐	☐

2. How helpful did you find the product in enabling you to keep from smoking?

Not at all helpful	Slightly helpful	Somewhat helpful	Very Helpful	Extremely helpful
☐	☐	☐	☐	☐

3. How pleasant was the product to use?

Not at all pleasant	Slightly pleasant	Somewhat pleasant	Very Pleasant	Extremely pleasant
☐	☐	☐	☐	☐

4. How embarrassing was the product to use in the company of others?

Not at all embarrassing	Slightly embarrassing	Somewhat embarrassing	Very embarrassing	Extremely embarrassing
☐	☐	☐	☐	☐

5. Would you use this product to help you to stop smoking?

Definitely not	Probably not	Maybe	Probably	Definitely
☐	☐	☐	☐	☐

6. Would you recommend this product to a friend who wanted to stop smoking?

Definitely not	Probably not	Maybe	Probably	Definitely
☐	☐	☐	☐	☐

7. What did you like most about the product you used today?

---

8. What did you like least about the product you used today?

---

9. Please describe any unpleasant effects that you may have experienced when using the product, and rate how strong this effect was.

Unpleasant effect	Strength *(tick one box)*		
1.	Weak ☐	Moderate ☐	Strong ☐
2.	Weak ☐	Moderate ☐	Strong ☐
3.	Weak ☐	Moderate ☐	Strong ☐
4.	Weak ☐	Moderate ☐	Strong ☐
5.	Weak ☐	Moderate ☐	Strong ☐
6.	Weak ☐	Moderate ☐	Strong ☐

TEST SESSION 2: EVENING

Please answer the following questions by ticking one box.

1.	**Which product did you like the most?**	E-cigarette ☐	De-nicotinised cigarette** ☐
2.	**Which product was easier to use?**	E-cigarette ☐	De-nicotinised cigarette ☐
3.	**Which product was more embarrassing to use?**	E-cigarette ☐	De-nicotinised cigarette ☐
4.	**Which product was most helpful in enabling you to keep from smoking?**	E-cigarette ☐	De-nicotinised cigarette ☐
5.	**Which product would you be more likely to use to help you stop smoking?**	E-cigarette ☐	De-nicotinised cigarette ☐
6.	**Which product would you be more likely to recommend to a friend who wanted to stop smoking?**	E-cigarette ☐	De-nicotinised cigarette ☐

TEST SESSION 2: EVENING

Please respond to the following questions by ticking the appropriate box (tick **ONLY ONE** box on each line).

Right now, how strong is your urge to smoke?

	Not at all										Extremely
Baseline	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Post cue	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
5 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
10 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
30 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
60 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Right now, how irritable do you feel?

	Not at all										Extremely
Baseline	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Post cue	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
5 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
10 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
30 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
60 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Right now, how restless do you feel?

	Not at all										Extremely
Baseline	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Post cue	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
5 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
10 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
30 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
60 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

Right now, how difficult are you finding it to concentrate?

	Not at all										Extremely
Baseline	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
Post cue	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
5 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
10 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
30 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐
60 mins	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐

3 Baseline Questionnaire (used in all studies)[3]

CLIENT TREAT NO: 201 _ : _ _ _ _

Smokers Clinic Questionnaire

Please complete this form and bring it to your first appointment. If you have any problems with the questions, please don't worry or be put off coming. We will help you if necessary. The information collected is strictly confidential, for use by Trust staff. Some items, e.g. age, sex, ethnicity, are required by the Department of Health to monitor the service we provide. Other items, including those obtained from all sessions and follow-ups, will be used by the clinic to guide your treatment, and may be used in research on smoking. No names or information that might identify you will be used in any reports, only figures from many smokers together. The information will be stored in accordance with the Data Protection Act and you have the right to review it, or withdraw your permission for us to use it. Your participation in this work is voluntary and your treatment at the clinic will not be affected if you refuse. Please discuss any concerns you may have regarding this information with the clinic staff. Signing below indicates that you have read this notice and agree to your information being used in this way.

Signature _____ **Date** _____

Please write where you see the lines. Circle the word which applies to you

Your name: _____ **Are you?** 1 **Male** 2 **Female** (*circle ONE only*)

Your date of Birth: _____ **Your age?** _____ **years**

Your address: _____

_____ **Post Code:** _____

Home tel no: _____ **Work tel no:** _____

Mobile tel no: _____ **Email:** _____

Person to contact if we cannot reach you: _____ **Tel No:** _____

Name/Address of your GP: _____

_____ **Post Code:** _____ **Tel No:** _____

1. **Are you?** 1 **Married** 2 **Divorced** 3 **Separated** 4 **Widowed** 5 **Single (never married)** (*circle ONE*)

2. **Do you live?** 1 **With your spouse/partner** 2 **Family/friends** 3 **On your own** 4 **Hostel/residential home** (*circle ONE*)

3. **Are you? (** *circle ONE* **)**

1 **Working in a routine or manual occupation**
2 **Working in an intermediate occupation**
3 **Working in a managerial or professional occupation**
4 **Unemployed / not working for a year or more**
5 **Full time student**
6 **Retired**
7 **Sick / Disabled / Unable to return to work**
8 **Home carer (unpaid)**
9 **None of these**

4. **What is your most recent or current occupation?** _____

5. **Which qualifications do you have?** 1 **None** 2 **GCSE/CSE** 3 **A-Level** 4 **Diploma/HND** 5 **Degree** 6 **Other**_____

6. **Are you entitled to free prescriptions?** 1 **Yes** 2 **No** (*circle one*)

7. **Which of these best describes your ethnic origin?** (*circle ONE category below*)

1 **WHITE - British**	2 **WHITE - Irish**	3 **WHITE - other background**
4 **MIXED - White and Black Caribbean**	5 **MIXED - White and Black African**	6 **MIXED - White and Black Asian**
7 **MIXED - other background**	8 **ASIAN / Asian British - Indian**	9 **ASIAN / Asian British - Pakistani**
10 **ASIAN / Asian British - Bangladeshi**	11 **ASIAN or Asian British - other**	12 **BLACK or Black British - Caribbean**
13 **BLACK or Black British - Africa**	14 **BLACK or Black British - other**	15 **CHINESE**
16 **TURKISH or KURDISH**	17 **Another ethnic group:** _____	18 **Don't wish to answer**

[3] Note: **FTND**= Qs.8 and10-14; **GN-SBQ**= Qs. 18-28; **SM-MFS**= Qs. 29-33.

Questions about your smoking

8. **How many cigarettes do you usually smoke each day?** _____ (*write a SINGLE average number*)

9. **How many of these are hand-rolled cigarettes?** _____ (*write a single average number*)

10. **How soon after waking up do you usually smoke?** (*circle one*)

1 **Within 5 mins** 2 **6 to 15 mins** 3 **16 to 30 mins** 4 **31 to 60 mins** 5 **After 1 hour**

11. **Do you find it difficult not to smoke in places where smoking is not allowed?** 1 **Yes** 2 **No** (*circle one*)

12. **Do you smoke more in the first hours after waking up than during the rest of the day?** 1 **Yes** 2 **No** (*circle one*)

13. **Which cigarette would you hate most to give up?** 1 **The first of the morning** 2 **Another one** (*circle one*)

14. **Do you smoke if you are so ill that you are in bed most of the day?** 1 **Yes** 2 **No** (*circle one*)

15. **How often do you wake up at night and smoke?** (*circle one*)

1 **Never** 2 **Less than once a month** 3 **1 or 2 times a month** 4 **1 or 2 times a week** 5 **Most nights**

16. **How old were you when you first started smoking regularly?** _____ **years old**

17. **Do you smoke mainly to cope or because you enjoy it?** (*circle one*)

1 **Mainly to cope** 2 **Mainly because I enjoy it** 3 **About the same**

How much do you value the following

18. **My cigarette habit is very important to me**

1 **Not at all** 2 **Somewhat** 3 **Moderately so** 4 **Very much so** 5 **Extremely so** (*circle one*)

19. **I handle and manipulate my cigarette as part of the ritual of smoking**

1 **Not at all** 2 **Somewhat** 3 **Moderately so** 4 **Very much so** 5 **Extremely so** (*circle one*)

20. **Do you place something in your mouth to distract you from smoking?**

1 **Never** 2 **Seldom** 3 **Sometimes** 4 **Often** 5 **Always** (*circle one*)

21. **Do you reward yourself with a cigarette after accomplishing a task?**

1 **Never** 2 **Seldom** 3 **Sometimes** 4 **Often** 5 **Always** (*circle one*)

22. **If you find yourself without cigarettes, will you have difficulties in concentrating before attempting a task?**

1 **Never** 2 **Seldom** 3 **Sometimes** 4 **Often** 5 **Always** (*circle one*)

23. **If you are not allowed to smoke in certain places do you then play with your cigarette pack or a cigarette?**

1 **Never** 2 **Seldom** 3 **Sometimes** 4 **Often** 5 **Always** (*circle one*)

24. **Do certain environmental cues trigger your smoking, e.g. favourite chair, sofa, room, car, drinking alcohol?**

1 **Never** 2 **Seldom** 3 **Sometimes** 4 **Often** 5 **Always** (*circle one*)

25. **Do you find yourself lighting up a cigarette routinely (without craving)?**

1 **Never** 2 **Seldom** 3 **Sometimes** 4 **Often** 5 **Always** (*circle one*)

26. **Do you find yourself placing an unlit cigarette or other objects (pen, toothpick, chewing gum, etc.) in your mouth and sucking to get relief from stress, tension or frustration, etc.)?**

1 **Never** 2 **Seldom** 3 **Sometimes** 4 **Often** 5 **Always** (*circle one*)

27. **Does part of your enjoyment of smoking come from the steps (ritual) you take when lighting up?**

1 **Never** 2 **Seldom** 3 **Sometimes** 4 **Often** 5 **Always** (*circle one*)

28. **When you are alone in a restaurant, bus terminal, party etc, do you feel safe, secure, or more confident if you are holding a cigarette?**

1 **Never** 2 **Seldom** 3 **Sometimes** 4 **Often** 5 **Always** (*circle one*)

Please indicate how much each statement applies to you

29. **Handling a cigarette is part of the enjoyment of smoking it**

1 **Uncertain or Not at all** 2 **A little** 3 **Quite a bit** 4 **Very much so** (*circle one*)

30. **I smoke for the pleasure of having something to put in my mouth**

1 **Uncertain or Not at all** 2 **A little** 3 **Quite a bit** 4 **Very much so** (*circle one*)

31. **Part of the enjoyment of smoking is watching the smoke as I blow it out**

1 **Uncertain or Not at all** 2 **A little** 3 **Quite a bit** 4 **Very much so** (*circle one*)

32. **Part of the enjoyment of smoking comes from the steps I take to light up**

1 **Uncertain or Not at all** 2 **A little** 3 **Quite a bit** 4 **Very much so** (*circle one*)

33. **I smoke because I like the smell so much**

1 **Uncertain or Not at all** 2 **A little** 3 **Quite a bit** 4 **Very much so** (*circle one*)

34. **Does your spouse or partner smoke?** 1 **Yes** 2 **No** 3 **No spouse/partner** (*circle one*)

35. **How many times have you tried to stop smoking in the last 5 years?** **** (*circle one*)

1 **Not at all** 2 **Once** 3 **2 or 3 times** 4 **4 or 5 times** 5 **More than 5 times**

36. **What is the longest time you've succeeded in giving up smoking in the last 5 years?** **** (*circle one*)

1 **Few hours** 2 **1 day** 3 **2 -3 days** 4 **4 -7 days** 5 **1-3 weeks** 6 **1-3 months** 7 **More than 3 months** 8 **Not tried**

37. **How long ago was your last serious attempt to stop?** (*circle one*)

1 **1 - 3 weeks** 2 **1 - 6 months** 3 **More than 6 months** 4 **More than a year** 5 **Never tried before**

38. **What was the ONE MAIN THING that led you back to smoking last time?** (*circle JUST ONE reason below*)

1 **Never stopped before** 2 **Got too miserable** 3 **Craved too much** 4 **Put on too much weight** 5 **Got too bad-tempered**
6 **Got too stressed** 7 **Thought I could smoke and stop easily** 8 **Cannabis smoking** 9 **Getting drunk** 10 **Something else**

39. **If you have tried to stop smoking before, which of these was more difficult to cope with?** (*circle one*)

1 **That something was constantly missing and that I could not function normally without smoking**
2 **That I could not smoke at those special moments when smoking was really enjoyable and made me feel good**
3 **Both were equally difficult**

40. **If you try stopping smoking now with clinic help, how confident are you of succeeding?** (*circle one number below*)

Not at all confident **1** **2** **3** **4** **5** **6** **7** **8** **9** **10** **Totally confident**

41. **How determined are you to stop for good in the next few weeks?** (*circle one*)

1 **Not sure** 2 **Fairly determined** 3 **Very determined** 4 **Totally determined**

42. **How recently has your GP advised you to stop?** 1 **In the last year** 2 **More than a year ago** 3 **Never** (*circle one*)

43. **What is your ONE MAIN REASON for wanting to stop now?** (*circle JUST the most important ONE*)

1 **To save money** 2 **To stop being addicted** 3 **To protect my health** 4 **To please others** 5 **It's anti-social** 6 **Another reason**

44. **Which of these medicines have you tried before to help you stop?** (*circle ALL THE ONES you have ever tried*)

(a) **None** 1 (b) **Nicotine Gum** 1 (c) **Nicotine Inhalator** 1 (d) **Nicotine Patch** 1 (e) **Nicotine Microtab** 1

(f) **Zyban** 1 (g) **Nicotine Lozenge** 1 (h) **Nicotine Nasal Spray** 1 (i) **Champix (Varenicline)** (j) **Nicotine Minis**

45. **Have you ever suffered any unpleasant reactions to any of the above medications?** (a) 1 **Yes** 2 **No**

If yes,

(b) **Which medication?** _____

(c) **What reaction?** _____

46 a. **If you have taken Champix before, please answer the following questions:**

(a) How many weeks ago did you start the previous course of Champix? ____

(b) For how many days did you take Champix? ____

(c) For how long did you manage to stop smoking?

Less than 24 hours$_1$ **More than 24 hours$_2$** (state how long) _____

46 b. **If you have used Nicotine Replacement Therapy (NRT) before, please answer the following questions**

(a) How many weeks ago did you start the previous course of NRT? ____

(b) For how many days did you take NRT? ____

(c) What type/s of NRT did you use? (List all products that you used) _____

(d) For how long did you manage to stop smoking?

Less than 24 hours$_1$ **More than 24 hours$_2$** (state how long) _____

47. **Which of these methods have you tried before to help you stop?** (*circle all the ones you have tried*)

(a) **None** 1 (b) **Hypnosis** 1 (c) **Help-lines** 1 (d) **Books/videos** 1 (e) **Counselling** 1 (f) **Herbal cigarettes** 1

(g) **Acupuncture** 1 (h) **Alan Carr** 1 (i) **NicoBloc** 1 (j) **Nicobrevin** 1 (k) **Stoppers** 1 (x) **Other** 1 _____

48. **How did you hear about this smokers' clinic?** (*circle one*)

1 **Told about it by a GP** 2 **Hospital doctor** 3 **Nurse** 4 **Friend or family member** 5 **Telephone Help-line** 6 **Advert** 7 **Newspaper/magazine** 8 **A leaflet or poster (** 8a **where?** _____ **)** 9 **Street recruitment** 10 **Another way**

49. **Have you been to this Smokers' Clinic before?** (a) 1 **Yes** 2 **No** (b) **If Yes, which year was it?** _____

Questions about your health

What is your weight _____ **What is your height** _____

50. **How many times have you been to your GP about your health in the last year?**

1 **Not at all** 2 **1 or 2 times** 3 **3 or 4 times** 4 **5 to 10 times** 5 **More than 10 times** (*circle one*)

51. **Do you regularly use cannabis?** 1 **No** 2 **Yes, with tobacco** 3 **Yes, but not with tobacco** (*circle one*)

52. **How many units of alcohol do you drink during a typical WEEK?** _____ **units** *
(one unit = glass of wine / half pint of beer / single spirit)

53. **If you are female, are you?** 1 **Pregnant** 2 **Trying to conceive** 3 **Breast Feeding** 4 **None of these** *

If you join the clinic programme, you may be prescribed a medicine to help. Some medicines can be harmful for some people, so we ask everyone to complete the medical checklist below. If you don't understand some of the questions, a therapist at the clinic will help you.

Have you EVER suffered from these illnesses?	(*circle one*)		&	**Do you take any medicines for these illnesses?** (*circle one*)		**Name of any medicine you are taking**
54. **Heart disease or condition?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	
55. **Cancer?**	1 **YES**	2 **NO**	A B	1 **YES**	2 **NO**	

56. **Bronchitis?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO**
57. **High blood pressure?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO**
58. **Emphysema or lung disease**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO**
59. **Asthma?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO**
60. **Alcohol problems?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO**
61. **Drug problems?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO**
62. **Depression?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO**
63. **Any form of psychosis?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO**
64. **Skin allergies or eczema?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO**
65. **Nasal problems or nose bleeds?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO**
66. **Bi-polar (high-low) depression?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO** *
67. **A stroke?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO** *
68. **An eating disorder?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO** *
69. **Liver or kidney disease?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO** *
70. **A brain tumour?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO** *
71. **A head injury?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO** *
72. **Fits or seizures or epilepsy?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO** *
73. **Diabetes?**	1 **YES**	2 **NO**	A	B	1 **YES**	2 **NO** *

Other CURRENT illness not listed above :	**Name of other medicines / tablets / injections not listed above:**
74.	
75.	
76.	

Please check that you have included ALL the medicines you are currently taking somewhere above

77. **To my knowledge the information I have given above is correct. Signed:**_____

Thank you very much. Please remember to bring this form with you to the clinic

Official Use Only 78. ELIG FOR NRT? 1 Y 2 N 3 NK 79. ELIG FOR CHAMPIX 1 Y 2 N 80. ELIG FOR ZYB? 1 Y 2 N 3 NK
81. REC SUPP TX? 1 G 2 I 82. ELIG FOR FREE PRESC? 1 Y 2 N 83. THERAPIST INIT __ __ 84. DATE __ __ : __ __ : 2 0 1 __
85.THERAPIST NOTES:-

4 Study 1 Participant Information Sheet

Barts and The London
School of Medicine and Dentistry

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

Sensorimotor Replacement of Cigarettes

(SeROC STUDY)

Barts and The London

Queen Mary's School of Medicine and Dentistry

We would like to invite you to take part in a research study. The information which follows tells you about it. It is important that you understand what is in this leaflet. It says what will happen if you take part and what the study entails. Try to make sure you know what will happen to you if you decide to take part. Whether or not you do take part is entirely your choice. Please ask any questions you want to about the research and we will try our best to answer them.

The Study

People wanting to quit smoking are normally treated with medications such as nicotine patches and gum or Champix, and support from NHS stop-smoking advisors. Although this approach is effective, it does not work with everyone. Many smokers miss the action and sensations of smoking (e.g. holding something in their hands or mouth, puffing, inhaling smoke). Scientists refer to these as the 'behavioural' and sensory aspects of smoking. We are investigating whether products that replace some of these aspects can help to ease urges to smoke and other withdrawal symptoms that most smokers experience when they stop smoking. In this study, we will be evaluating two such products: a **nicotine-free electronic cigarette** and a **stress ball**.

Why should stress balls and electronic cigarettes help?

Stress balls are made from soft material and are pleasant to handle. They may distract you and give you something to do with your hands, which may be useful during the first few days of stopping smoking.

Electronic cigarettes (ECs) are battery operated devices which mimic the act of smoking. ECs may be purchased with differing levels of nicotine, but in this study we will be using ECs containing no nicotine. ECs also provide distraction and some sensations and actions similar to normal cigarettes (e.g. they produce a mist when you puff on them) which may be useful during the early quit attempt.

What will happen if you take part?

If you would like to take part and are eligible, you will be invited to attend two study sessions. The table below provides further details of what will happen on each day. You will also be offered treatment at the Royal London Hospital Smokers' Clinic to help you stop smoking, once the study has been completed.

Information Session	At this first ***visit*** to the Smokers' Clinic we will describe the study and go through this information sheet. You will then have the opportunity to ask any questions. We will then ask you to sign a consent form to show that you have agreed to take part. We will show you the ECs and Stress balls so you know what they look like and how to use them.
Session 1	You will ***visit*** the smokers' clinic in the ***morning***, after having not smoked the night before. We will measure the amount of carbon-monoxide (CO) in your breath to check this. You will then be randomly allocated (by chance) to either use the stress ball or EC. Before using the product, you will complete a short questionnaire to tell us about your mood and urges to smoke. We will then measure how you react to smoking related cues. For this you will be asked to hold a lit cigarette for a short period of time, without smoking it. You will then be instructed to use the product for a short period of time, and over the following hour you will be asked to answer some questions about your urges to smoke and mood. We will give you your product to use during the day when you ***leave*** the clinic, but you will be expected ***not to smoke any normal cigarettes for the rest of the day***, ***or to use any nicotine replacement therapy***. You will also be asked to record how often you are using your product during the day. You will be asked to ***stop using the product 1 hour before you return to the clinic in the evening.*** When you return we will measure the amount of CO in your breath and you will complete a questionnaire about your mood. We will measure your reaction to smoking related cues, (like in the morning), and you will then be asked to use your product for a short period of time, and answer some questions about your urges to smoke and mood over the following hour. You will then complete a short questionnaire about the product you used during the day.
Session 2	One week after session 1, the procedure above will be repeated with the other product (stress ball or EC).

Who can take part?

You will be able to take part if you are

- **Aged 18 years or over**
- Smoke at least **10 cigarettes per day** and smoke your **first cigarette within the first hour of waking**

You will **not** be able to take part if you

- Are **pregnant or breast feeding**

- Have been diagnosed with an **acute psychiatric illness**
- Are currently **using Electronic Cigarettes or Nicotine Replacement Therapy (e.g. patches, gum etc.)**
- Are currently enrolled in **another research project**

Risks/Side effects

We do not expect there to be any risks from using ECs or stress balls. ECs do not contain tobacco, and therefore do not deliver the many harmful substances found in normal cigarettes. As a result they pose no increased risk compared to your normal cigarettes.

Data Protection

If you agree to take part you will be asked to fill out several questionnaires. Any information you give us will be kept confidential, and only study staff will have access to this data. The results of this study may be presented to other individuals working in the field of smoking cessation or may be printed in journals; however there will be no information included which could identify you.

Your Rights

Your participation in this study is entirely voluntary, and you are free to drop out of the study at any time. Your records will be kept strictly confidential and your ordinary medical care will not be put at risk if you decide not to take part or drop out.

What happens if you are concerned or have any questions?

You will be able to contact Dunja Przulj at the Smokers' Clinic if you are worried about anything or have any questions. The number is 020 7882 8230 or email smokers-clinic@qmul.ac.uk.

The principal investigator of this study is Dunja Przulj, Tobacco Dependence Research Unit, Wolfson Institute of Preventative Medicine, Barts and The London School of Medicine and Dentistry, 55 Philpot Street, London, E1 2JH, Tel: 020 7882 8230.

A summary of the results of this study will be available upon request from Dunja Przulj (see above for contact details).

We believe that this study is safe and do not expect you to suffer any harm or injury because of your participation in it. However, *Queen Mary and Westfield College, University of London* has agreed that if your health does suffer as a result of your being in the study then you will be compensated. In such a situation, you will not have to prove that the harm or injury which affects you is anyone's fault. If you are not happy with any proposed compensation, you may have to pursue your claim through legal action.

If you have a complaint please contact Christine Bevan-Davies, Quality Development, Barts and the London NHS Trust, Healthcare Governance Directorate, Tel: 020 7480 4857, Email: christine.bevan davies@bartsandthelondon.nhs.uk

We would like to thank you for your interest in this study, even if you decide not to take part.

5 Example Consent Form (Studies 1 and 2)

Barts and The London School of Medicine and Dentistry

Sensorimotor Replacement of Cigarettes (SeROC STUDY)

Informed Consent Form

Principal Investigator: Dunja Przulj

Participant Name:_____

Participant Number:

	Please initial each line
I confirm that I have read (or someone else has read to me) and I understand the Participant Information Sheet (*insert version and date*) for the above study.	
I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.	
I understand that my participation is voluntary (my choice) and that I may withdraw from the study at any time without giving reason, and that my medical care or legal rights will not be affected because of this.	
I understand that all information collected will be in accordance to the Data Protection Act of 1998.	
I agree to take part in the above study	

I understand that the research data collected during the study may be looked at by other individuals from the research team, sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.

_____	_____	_____
Participant Name (please print)	Signature of Participant	Date
_____	_____	_____
Name of person explaining consent	Signature of person explaining consent	Date

Please complete two forms (one for the participant and one for the study file)

6 Summry of sensitivity analysis on primary outcome (Study 1)

	Mean change score (SD)**		Test statistic	
N= 30*	EC	SB	Z	p
	1.20 (1.95)	0.7 (1.24)	-1.77	0.076

**N= 5 removed with morning CO levels >15ppm*

*** change in urge to smoke from post-cue to 10mins post-product use.*

7 Mean ratings and standard deviations for urge to smoke over 1 hour (Study1)

	Time point					
	Baseline	PC	5	10	30	60
	Mean (SD)					
Abstainers (N=17)						
Morning						
EC	5.94	6.53	4.71	4.71	5.41	6.35
	(2.73)	(2.83)	(3.10)	(2.97)	(2.77)	(2.60)
SB	6.88	7.29	6.18	6.47	6.35	7.18
	(2.62)	(2.60)	(2.37)	(2.68)	(2.29)	(2.60)
Evening						
EC	6.24	6.76	6.06	6.06	6.47	6.82
	(2.66)	(2.80)	(2.58)	(2.75)	(2.83)	(2.88)
SB	6.29	6.88	6.00	5.88	6.29	7.29
	(2.69)	(2.89)	(2.87)	(2.96)	(3.10)	(2.78)
Whole sample (N= 35)						
Morning						
EC	5.51	5.66	4.43	4.46	5.34	6.34
	(3.37)	(2.95)	(3.04)	(2.91)	(2.93)	(2.77)
SB	6.63	6.80	6.09	6.17	6.11	6.91
	(2.90)	(2.93)	(3.20)	(2.93)	(3.21)	(2.98)
Evening						
EC	5.69	5.71	4.89	5.00	5.57	6.26
	(3.12)	(3.30)	(3.21)	(3.24)	(3.31)	(3.03)
SB	6.37	6.63	6.11	5.94	6.09	6.83
	(2.95)	(3.25)	(3.11)	(3.20)	(3.23)	(3.20)

8 Mean ratings and standard deviations for irritability over 1 hour (Study 1)

	Time point					
	Baseline	PC	5	10	30	60
	Mean (SD)					
Abstainers (N=17)						
Morning						
EC	4.59	4.94	3.71	4.06	4.06	4.41
	(2.79)	(2.90)	(2.89)	(2.77)	(2.41)	(2.67)
SB	5.47	5.53	4.82	4.94	5.06	5.41
	(2.70)	(3.00)	(2.48)	(2.68)	(2.54)	(2.65)
Evening						
EC	5.00	5.53	4.71	4.59	4.65	4.88
	(2.65)	(2.65)	(2.60)	(2.65)	(2.71)	(2.67)
SB	5.00	5.24	4.71	4.76	5.00	5.00
	(2.94)	(3.07)	(2.85)	(3.11)	(3.14)	(3.16)
Whole sample (N= 35)						
Morning						
EC	4.14	4.31	3.43	3.51	4.03	4.40
	(3.46)	(3.26)	(2.97)	(2.90)	(2.78)	(2.66)
SB	5.26	5.11	4.74	4.74	5.06	5.51
	(3.13)	(3.42)	(2.99)	(3.07)	(3.03)	(3.08)
Evening						
EC	4.23	4.34	3.74	3.91	3.97	4.46
	(2.79)	(2.95)	(2.79)	(2.83)	(2.61)	(2.87)
SB	4.69	4.83	4.69	4.57	4.57	4.63
	(3.09)	(3.36)	(3.21)	(3.31)	(3.36)	(3.56)

9 Mean ratings and standard deviations for restlessness over 1 hour (Study 1)

	Time point					
	Baseline	PC	5	10	30	60
	Mean (SD)					
Abstainers (N=17)						
Morning						
EC	4.94	5.00	3.76	4.00	4.18	5.06
	(2.95)	(2.81)	(2.66)	(2.65)	(2.48)	(2.68)
SB	5.47	6.00	5.53	5.53	5.82	5.94
	(2.79)	(2.72)	(2.15)	(2.18)	(2.67)	(2.46)
Evening						
EC	4.88	5.06	4.76	4.71	4.76	5.12
	(2.60)	(2.90)	(2.70)	(2.71)	(2.66)	(2.47)
SB	5.06	5.24	4.88	4.88	5.12	5.47
	(2.70)	(2.99)	(3.08)	(3.06)	(2.93)	(3.30)
Whole sample (N= 35)						
Morning						
EC	4.26	4.57	3.49	3.57	4.29	5.11
	(3.00)	(2.98)	(2.67)	(2.59)	(2.79)	(2.56)
SB	5.06	5.2	4.91	5.14	5.69	6.06
	(2.91)	(3.06)	(2.89)	(2.63)	(2.77)	(2.85)
Evening						
EC	4.46	4.46	4.03	4.26	4.54	5.17
	(2.76)	(3.04)	(3.03)	(2.83)	(2.80)	(2.67)
SB	4.91	5.17	5.03	4.91	4.97	5.46
	(2.61)	(2.82)	(2.94)	(2.92)	(3.03)	(3.32)

10 Mean ratings and standard deviations of difficulty concentrating over 1 hour (Study 1)

	Time point					
	Baseline	PC	5	10	30	60
	Mean (SD)					
Abstainers (N=17)						
Morning						
EC	4.24	4.65	4.24	4.35	4.41	4.65
	(2.68)	(2.83)	(2.95)	(2.74)	(2.60)	(2.87)
SB	5.06	5.24	5.00	4.94	5.24	5.53
	(2.82)	(2.66)	(2.74)	(2.86)	(3.07)	(2.90)
Evening						
EC	4.94	4.94	5.00	4.65	4.82	4.94
	(2.73)	(2.73)	(2.81)	(2.78)	(2.83)	(2.82)
SB	5.24	5.41	5.18	4.88	4.94	5.24
	(2.88)	(2.94)	(2.90)	(2.98)	(2.86)	(3.05)
Whole sample (N= 35)						
Morning						
EC	3.63	3.94	3.40	3.54	3.91	4.23
	(2.95)	(2.97)	(3.03)	(2.82)	(3.00)	(3.04)
SB	4.40	4.54	4.34	4.37	4.69	4.66
	(2.86)	(3.00)	(2.91)	(2.94)	(3.02)	(2.86)
Evening						
EC	4.17	4.14	3.97	3.91	3.89	4.26
	(2.77)	(2.96)	(3.07)	(2.99)	(2.85)	(3.02)
SB	4.17	4.46	4.20	4.03	4.11	4.31
	(2.99)	(3.08)	(3.01)	(3.26)	(3.18)	(3.31)

11 Mean ratings and standard deviations of composite withdrawal over 1 hour (Study 1)

	Time point					
	Baseline	PC	5	10	30	60
	Mean (SD)					
Abstainers (N=17)						
Morning						
EC	4.59	4.86	3.90	4.14	4.22	4.71
	(2.60)	(2.65)	(2.63)	(2.54)	(2.36)	(2.57)
SB	5.33	5.59	5.12	5.14	5.37	5.63
	(2.51)	(2.53)	(2.12)	(2.31)	(2.62)	(2.50)
Evening						
EC	4.94	5.18	4.82	4.65	4.75	4.98
	(2.44)	(2.59)	(2.58)	(2.51)	(2.54)	(2.43)
SB	5.10	5.29	4.92	4.84	5.02	5.24
	(2.71)	(2.90)	(2.84)	(2.94)	(2.87)	(3.02)
Whole sample (N= 35)						
Morning						
EC	4.01	4.28	3.44	3.54	4.08	4.58
	(2.90)	(2.90)	(2.69)	(2.61)	(2.73)	(2.55)
SB	4.90	4.95	4.67	4.75	5.14	5.41
	(2.61)	(2.87)	(2.63)	(2.62)	(2.74)	(2.53)
Evening						
EC	4.29	4.31	3.91	4.03	4.13	4.63
	(2.58)	(2.83)	(2.87)	(2.73)	(2.56)	(2.64)
SB	4.59	4.82	4.64	4.50	4.55	4.80
	(2.69)	(2.87)	(2.80)	(2.94)	(2.97)	(3.13)

12 Summary statistics: Simple contrasts for urge to smoke over 1 hour during morning session (Study 1; whole sample)

Contrast (Product*Time)		F(1, 34)	p
EC vs. SB	PC* vs. 5mins	1.91	0.176
	PC vs. 10mins	3.28	0.079
	PC vs. 30mins	0.89	0.352
	PC vs. 60mins	1.58	0.218

*N= 35, *PC= post-cue*

13 Summary of mean scores and test statistics for individual MPSS items (Study 1)

MPSS Item:	Depression	Irritability	Restlessness	Difficulty concentrating	Hunger
Abstainers (N= 17)			**M (SD)**		
EC	2.12 (1.32)	2.53 (1.07)	2.53 (1.01)	2.59 (1.37)	2.82 (1.19)
SB	1.65 (0.79)	2.82 (1.33)	2.76 (1.25)	2.59 (1.18)	2.71 (0.99)
Test statistic	z= -1.64	z= -1.16	z= -0.79	z= -0.09	t= 0.49
(p)	(0.101)	(0.238)	(0.429)	(0.927)	(0.632)
Whole Sample (N= 37)*					
EC	2.00 (1.20)	2.49 (1.17)	2.51 (0.99)	2.32 (1.13)	2.54 (1.07)
SB	1.70 (0.88)	2.84 (1.39)	2.81 (1.18)	2.38 (1.09)	2.59 (1.14)
Test statistic	z= -1.81	z= -2.08	z= -1.73	z= -0.43	z= -0.40
Sig. (p)	(0.070)	(0.038)	(0.083)	(0.664)	(0.691)

**Two participants who did not attend the evening session gave responses via telephone*

14 Study 2 Participant Information Sheet

Barts and The London
School of Medicine and Dentistry

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

Sensorimotor Replacement of Cigarettes

(SeROC STUDY)

Barts and The London

Queen Mary's School of Medicine and Dentistry

We would like to invite you to take part in a research study. The information which follows tells you about it. It is important that you understand what is in this leaflet. It says what will happen if you take part and what the study entails. Try to make sure you know what will happen to you if you decide to take part. Whether or not you do take part is entirely your choice. Please ask any questions you want to about the research and we will try our best to answer them.

The Study

People wanting to quit smoking are normally treated with medications such as nicotine patches and gum or Champix, and support from NHS stop-smoking advisors. Although this approach is effective, it does not work with everyone. Many smokers miss the action and sensations of smoking (e.g. holding something in their hands or mouth, puffing, inhaling smoke). Scientists refer to these as the 'behavioural' and sensory aspects of smoking. We are investigating whether products that replace some of these aspects, can help to ease urges to smoke and other withdrawal symptoms that most smokers experience when they stop smoking. In this study, we will be evaluating two such products: a **nicotine-free electronic cigarette** and a **de-nicotinised cigarette**.

Why should electronic cigarettes and de-nicotinised cigarettes help?

Electronic cigarettes (ECs) are battery operated devices which mimic the act of smoking. ECs may be purchased with differing levels of nicotine, but in this study we will be using ECs containing no nicotine. ECs also provide distraction and some sensations and actions similar to normal cigarettes (e.g. they produce a mist when you puff on them) which may be useful during the first few days of stopping smoking.

De-nicotinised cigarettes (Denics) contain tobacco but do not contain nicotine. Like ECs, they provide distraction and are similar in taste and other sensations to normal cigarettes, which may be useful during the early quit attempt.

What will happen if you take part?

If you would like to take part and are eligible, you will be invited to attend two study sessions. The table below provides further details of what will happen on each day. You will also be offered treatment at the Royal London Hospital Smokers' Clinic to help you stop smoking, once the study has been completed.

Information Session	At this first ***visit*** to the Smokers' Clinic we will describe the study and go through this information sheet. You will then have the opportunity to ask any questions. We will then ask you to sign a consent form to show that you have agreed to take part. We will show you the ECs and Denics so you know what they look like and how to use them.
Session 1	You will ***visit*** the smokers' clinic in the ***morning***, after having not smoked the night before. We will measure the amount of carbon-monoxide (CO) in your breath to check this. You will be randomly allocated (by chance) to either use the Denic or EC. Before using the product, you will complete a short questionnaire to tell us about your mood and urges to smoke. We will then measure how you react to smoking related cues. For this you will be asked to hold a lit cigarette for a short period of time, without smoking it. You will then be instructed to use the product for a short period of time, and over the following hour you will be asked to answer some questions about your urges to smoke and mood. We will give you your product to use during the day when you ***leave*** the clinic, but you will be expected ***not to smoke any normal cigarettes for the rest of the day***, ***or to use any nicotine replacement therapy***. You will also be asked to record how often you are using your product during the day. You will be asked to ***stop using the product 1 hour before you return to the clinic in the evening.*** When you return we will measure the amount of CO in your breath and you will complete a questionnaire about your mood. We will measure your reaction to smoking related cues, (like in the morning), and you will then be asked to use your product for a short period of time, and answer some questions about your urges to smoke and mood over the following hour. You will then complete a short questionnaire about the product you used during the day.
Session 2	One week after session 1, the procedure above will be repeated with the other product (Denic or EC).

Who can take part?

You will be able to take part if you are

- **Aged 18 years or over**
- Smoke at least **10 cigarettes per day** and smoke your **first cigarette within the first hour of waking**

You will **not** be able to take part if you

- Are **pregnant or breast feeding**
- have been diagnosed with an **acute psychiatric illness**

- are currently **using Electronic or De-nicotinised Cigarettes or Nicotine Replacement Therapy (e.g. patches, gum etc.)**
- are currently enrolled in **another research project**

Risks/Side effects

We do not expect there to be any risks from using ECs or Denics for this short period of time. ECs do not contain tobacco, and therefore do not deliver the many harmful substances found in normal cigarettes. As a result they pose no increased risk compared to your normal cigarettes.

Denics still contain tobacco, and therefore do deliver similar substances to that of normal cigarettes; however these cigarettes pose no greater harm compared to the cigarettes you normally smoke.

Data Protection

If you agree to take part you will be asked to fill out several questionnaires. Any information you give us will be kept confidential, and only study staff will have access to this data. The results of this study may be presented to other individuals working in the field of smoking cessation or may be printed in journals; however there will be no information included which could identify you.

Your Rights

Your participation in this study is entirely voluntary, and you are free to drop out of the study at any time. Your records will be kept strictly confidential and your ordinary medical care will not be put at risk if you decide not to take part or drop out.

What happens if you are concerned or have any questions?

You will be able to contact Dunja Przulj at the Smokers' Clinic if you are worried about anything or have any questions. The number is 020 7882 8230 or email smokers-clinic@qmul.ac.uk.

The principal investigator of this study is Dunja Przulj, Tobacco Dependence Research Unit, Wolfson Institute of Preventative Medicine, Barts and The London School of Medicine and Dentistry, 55 Philpot Street, London, E1 2JH, Tel: 020 7882 8230.

A summary of the results of this study will be available upon request from Dunja Przulj (see above for contact details).

We believe that this study is safe and do not expect you to suffer any harm or injury because of your participation in it. However, *Queen Mary and Westfield College, University of London* has agreed that if your health does suffer as a result of your being in the study then you will be compensated. In such a situation, you will not have to prove that the harm or injury which affects you is anyone's fault. If you are not happy with any proposed compensation, you may have to pursue your claim through legal action.

For participants who wish to raise a complaint or would like to seek independent advice outside the study team, the number for the local patient advice and liaison service (PALS) will be provided (Telephone number: 0203 594 2040/2050 or email PALS@bartsandthelondon.nhs.uk)

We would like to thank you for your interest in this study, even if you decide not to take part.

15 Summary of sensitivity analysis on primary outcome (Study 2)

	Mean change score (SD)**		Test statistic	
N= 39*	EC	DNC	Z	p
	3.05 (2.86)	3.18 (2.74)	-0.67	0.506

**N= 2 removed with morning CO levels >15ppm*

*** change in urge to smoke from post-cue to 10mins post-product use.*

16 Mean ratings and standard deviations of urge to smoke over 1 hour (Study 2)

	Time point					
	Baseline	PC	5	10	30	60
	Mean (SD)					
Abstainers (N=28)						
Morning						
EC	6.89	7.54	4.82	4.29	5.32	5.96
	(2.81)	(2.77)	(3.07)	(3.20)	(3.38)	(3.46)
DNC	7.14	6.89	3.96	3.79	4.25	5.57
	(2.19)	(2.78)	(3.21)	(3.00)	(3.41)	(3.26)
Evening						
EC	6.57	6.29	4.54	4.39	4.86	5.93
	(2.67)	(3.00)	(2.89)	(2.86)	(2.97)	(3.20)
DNC	4.75	5.00	3.21	3.39	3.89	5.14
	(3.22)	(3.50)	(3.12)	(3.19)	(3.04)	(3.03)
Whole sample (N= 41)						
Morning						
EC	6.80	7.41	4.98	4.46	5.24	5.88
	(2.87)	(2.78)	(2.94)	(3.02)	(3.24)	(3.39)
DNC	6.85	7.05	4.24	3.95	4.37	5.66
	(2.52)	(2.76)	(3.18)	(3.02)	(3.18)	(3.29)
Evening						
EC	6.41	6.49	4.71	4.51	4.93	6.00
	(2.76)	(2.97)	(2.94)	(2.88)	(2.92)	(3.23)
DNC	4.98	5.07	3.73	3.68	4.02	5.15
	(3.33)	(3.42)	(3.42)	(3.26)	(3.24)	(3.26)

17 Mean ratings and standard deviations of irritability over 1 hour (Study 2)

	Time point					
	Baseline	PC	5	10	30	60
	Mean (SD)					
Abstainers (N=28)						
Morning						
EC	4.89	5.57	3.93	3.68	4.14	4.71
	(3.06)	(3.12)	(3.06)	(3.19)	(3.40)	(3.54)
DNC	5.07	4.96	3.64	3.00	3.46	4.04
	(2.45)	(2.84)	(2.86)	(2.61)	(3.12)	(3.33)
Evening						
EC	5.43	5.29	3.71	3.82	3.96	4.39
	(3.21)	(3.45)	(2.67)	(3.06)	(3.16)	(3.28)
DNC	3.43	3.54	2.79	2.61	3.04	3.50
	(3.36)	(3.36)	(2.73)	(2.63)	(2.89)	(2.98)
Whole sample (N= 41)						
Morning						
EC	4.61	5.32	3.80	3.59	3.95	4.44
	(3.08)	(3.16)	92.97)	(2.98)	(3.20)	(3.39)
DNC	4.88	4.83	3.63	3.10	3.37	4.02
	(2.70)	(2.85)	(2.95)	(2.72)	(2.89)	(3.28)
Evening						
EC	5.02	4.95	3.68	3.63	3.73	4.24
	(3.09)	(3.29)	(2.59)	(2.79)	(2.82)	(2.98)
DNC	3.34	3.46	2.88	2.78	3.00	3.61
	(3.24)	(3.16)	(2.71)	(2.67)	(2.85)	(3.06)

18 Mean ratings and standard deviations of restlessness over 1 hour (Study 2)

	Time point					
	Baseline	PC	5	10	30	60
	Mean (SD)					
Abstainers (N=28)						
Morning						
EC	5.07	5.64	3.54	3.18	4.07	4.64
	(2.96)	(2.95)	(2.85)	(3.04)	(3.24)	(3.02)
DNC	4.96	4.96	3.32	3.18	3.43	3.86
	(2.59)	(2.81)	(2.70)	(2.78)	(3.23)	(3.21)
Evening						
EC	4.89	4.96	3.89	3.89	4.21	4.39
	(3.26)	(3.23)	(2.99)	(2.99)	(3.20)	(3.30)
DNC	3.43	3.61	2.96	3.00	3.07	3.61
	(3.28)	(3.51)	(3.19)	(3.04)	(3.16)	(3.25)
Whole sample (N= 41)						
Morning						
EC	4.98	5.59	3.68	3.39	4.00	4.61
	(3.11)	(2.95)	(2.82)	(2.93)	(3.15)	(3.15)
DNC	4.98	4.95	3.44	3.12	3.41	3.93
	(2.78)	(2.77)	(2.82)	(2.65)	(3.01)	(3.00)
Evening						
EC	4.85	4.95	3.90	3.83	4.17	4.39
	(3.05)	(3.10)	(2.84)	(2.85)	(2.96)	(3.11)
DNC	3.44	3.63	2.93	3.07	3.15	3.78
	(3.06)	(3.35)	(3.01)	(2.90)	(3.03)	(3.26)

19 Mean ratings and standard deviations for difficulty concentrating over 1 hour (Study 2)

	Time point					
	Baseline	PC	5	10	30	60
	Mean (SD)					
Abstainers (N=28)						
Morning						
EC	4.46	5.04	3.75	3.57	3.71	4.04
	(2.72)	(3.09)	(3.04)	(3.19)	(3.33)	(3.43)
DNC	4.18	4.29	3.32	3.04	3.04	3.36
	(2.78)	(2.79)	(2.80)	(2.65)	(3.01)	(3.11)
Evening						
EC	4.36	4.36	3.57	3.61	3.86	4.18
	(3.26)	(3.39)	(2.95)	(2.92)	(3.22)	(3.26)
DNC	2.93	3.14	2.86	2.68	2.71	3.11
	(2.89)	(3.26)	(2.89)	(2.86)	(2.84)	(2.66)
Whole sample (N= 41)						
Morning						
EC	4.54	5.05	3.80	3.63	3.71	4.07
	(2.81)	(3.06)	(2.93)	(3.02)	(3.16)	(3.34)
DNC	4.32	4.51	3.37	2.98	3.05	3.54
	(2.91)	(2.79)	(2.84)	(2.58)	(2.74)	(2.92)
Evening						
EC	4.32	4.54	3.63	3.56	3.80	4.10
	(3.17)	(3.26)	(2.79)	(2.69)	(2.90)	(3.04)
DNC	2.80	2.95	2.78	2.59	2.56	3.27
	(2.74)	(3.05)	(2.75)	(2.69)	(2.72)	(2.75)

20 Mean ratings and standard deviations of composite withdrawal over 1 hour (Study 2)

	Time point					
	Baseline	PC	5	10	30	60
	Mean (SD)					
Abstainers (N=28)						
Morning						
EC	4.81	5.42	3.74	3.48	3.98	4.46
	(2.68)	(2.91)	(2.84)	(3.01)	(3.14)	(3.11)
DNC	4.74	4.74	3.43	3.07	3.31	3.75
	(2.11)	(2.63)	(2.62)	(2.54)	(3.00)	(3.07)
Evening						
EC	4.89	4.87	3.73	3.77	4.01	4.32
	(3.09)	(3.21)	(2.71)	(2.90)	(3.10)	(3.16)
DNC	3.26	3.43	2.87	2.76	2.94	3.40
	(3.06)	(3.30)	(2.81)	(2.74)	(2.87)	(2.83)
Whole sample (N= 41)						
Morning						
EC	4.71	5.32	3.76	3.54	3.89	4.37
	(2.77)	(2.89)	(2.78)	(2.85)	(3.01)	(3.09)
DNC	4.72	4.76	3.48	3.07	3.28	3.83
	(2.42)	(2.64)	(2.74)	(2.52)	(2.76)	(2.92)
Evening						
EC	4.73	4.81	3.74	3.67	3.90	4.24
	(2.94)	(3.04)	(2.59)	(2.68)	(2.79)	(2.87)
DNC	3.20	3.35	2.86	2.81	2.90	3.55
	(3.02)	(3.02)	(2.63)	(2.57)	(2.72)	(2.86)

21 Summary of mean scores and test statistics for individual MPSS items (Study 2)

MPSS Item:	Depression	Irritability	Restlessness	Difficulty concentrating	Hunger
Abstainers (N= 28)			**M (SD)**		
EC	1.71 (0.98)	2.54 (0.92)	2.64 (0.95)	2.57 (1.1.7)	2.89 (1.07)
DNC	1.39 (0.88)	2.21 (0.74)	2.21 (1.00)	1.86 (0.85)	2.39 (1.07)
Test statistic	z= -2.22	z= -1.50	z= -1.93	z= -3.03	z= -1.72
(p)	(0.026)	(0.133)	(0.053)	(0.002)	(0.084)
Whole Sample (N= 41)					
EC	1.71 (0.93)	2.59 (0.89)	2.66 (0.99)	2.56 (1.12)	2.93 (1.06)
DNC	1.39 (0.80)	2.27 (0.81)	2.22 (0.96)	1.95 (0.84)	2.49 (1.12)
Test statistic	z= -2.40	z= -1.79	z= -2.43	z= -3.30	z= -2.02
Sig. (p)	(0.016)	(0.073)	(0.015)	(0.001)	(0.043)

Barts and The London
School of Medicine and Dentistry

INVITATION TO PARTICIPATE IN A RESEARCH PROJECT

Complementing current NHS Stop Smoking Service treatments for smokers with behavioural replacement: The role of de-nicotinised cigarettes

Barts and The London

Queen Mary's School of Medicine and Dentistry

We would like to invite you to take part in a research study which we think may be important. The information which follows tells you about it. It is important that you understand what is in this leaflet. It says what will happen if you take part and what the study entails. Try to make sure you know what will happen to you if you decide to take part. Whether or not you do take part is entirely your choice. Please ask any questions you want to about the research and we will try our best to answer them.

The Study

People wanting to quit smoking are normally treated with medications such as nicotine replacement therapy or Champix and support from stop-smoking advisors. Although this approach is effective, it does not work with everyone. Many smokers miss the 'behavioural' and sensory aspects of smoking such as the taste, smell, handling the cigarettes etc. In this study, we are evaluating an idea that cigarettes which do not contain nicotine but which have a similar taste to normal cigarettes can provide these behavioural and sensory aspects over the first two weeks of quitting and help more people to stop smoking for good. We aim to recruit a total of 200 people who want to quit smoking (100 using varenicline and 100 using nicotine replacement therapy).

If you agree to take part in the study, you will be randomly allocated (by chance) to one of two groups. Both groups will receive the usual treatment with medication and support, but in addition to this, one group will receive de-nicotinised cigarettes for the first two weeks after they stop smoking their normal cigarettes.

What is in the de-nicotinised cigarettes?

The tobacco used in these cigarettes is from a transgenic (genetically modified) tobacco variety where an enzyme involved in making nicotine has been suppressed. However the leaves from these tobacco plants still contain a small amount of nicotine (about 5% of the normal nicotine content), but this is so small that it has little effect on the smoker. Normal

cigarettes are dangerous, and the de-nicotinised cigarettes are not much safer, but they are not meant to replace normal cigarettes with a safer alternative. Their use for two weeks is to see if they alleviate the discomfort and urges to smoke many smokers experience when quitting and whether they have a potential to improve the efficacy of the existing treatments.

What will happen if you take part?

If you are eligible and would like to take part, you will receive the normal treatment that we provide at our clinic, with three additional sessions. The table below shows what will happen in each session.

Outline of the study and treatment sessions		
Session 1	Baseline visit 2 weeks before quit day	At this first ***visit*** to the Smokers' Clinic we will describe the study and go through this information sheet. You will then have the opportunity to ask any questions. We will then ask you to sign a consent form to show that you have agreed to take part. You will then complete a short questionnaire to tell us about your smoking and mood. We will also measure the amount of carbon monoxide (CO) in your breath and your reaction to smoking-related pictures. You will be helped to select stop-smoking medication best suited to your needs (e.g. NRT, Champix).
Session 2	Preparation visit 1 week before quit day	At this second ***visit*** to the Smokers' Clinic we will ask you to complete a short questionnaire. We will also record the number of cigarettes that you are smoking per day and measure the amount of CO in your breath. You will be given a prescription for your stop-smoking medication. We will also help you prepare for your Quit Day the next week.
Session 3	Quit Day	You will ***visit*** the Smokers' Clinic and we will ask you to complete some short questionnaires to measure any withdrawal symptoms. We will also record the number of cigarettes that you are smoking per day and we will measure the amount of CO in your breath. You will be given a prescription for your stop-smoking medication. We will provide you with some counselling to help you get through the first week. You will be randomised at this session to either use de-nicotinised cigarettes along with usual care or to continue with usual care only. If you are in the de-nicotinised cigarettes group, you will be given a week's supply of these cigarettes. You will be asked to try one and to rate it on a short questionnaire at this session.
Phone call – 24 hours after quitting		We will ***call*** you to assess your withdrawal symptoms and if you are using the de-nicotinised cigarettes we will ask you to rate your experience with them.
Session 4	1 week after quit day	You will ***visit*** the Smokers' Clinic and we will ask if you have smoked or not, measure the amount of CO in your breath and ask whether you are experiencing withdrawal symptoms. Medication will be given to you if required at this session. We will also assess your reaction to smoking-related pictures. If you are in the de-nicotinised cigarettes group, you will be provided with another week's supply.
Session 5	2 weeks after quit day	You will ***visit*** the Smokers' Clinic and we will ask if you have smoked or not, measure the amount of CO in your breath and ask whether you are experiencing withdrawal symptoms. Medication will be given to you if required at this session. Participants who have been using the de-nicotinised cigarettes will also complete a questionnaire regarding their thoughts on using these cigarettes. Any unused cigarettes will be returned, and participants will be asked to stop using them.
Sessions 6-9	3-6 weeks after quit day	At each of these sessions you will ***visit*** the Smokers' Clinic and we will ask if you have smoked or not, measure the amount of CO in your breath and ask whether you are experiencing withdrawal symptoms. Medication will be given to you at each session. Medication will be given to you if required at this session. During **session 7 only**, we will also assess your reaction to smoking-related pictures. Support and advice will be provided at all sessions. After session 9 we will not formally contact you again until you have finished the

		course of treatment (8 weeks later). Of course you should feel able to contact us during this time if you have any questions or concerns.
Sessions 10	12 weeks after quit date	We will ask you to attend one final ***visit*** to see how you are after finishing the medication and how you are managing with not smoking. We will ask if you have smoked or not, measure the amount of CO in your breath and ask whether you are experiencing withdrawal symptoms. Advice will be given on how to stay stopped or try to quit again if you have not been able to stop.

As standard NHS treatment usually ends at session 7, you will be reimbursed for your time and travel for the additional treatment sessions. You will be given £20 at the end of session 9, and a further £10 at the final visit (session 10).

Who can take part?
You will be able to take part if you are aged 18 years or over and are seeking treatment to stop smoking.
You will **not** be able to take part if you are **pregnant or breast feeding** or have been diagnosed with an **acute psychiatric illness**.

Risks/Side effects
We do not anticipate that there will be any risks from using de-nicotinised cigarettes. As with any cigarettes you will still be exposed to tobacco smoke; however there are no increased health risks with de-nicotinised cigarettes compared to your normal cigarettes.

Data Protection
If you agree to take part you will be asked to fill out several questionnaires. Any information you do give us will be kept confidential, and only study staff will have access to this data. No medical information about you will be requested from your doctor, however your GP will be informed about your participation in this study, with your consent. The results of this study may be presented to other individuals working in the field of smoking cessation or may be printed in journals; however there will be no information included which could identify you.

Your Rights
Your participation in this study is entirely voluntary, and you are free to drop out of the study at any time. Your records will be kept strictly confidential and your ordinary medical care will not be put at risk if you decide not to take part or drop out.

What happens if you are concerned or have any questions?
You will be able to contact Dunja Przulj or Hayden McRobbie at the Smokers Clinic if you are worried about anything or have any questions. The number is 020 7882 8230 or email smokers-clinic@qmul.ac.uk. Outside office hours you can call this number 07866846818.

The principal investigator of this study is Hayden McRobbie, Tobacco Dependence Research Unit, Wolfson Institute of Preventative Medicine, Barts and The London School of Medicine and Dentistry, 55 Philpot Street, London, E1 2JH, Tel: 020 7882 8230.

A summary of the results of this study will be available upon request from Dunja Przulj or Hayden McRobbie (see above for contact details).

We believe that this study is safe and do not expect you to suffer any harm or injury because of your participation in it. However, *Queen Mary and Westfield College, University of London* has agreed that if your health does suffer as a result of your being in the study then you will be compensated. In such a situation, you will not have to prove that the harm or injury which affects you is anyone's fault. If you are not happy with any proposed compensation, you may have to pursue your claim through legal action.

If you have a complaint please contact Christine Bevan-Davies, Quality Development, Barts and the London NHS Trust, Healthcare Governance Directorate, Tel: 020 7480 4857, Email: christine.bevan davies@bartsandthelondon.nhs.uk

We would like to thank you for your interest in this study, even if you decide not to take part.

23 Study 3 Consent Form

Barts and The London
School of Medicine and Dentistry

Complementing current NHS Stop Smoking Service treatments for smokers with behavioural replacement: The role of de-nicotinised cigarettes

Informed Consent Form

Principal Investigator: Dr Hayden McRobbie

Participant Name:_____

Participant Number:

	Please initial each line
I confirm that I have read (or someone else has read to me) and I understand the Participant Information Sheet (*insert version and date)*, for the above study.	
I have had the opportunity to consider the information, ask questions and have had these questions answered satisfactorily.	
I understand that my participation is voluntary (my choice) and that I may withdraw from the study at any time without giving reason, and that my medical care or legal rights will not be affected because of this.	
I agree to my GP being informed about my participation in this study	
I understand that all information collected will be in accordance to the Data Protection Act of 1998.	
I agree to take part in the above study	

I understand that the research data collected during the study may be looked at by other individuals from the research team, sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.

_____	_____	_____
Participant Name (please print)	Signature of Participant	Date
_____	_____	_____
Name of person explaining consent	Signature of person explaining consent	Date

24 Summary of test statistics for between groups baseline comparisons (Study 3; DNC+ST vs. ST)

Baseline variable	Test statistic	Sig (p).
	Chi-square (x^2)	
Gender	0	1.00
Ethnicity	12.49	0.567
Employment status	11.23	0.129
Education	0.19	0.667
GN-SBQ (high/low)	0.04	0.839
SM-MFS (high/low)	0.66	0.416
	One-way ANOVA (F[df])	
Age	F(1, 199) = 0.85	0.358
CPD	F(1, 199) = 0.05	0.823
FTND	F(1, 193) = 0.48	0.491
GN-SBQ total	F(1, 194) = 1.27	0.261
SM-MFS total	F(1, 198) = 1.25	0.265

Supplementary Material: Published Papers

The Open Addiction Journal, 2012, *5*, 41-50 41

Open Access

The Effect of Sensorimotor Replacement on Smoking Cessation and Craving

Dunja Przulj*, Hayden McRobbie and Peter Hajek

Tobacco Dependence Research Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London, UK

Abstract: Current treatments for smoking cessation such as nicotine replacement therapy or varenicline address the primary reinforcer of smoking (nicotine), but sensorimotor stimuli (e.g. smell/taste of smoke, inhaling/exhaling, airway sensations, holding the cigarette) may act as secondary reinforcers and also contribute to smoking reward. Addressing both these aspects of smoking may help to enhance smoking cessation treatment. The aim of this review was to examine whether sensorimotor replacement can help to alleviate craving and aid smoking cessation. Three sensorimotor replacement products were examined: non-nicotine inhalators/aerosols, de-nicotinised cigarettes and electronic cigarettes. The current research suggests that sensorimotor replacement may enhance the efficacy of nicotine replacement therapy, but is unlikely to be useful if used alone. Electronic cigarettes may be the most promising approach, due to the combination of nicotine delivery and sensorimotor input.

Keywords: Craving, de-nicotinised cigarettes, electronic cigarettes, inhalator, nicotine, sensorimotor replacement, smoking cessation.

INTRODUCTION

Nicotine has long been identified as the fundamental component in tobacco addiction. Recognising the addictive nature of nicotine has led to the development of effective treatments for smoking cessation such as nicotine replacement therapy (NRT) and varenicline. Although medication can enhance people's chances of successfully quitting [1], long-term cessation rates are overall low. This suggests there may be more to smoking and tobacco addiction than just nicotine.

It could be argued that the efficacy of NRT is limited because it is underused and/or does not deliver nicotine in large enough doses or quickly enough in comparison to cigarettes. Although it is likely that these are contributing factors, it has also been proposed that sensorimotor factors such as holding the cigarette, inhaling/exhaling, smell/taste of smoke, airway sensations, play a role in tobacco addiction, which current treatments do not fully address [2]. Sensorimotor stimuli may contribute to smoking reward through their association with the pharmacological effects of nicotine [3]. This happens through classical or 'Pavlovian' conditioning, whereby a previously neutral stimulus becomes rewarding if it is closely followed by a real reward and may eventually acquire an independent incentive value. There is some evidence that such factors can play a role in the rewarding effects of smoking. Blocking the sensations of cigarette smoke by anesthetising the upper and lower respiratory tract led to less enjoyment of smoking [4]. Nicotine administered intravenously was perceived as less subjectively rewarding than smoking, even when the dose of nicotine was matched to the dose inhaled from the cigarette [5-7].

Such observations and theories raise the possibility that smoking cessation treatments could perhaps be enhanced if both nicotine and sensorimotor aspects of smoking were addressed. The nicotine inhalator is currently the only licensed smoking cessation medication which attempts to address both these factors [8, 9]. However it remains a poor substitute for smoking. The inhalator needs to be puffed intensely over 20 minutes to provide appreciable nicotine levels and compliance with its recommended use is low [10]. It is thus possible that whatever gains the inhalator may provide in terms of behavioural replacement are cancelled by its limited nicotine delivery. The inhalator also provides only limited sensory replacement in that its taste, smell, airway stimulation etc. do not resemble cigarette effects closely.

A growing body of research exists investigating the efficacy of several other sensorimotor replacement products in alleviating tobacco withdrawal symptoms and aiding cessation. These include flavoured non-nicotine inhalators and aerosols, de-nicotinised cigarettes, and more recently, electronic cigarettes. This review aims to evaluate the evidence examining whether these three products can help to reduce cravings to smoke and facilitate smoking cessation. Tables **1** and **2** provide a summary of the effects of sensorimotor replacement on craving and smoking cessation, respectively.

NON-NICOTINE INHALATORS AND AEROSOLS

The main body of research in this area originates from Jed Rose and his group, currently at the Duke Centre for Nicotine and Smoking Cessation Research. Their early studies focused on three sensory replacement products; the citric acid aerosol, black pepper extract inhalator, and

*Address correspondence to this author at the Tobacco Dependence Research Unit, Bart's and the London School of Medicine and Dentistry, Wolfson Institute of Preventive Medicine, Queen Mary University of London, 55 Philpot Street, London, E1 2JH, UK; Tel: +44 207 882 5949; Fax: +44 207 377 7237; E-mail:d.przulj@qmul.ac.uk

1874-9410/12

ascorbic acid aerosol, were chosen because of their ability to mimic the throat 'scratch' delivered by tobacco smoke [11].

The citric acid aerosol significantly reduced craving compared to controlled puffs of air [12], to a placebo aerosol which was unflavoured [13, 14], and produced effects comparable to a low nicotine and tar cigarette [12]. Any craving relief from the citric acid aerosol may however be short-lived; Levin *et al.* found significant craving reduction in the morning, compared to the placebo group, but no differences between groups at later time points [13]. Additionally, Behm *et al.* found a significant difference between the citric acid group and placebo controls on the first day of abstinence, but equivalent craving ratings from day 5 of abstinence [14]. In a smoking cessation trial comparing a combination of the citric acid aerosol with a nicotine patch and a placebo aerosol also in combination with the patch [15], relief from craving on the quit day was significantly higher in the citric acid group; however no differences were found on the Shiffman-Jarvik withdrawal questionnaire [16]. Two randomised, placebo-controlled smoking cessation trials have been conducted with the citric acid aerosol. The first (N=74) examined the efficacy of the citric acid aerosol alone, *vs* a placebo aerosol [14]. There was a significantly higher point prevalence abstinence rate in the citric acid group (20% abstinent *vs* 0% of controls) at day 19 post-quit, as verified with exhaled carbon monoxide (CO) readings, but only in participants with high baseline CO. An analysis of overall abstinence rates was not reported. In the second trial (N=100), nicotine patches were used in combination with a citric acid inhalator or placebo for 10 weeks [15]. Ten-week CO-validated continuous abstinence rates were significantly higher in the citric acid group than placebo (19.5% *vs* 6.8%). However, when adjusted for baseline differences in participant characteristics (e.g. number of cigarettes smoked per day, number of years smoked, CO) this effect was marginal (p = 0.06). By 24 weeks, nearly all participants had relapsed and there was no difference between the two groups.

Two trials studied an ascorbic acid aerosol in craving relief and smoking cessation [17]. In study 1 (N=63), *greater* levels of craving were reported one week post-cessation in those using the aerosol compared to controls using nothing. Three weeks post-cessation, this effect was marginal. CO-validated point prevalence abstinence rates were significantly higher in the ascorbic acid group at days 3 and 22 post-cessation and marginally higher at one week. Abstinence rates by the 6 and 12 week follow ups fell below 20%, with no differences between conditions. In study 2, two different types of ascorbic acid aerosols were compared (fine *vs* coarse particles). Since no control group was included, the findings are difficult to interpret.

One study investigated the use of a black pepper inhalator [18]. During a three-hour session following overnight abstinence, where participants used their allocated inhalators ad-libitum whilst remaining abstinent, the black pepper inhalator decreased craving to a greater extent than an inhalator with no cartridge, and a menthol flavoured inhalator. It could be argued that these results may be due to the distraction caused by the irritating effects of black pepper, although participants reported liking the black pepper and menthol inhalators more than the placebo, and airway sensory effects were only rated stronger for the black pepper in the chest, with no differences between inhalators in other areas.

No further work has been conducted with the citric, ascorbic and black pepper inhalators due to extensive regulatory requirements. However, a recent smoking cessation trial (N=120) has investigated the use of a tobacco flavoured nicotine-free inhalator in combination with pharmacological (nicotine patch plus bupropion) and behavioural treatment [19]. The inhalator had no effect on abstinence rates at 4 or 24 weeks overall. However, there was a significant effect of the inhalator in smokers who reported high levels of 'behavioural dependence' at baseline, measured by the Glover-Nilsson Smoking Behaviour Questionnaire [20]. This post-hoc finding requires a replication.

In summary, flavoured non-nicotine inhalators used alone or in combination with the nicotine patch may alleviate craving to some extent compared with placebo, but the effects are likely to be short-lived. Theories of learning would predict that the removal of the unconditioned reinforcer (nicotine) would gradually weaken any effects of conditioned reinforcers (sensorimotor stimuli) until the reaction to them extinguishes altogether. However, even a short-term reduction of urges to smoke may facilitate the initial abstinence, which may in turn affect continuous cessation long-term. It is unfortunate that further work with the citric, ascorbic acid and black pepper inhalators had to be halted, but recently two other promising approaches have emerged.

DE-NICOTINISED CIGARETTES

De-nicotinised cigarettes (DNCs) contain tobacco with almost all the nicotine removed (machine yield <0.1 mg nicotine). DNCs differ from 'light' and 'ultra-light' cigarettes which also register low levels of nicotine when assessed mechanically, but allow smokers to obtain standard doses of nicotine by blocking ventilation holes and puffing more intensively. This is possible because the tobacco in such cigarettes still contains nicotine levels similar to high nicotine yield cigarettes [21]. DNCs provide negligible levels of nicotine to smokers even with intensive puffing. Otherwise however, they deliver all other chemicals normally present in cigarette smoke and provide a virtually complete behavioural and sensory replacement for cigarettes. If sensorimotor replacement helps smokers over the initial withdrawal period, DNCs should be more helpful than other sensorimotor replacement products. Since DNCs deliver most of the chemicals found in conventional cigarettes, including those assumed to enhance nicotine effects, they may also potentiate the therapeutic effects of NRT.

The majority of studies with DNCs have examined the acute effects of DNCs after overnight abstinence. Measures of craving have varied across studies, from single item questions to more comprehensive questionnaires such as the Questionnaire of Smoking Urges (QSU) [22] which measures desires or intentions to smoke (Factor 1) and anticipation of relief from withdrawal and negative affect (Factor 2). Most studies have compared DNCs to conventional cigarettes.

Table 1. Summary of the Effects of Sensorimotor Replacement Products on Craving

Author	Product	N	Design	Findings
Rose & Hickman (1987)	Citric acid aerosol	15	Within-subjects. Single-blind. Pre-study abstinence: 1 hour.	Sig. less craving *vs* inhalations of air. Comparable levels *vs* 'light' cigarette. Sig. more craving *vs* OB*
Levin *et al.* (1990), exp. 2.	Citric acid aerosol	11	Between-subjects, randomised. Single-blind. Pre-study abstinence: unknown.	Sig. less craving *vs* placebo, in the morning only.
Behm *et al.* (1993)	Citric acid aerosol	74	Randomised smoking cessation trial. Double-blind.	Sig. less craving *vs* placebo on day 1 of abstinence only.
Westman *et al.* (1995)	Citric acid aerosol + nicotine patch	100	Randomised smoking cessation trial. Double-blind.	"Craving relief": Sig. greater *vs* placebo on day 1 of abstinence. Shiffman-Jarvik craving subscale: Comparable levels of craving *vs* placebo.
Levin *et al.* (1993), Study 1.	Ascorbic acid	63	Randomised smoking cessation trial.	Sig. greater craving *vs* controls on day 8 of abstinence. Comparable levels thereafter.
Rose &Behm (1994)	Black pepper inhalator	48	Between- subjects, randomised. Pre-study abstinence: overnight.	Sig. greater reduction in craving *vs* placebo and menthol flavoured inhalator.
Hasenfratz *et al.* (1993)	DNCs	12	Within-subjects. Pre-study abstinence: overnight.	Comparable levels of craving reduction *vs* 'light' cigarettes. Sig. greater reduction with OB.
Rose *et al.* (1994)	DNCs	12	Within-subjects. Pre-study abstinence: overnight.	Comparable levels of craving reduction *vs* nicotine cigarette.
Butchsky *et al.* (1995)	DNCs	7	Within-subjects, randomised. Pre-study abstinence: 12 hours.	Comparable levels of craving reduction *vs* nicotine cigarette.
Baldinger *et al.* (1995)	DNCs	12	Within-subjects. Pre-study abstinence: overnight.	Comparable levels of craving *vs* 'light' cigarettes and OB.
Baldinger *et al.* (1995)	DNCs	12	Within-subjects. Pre-study abstinence: overnight.	Sig. less craving *vs* no-intervention condition. Comparable levels of craving *vs* OB.
Lane *et al.* (1995)	DNCs	18	Within-subjects. Single-blind. Pre-study abstinence: overnight.	Sig. less craving *vs* no-intervention condition. Sig. more craving *vs* OB
Westman *et al.* (1996)	DNCs	6	Within-subjects, randomised. Pre-study abstinence: overnight.	Comparable levels of craving *vs* nicotine cigarette.
Gross *et al.* (1997)	DNCs	10	Within-subjects, randomised. Single-blind. . Pre-study abstinence: none.	Comparable levels of craving *vs* 'light' cigarettes and OB.
Pickworth *et al.* (1999)	DNCs	20	Within-subjects, randomised. Double-blind. Pre-study abstinence: overnight and 3 hours.	Comparable levels of craving reduction *vs* nicotine cigarettes. No main effect of abstinence length.
Buchhalter *et al.* (2001)	DNCs	32	Within-subjects. Single-blind. Pre-study abstinence: 8 hours.	QSU: Sig. less craving *vs* Accord device. Comparable levels *vs* OB. "Craving a cigarettes/nicotine": Comparable levels of craving *vs* Accord device.
Breland *et al.* (2002)	DNCs	20	Within-subjects. Single-blind. Pre-study abstinence: overnight.	Sig. less craving *vs* Accord device. Comparable levels of craving *vs* Eclipse device and OB.
Rose *et al.* (2003)	DNCs	18	Within-subjects. Pre-study abstinence: overnight.	Sig. greater craving reduction *vs* saline control condition. Sig less craving reduction *vs* OB.

(Table 1) contd…..

Author	Product	N	Design	Findings
Dallery *et al.* (2003)	DNCs	15	Within-subjects. Pre-study abstinence: 30 minutes.	Comparable reductions in craving *vs* nicotine cigarettes.
Rose &Behm (2004)	DNCs	16	Within-subjects. Single-blind. Pre-study abstinence: overnight.	Comparable reductions in craving *vs* 'light' cigarettes.
Buchhalter *et al.* (2005)	DNCs	32	Within-subjects. Double-blind. Pre-study abstinence: N/A, participants remained abstinent over 4 days.	"Urges to smoke": No increase in craving over 4 days in DNC and nicotine cigarette condition, but sig. increase in no-intervention condition. "Craving a cigarette ": Sig. increases on most days *vs* baseline, in both DNC and no-intervention conditions, but no changes in craving in nicotine cigarette condition. QSU-Factor 1: No increase in craving over 4 days in DNC and nicotine cigarette condition, but sig. increase in no-intervention condition. QSU-Factor 2: Sig. increases on most days *vs* baseline, in both DNC and no-intervention conditions, but no changes in craving in nicotine cigarette condition.
Eid *et al.* (2005)	DNCs	8	Within-subjects, randomised. Pre-study abstinence: none.	Comparable reductions in craving *vs* nicotine cigarette.
Juliano *et al.* (2006)	DNCs	60	Between-subjects, randomised. Double-blind. Pre-study abstinence: 4 days.	Sig. greater reduction in craving *vs* no-intervention control group. Comparable levels of craving reduction *vs* nicotine cigarette.
Rose *et al.* (2006)	DNCs + nicotine patch (before TQD).	96	Randomised smoking cessation trial. DNCs un-blinded.	During treatment, and 1 week post-quit day, sig. less craving in the DNC + placebo patch group *vs* OB + placebo patch group. Comparable levels at 4 weeks post-quit.
Donny *et al.* (2007)	DNCs	30	Between-subjects, randomised, Double-blind. Pre-study abstinence: N/A, participants remained abstinent over 11 days.	Comparable levels of craving *vs* no-intervention group and nicotine cigarette group.
Rezaishiraz *et al.* (2007)	DNCs + nicotine patch (before TQD)	98	Randomised smoking cessation trial. Un-blinded.	During treatment and 2 weeks post-quit day, sig. less craving *vs* 'light' cigarette group.
Brody *et al.* (2009)	DNCs	62	Between-subjects, randomisation unclear. Double-blind. Pre-study abstinence: 3 hours.	Comparable reductions in craving *vs* OB.
Barrett (2010)	DNCs	22	Within-subjects. Double-blind. Pre-study abstinence: 12 hours.	QSU-Factor 1: Sig. less craving *vs* nicotine and placebo inhalator. Comparable levels of craving *vs* nicotine cigarette. QSU-Factor 2: Sig. less craving *vs* placebo inhalator and comparable levels *vs* nicotine inhalator. Comparable levels of craving *vs* nicotine cigarette.
Cobb *et al.* (2010)	DNCs	28	Within-subjects. Single-blind. Pre-study abstinence: overnight.	Sig. less craving *vs* baseline measures. Comparisons between DNCs and other products not reported, but DNCs showed similar patterns of results to OB condition.
Hatsukami *et al.* (2010)	DNCs	165	Randomised smoking cessation trial. Single-blind.	No changes in craving 1 week post-quit. Craving increased sig. following cessation of smoking either DNCs or nicotine cigarettes *vs* previous week, but no increases in lozenge group.

(Table 1) contd.....

Author	Product	N	Design	Findings
Perkins *et al.* (2010)	DNCs	104	Between-subjects, randomised. Single-blind. Pre-study abstinence: overnight.	Sig. greater reduction in craving *vs* no-intervention control group. Comparable craving reduction *vs* nicotine cigarette group.
Rose *et al.* (2010)	DNCs	16	Within-subjects. Single-blind. Pre-study abstinence: overnight.	Sig. less craving *vs* sham smoking.
Walker *et al.* (2011)	DNCs + NRT	1410	Randomised smoking cessation trial. Single-blind.	Comparable levels of craving over 6 weeks post-quit *vs* NRT alone.
Bullen *et al.* (2010)	EC	40	Within-subjects. Double-blind. Pre-study abstinence: overnight.	Sig. greater reduction in craving with nicotine EC *vs* nicotine-free EC, only after 25 minutes post-product use. Comparable levels of craving *vs* nicotine inhalator. Sig. less craving reduction *vs* OB.
Eissenberg (2010)	EC	16	Within-subjects. Pre-study abstinence: 12 hours.	Comparable levels of craving *vs* baseline and sham smoking at most time points. Sig. less craving reduction *vs* OB.
Vansickel *et al.* (2010)	EC	32	Within-subjects. Pre-study abstinence: 12 hours.	Sig. less craving *vs* baseline and sham smoking at some time points. Sig. less craving reduction *vs* OB.

*OB: Own Brand.

Not surprisingly, data pooled from 9 studies showed DNCs' effects to be weaker [23]. Mean cigarette reward ratings (satisfaction and craving reduction) were 4.05 (SD = 0.15) for nicotine cigarettes, and 3.36 (SD = 0.14) for DNCs (p <.001). The size of this effect is unknown, and regression analyses revealed significant individual differences, in that males and more dependent smokers reported more similar ratings between the two types of cigarette. A fair number of studies have however found similar craving suppression to nicotine containing cigarettes [7, 24-42].

Of more interest in our context are the effects of DNCs compared to no intervention and to alternative craving reduction techniques. There is good evidence that DNCs alleviate craving acutely compared to no intervention [37, 41, 43]. DNCs were also more effective than puffing on an unlit cigarette or taking in puffs of air [40, 44]. In one study, DNCs smoked alongside intravenous delivery of saline, were more effective at reducing cravings compared to saline alone [6]. DNCs also reduced urges to smoke compared to baseline over two hours (following overnight abstinence), as did snus (non-combustible tobacco product), whilst nicotine lozenge and a compressed tobacco tablet had no significant effect [40]. The report however does not indicate whether there were any differences between the DNCs and non-combustible products. DNCs have also been compared to potential reduced exposure products such as Accord and Eclipse, which heat tobacco. Although both Accord and Eclipse were able to reduce cravings relative to baseline, DNCs were more effective than the Accord device [31, 32], and equivalent to the Eclipse [31]. Finally, DNCs were more effective than a placebo and nicotine inhalator in reducing intentions to smoke (Factor 1, QSU) and equal to a nicotine inhalator in alleviating withdrawal/negative affect (Factor 2, QSU) over 2 hours following at least 12 hours of abstinence [42].

Three studies have investigated the effects of DNCs over longer periods of time. Over 24 hours of abstinence, craving was significantly lower with DNCs than with no intervention [28] and this was also observed on some, though not all, measures of craving over 4 days of abstinence [36]. However, in a well-controlled study which hospitalised volunteers for 13 days, participants in the DNC and no-treatment conditions did not differ in ratings of craving over 11 days of abstinence [38].

In three randomised controlled trials DNCs have been used for several weeks prior to the quit date but not after it. In a complicated and underpowered trial which randomised 96 participants into 6 conditions, DNCs unexpectedly generated significantly greater reduction in craving compared to own brand smoking over two weeks of use, as well as on the quit day and one week post-quit. There was no effect on abstinence rates at 1 and 6 months [45]. In the second trial, 98 participants were given nicotine patches and were randomised to smoke DNCs or low-nicotine cigarettes for 2 weeks before quitting. Craving was significantly lower in the DNC group, both before the quit day and at 2 weeks post-quit, but self-reported abstinence rates at 3 and 6 months did not differ [46]. Finally, in a larger trial (N=346) participants used cigarettes with gradually reduced nicotine content over 6 weeks until DNCs were smoked in the final two weeks. Participants also used a placebo or nicotine patch, before and after the quit day. A control group smoked normal cigarettes during the pre-quit period and used a nicotine patch following the quit day. All groups were asked to stop smoking all cigarettes after the target quit date.

Table 2. Summary of the Effects of Sensorimotor Products on Smoking Cessation

Author	Design	N	Intervention	Abstinence Rates
Behm *et al.* (1993)	Randomised. Double-blind.	74	Citric acid aerosol. Placebo aerosol. All received group support.	PP*, day 19: High CO** group: 20% citric acid *vs* 0% placebo ($p < 0.05$). Low CO group: 20% citric acid *vs* 25% placebo (*ns*).
Westman *et al.* (1995)	Randomised. Double-blind.	100	Citric acid aerosol + nicotine patch. Placebo aerosol + nicotine patch. All received brief individual support.	Continuous, 10 weeks (primary outcome): 19.5% citric acid *vs* 6.8% placebo ($p < 0.05$, adjusted $p = 0.06$). Continuous, 24 weeks: 0% citric acid, *vs* 5.1% placebo, (*ns*). Continuous, 6 weeks: 34.1% citric acid *vs* 11.9% placebo (adjusted, $p < 0.01$). Continuous, 4 weeks: 36.6% citric acid *vs* 18.6% placebo (adjusted $p < 0.05$).
Levin *et al.* (1993), Study 1	Randomised.	63	Ascorbic acid + group support. Group support only.	PP, day 3: ~84% ascorbic acid *vs* 60% controls ($p = 0.05$) PP, day 8: ~73% ascorbic acid *vs* ~52% controls ($p = 0.09$). PP, day 22: ~58% ascorbic acid *vs* ~22% controls ($p < 0.01$). PP, day 43: 20%, both groups. PP, day 85: ~16%, both groups.
Caponnetto *et al.* (2011)	Randomised.	120	Nicotine free, flavoured inhalator + pharmacological and behavioural support. Pharmacological and behavioural support only.	PP, 4 weeks: 38.3% inhalator *vs* 35% controls (*ns*). PP, 24 weeks: 33.3% inhalator *vs* 28.3% controls (*ns*).
Rose *et al.* (2006)	Randomised. Cigarettes- un-blinded. Patches- double-blind.	96	2 weeks before TQD***: 1. DNC + nicotine patch or placebo. 2. 'Light' cigarette + nicotine patch or placebo. 3. OB+ nicotine patch or placebo. After TQD: 42mg, 21mg, or placebo patch. All received Mecamylamine or placebo, and brief support.	Continuous, 4 weeks: Sig. main effect of pre-cessation patch only ($p < 0.01$). 50% DNC + patch *vs* 23% placebo. 50% 'light' cigarette + patch *vs* 33% placebo. 50% OB + patch *vs* 12% placebo.
Rezaishiraz*et al.* (2007)	Randomised. Un-blinded.	98	2 weeks before TQD: DNC + nicotine patch. 'Light' cigarettes only. After TQD: All received nicotine patch and behavioural support.	PP, 3 months: 43% DNC + patch *vs* 34% control group (*ns*). PP, 6 months: 28% DNC + patch *vs* 21% control group (*ns*).
Becker *et al.* (2008)	Randomised. Double-blind.	346	6 weeks before TQD: Quest 1,2,3† (2 weeks each) + nicotine patch in last 2 weeks or placebo patch. Conventional cigarettes + placebo patch last 2 weeks (control group). After TQD: DNC groups received nicotine or placebo patch. Control group received nicotine patch. All received brief behavioural support.	Continuous, 4 weeks: 32.8% DNC + patch *vs* 21.9% control group ($p < 0.05$). 16.4% DNC + placebo *vs* 21.9% control group (*ns*).

(Table 2) contd.....

Author	Design	N	Intervention	Abstinence Rates
Hatsukami *et al.* (2010)	Randomised. Single-blind.	165	DNCs. 'Light' cigarettes. Lozenges. All received weekly brief support.	Continuous, 4 weeks: 43% DNC *vs* 35% lozenge *vs* 21% 'light' cigarette ($p = 0.05$). PP, 6 weeks: 47.2% DNC *vs* 23.1% 'light' cigarettes ($p < 0.05$). 47.2% DNC *vs* 36.7% lozenge (*ns*). 36.7% lozenge *vs* 23.1% 'light' cigarettes (*ns*).
Walker *et al.* (2011)	Randomised. Single-blind.	1,410	DNCs + NRT and behavioural support. NRT and behavioural support only.	PP, 6 months (primary outcome): 33% DNC *vs* 28% control group ($p< 0.05$, $RR = 1.18$, $CI = 1.01$-1.39). Continuous, 6 months: 23% DNC *vs* 15% Control group ($p< 0.001$, $RR = 1.50$, $CI = 1.20$-1.87).

*PP: Point prevalence,**CO: carbon monoxide, ***TQD: Target quit day.
†Quest 1,2,3: cigarettes with progressively reduced nicotine content. Quest 3 is de-nicotinised.

Craving measures were not reported in the study. Four week CO-validated continuous abstinence rates were significantly higher in the DNC plus patch group *vs* controls (33% *vs* 22%, respectively), but the DNC plus placebo patch group did not differ in outcome relative to controls (22% *vs* 16%, respectively). Differences between the two DNC groups were not examined. By 3 and 6 months no differences in abstinence rates were present [47].

Two studies have examined the use of DNCs following the quit day. In one of them, DNCs were compared to nicotine lozenge and to low-nicotine cigarettes. Participants (N=165) used their assigned products ad-libitum for a period of 6 weeks starting on their target quit day. Following cessation of products, craving increased significantly for the two cigarette groups. Continuous CO-validated quit rates at four weeks after discontinuation of the products (though use of lozenge was permitted) did not differ across conditions, but the trend favoured the DNC group (43%, 35%, and 21% for DNC, lozenge, and low-nicotine cigarettes, respectively) [48]. In the second trial[1] participants (N=1,410) were randomised to either standard care (NRT and behavioural support for 8 weeks) or standard care alongside DNC use for a period of 6 weeks after the quit day. There were no differences between groups in urges to smoke over 6 weeks. Abstinence rates were higher in the DNC group at all follow up points up to 6 months (23% *vs* 15%, $p < 0.001$). Abstinence however was not biochemically verified at any time point.

In summary, the existing evidence suggests that DNCs can alleviate craving acutely, and in some cases over longer periods of abstinence. DNCs have little effect on smoking cessation if used prior to quitting. However, they may provide some help if used alongside NRT following the quit day. There are some encouraging findings but the evidence is not conclusive and further trials with DNCs in combination with current smoking cessation treatments (NRT, varenicline) are needed.

[1]Walker N, Howe C, Bullen C *et al.* Can the use of nicotine free cigarettes as an adjunct to usual NRT-based cessation practice help people quit smoking? Findings from a randomised trial: 2011: Poster presentation at the 13th Annual Meeting of the SRNT- Europe; 2011 Sep 8-11; Antalya, Turkey.

ELECTRONIC CIGARETTES

The final product which may be of use as a sensorimotor replacement for smoking is the electronic cigarette (EC). ECs are tobacco free, battery powered devices. They typically resemble conventional cigarettes in appearance and with each puff a visible vapour or mist is created which resembles smoke. Importantly, this provides sensorimotor stimuli fairly close to smoking (e.g. throat scratch, inhaling/exhaling). Cartridges for ECs can be purchased with differing levels of nicotine, including nicotine-free, and in a variety of different flavours.

ECs have been commercially available since 2004, and five studies to date have been published examining their efficacy in acute craving reduction. Two of these have compared two brands of ECs (NPRO and Hydro) with own brand cigarettes and a sham smoking control condition, after 12 hours of abstinence [49, 50]. As expected, own brand cigarettes were found to reduce craving to a greater extent than ECs. ECs were reported to reduce cravings relative to baseline and sham smoking at some time points [50], but in the other trial they showed little impact on baseline craving or difference from sham smoking [49]. It should be noted that both of these early studies allowed only 10 puffs of the EC and no increases in plasma nicotine levels were observed. Any effects in these two studies were thus due to sensorimotor stimulation rather than nicotine.

In a direct comparison of a nicotine and placebo EC [51], significantly greater reductions in craving over one hour were evident with the nicotine EC. However the placebo EC also reduced craving initially, with the differences between the two arms only becoming apparent at 25 minutes post product use and onwards. This study also compared the ECs to own brand cigarettes and a nicotine inhalator. As before, own brand cigarettes reduced craving to a greater extent than all other products, but no differences were found between the ECs and inhalator. A further two studies have been published recently, one examining EC effects with experienced users [52] and another with naïve EC users [53]. However in both of these studies no control group was included.

The efficacy of ECs outside of controlled laboratory settings and over longer periods of time is as yet unknown. Several internet surveys of EC users have reported that the majority of respondents have successfully replaced their

usual cigarettes with ECs [54-57]. Additionally, in one study, participants who were not seeking to quit were given ECs to use ad-libitum for 6 months. At 6 months, 22.5% had quit smoking [58]. Clinical trials are now needed to investigate EC efficacy in smoking reduction and cessation.

DISCUSSION

This review has summarised the current evidence on the effects of three sensorimotor replacement products (non-nicotine inhalators and aerosols; de-nicotinised cigarettes; and electronic cigarettes) in craving reduction and smoking cessation. In summary, flavoured non-nicotine inhalators used alone or in combination with the nicotine patch may alleviate craving to some extent compared with placebo, but the effects are fairly small and short-lived. DNCs alleviate craving in the short term at least, and may be a useful tool for smoking cessation when used after the quit day, and in combination with NRT. The evidence base on ECs is currently limited, but these early studies suggest they may be a promising tool for withdrawal relief and smoking cessation.

DNCs appear to lend the most support for the sensorimotor replacement hypothesis, with a number of studies showing equivalent acute craving suppression to even conventional nicotine cigarettes. DNCs provide an almost full sensory and behavioural replacement to smoking, compared to for example nicotine-free inhalators, which provide fewer conditioned sensorimotor stimuli. The one study which has compared DNCs to a nicotine-free inhalator indeed found DNCs to be more effective in alleviating craving [42]. Furthermore, other constituents of tobacco smoke present in DNCs may have direct pharmacological effects or enhance effects of nicotine from NRT [2], adding to the potential efficacy of DNCs as a supplement to existing pharmacological treatments.

There are however several concerns which may be slowing down work in this area. In theory, DNCs may prevent patients' habituation to life without cigarettes, and cessation of their use may represent a loss of a coping tool and precipitate withdrawal discomfort and relapse. In one study, participants exposed to DNCs following 4 days of abstinence relapsed back to smoking faster than those in the no-lapse condition [37]; but the sample consisted of smokers not wanting to quit. It is unlikely that users can become dependent on DNCs in the absence of the primary reinforcer. Any conditioned effects should dissipate over time, leading to a reduction in the number of DNCs smoked. In the two studies which examined DNC use post quit day, there was indeed a significant reduction in DNC use over time. These issues however require further empirical examination. Another concern relates to the fact that DNCs are as harmful to health as conventional cigarettes, although using them for a few weeks instead of conventional cigarettes to facilitate cessation of all tobacco use should be acceptable. Regarding ECs, these deliver sensorimotor stimuli closer to smoking than inhalators and aerosols though not as close as DNCs. However, they also deliver nicotine. Survey data have shown that some smokers have successfully switched from conventional cigarettes to ECs, suggesting that ECs may have the potential to compete with cigarettes as a consumer product. Questions remain as to whether ECs should be seen in the same light as for instance consumer products containing caffeine (e.g. teabags, soft drinks), or whether they should be submitted to stricter regulation in the absence of any evidence of harm so far. Some governing bodies have banned or restricted the marketing and sales of ECs, while others such as the UK allow them on the basis that these products are not marketed for therapeutic use. The popularity of ECs is growing however [59], and regulations will no doubt be reviewed in light of further research on safety and efficacy.

This review has identified several pointers for future research. Regarding methodological issues, the majority of existing studies used laboratory procedures following overnight/12 hours of abstinence. Few studies have used more ecologically valid designs and examined effects of these products over longer periods of time. Studies of smoking cessation have not always complied with the Russell Standard [60], for example, not validating self-reported abstinence biochemically or reporting continuous abstinence. Regarding research priorities, studies are needed on the effects of DNCs and ECs as self-standing interventions for smoking reduction and cessation; and, perhaps more urgently, studies are needed on the effects of adding DNCs and ECs to existing treatments. Well powered large studies will also allow for testing the hypothesis that there are subgroups of smokers particularly likely to benefit from sensorimotor replacement.

In conclusion, sensorimotor replacement alone, used without nicotine, is likely to relieve cravings only briefly and it is unlikely to have a substantial effect in smoking cessation. However, it may increase the effectiveness of smoking cessation medications. ECs, which combine sensorimotor replacement with nicotine delivered contingent on the sensorimotor input, seem by far the most promising of the three approaches.

ACKNOWLEDGEMENT

Declared none.

CONFLICT OF INTEREST

Declared none.

REFERENCES

[1] Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2008; CD000146(1). Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000146.pub3/full. [cited: 3rd Oct 2011].

[2] Rose J. Nicotine and nonnicotine factors in cigarette addiction. Psychopharmacology 2006; 184: 274-85.

[3] Rose JE, Levin ED. Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. Br J Addict 1991; 86: 605-9.

[4] Rose JE, Tashkin DP, Ertle A, Zinser MC, Lafer R. Sensory blockade of smoking satisfaction. Pharmacol Biochem Behav 1985; 23: 289-93.

[5] Rose JE, Behm FM, Westman EC, Johnson M. Dissociating nicotine and nonnicotine components of cigarette smoking. Pharmacol Biochem Behav 2000; 67:71-81.

[6] Rose JE, Behm FM, Westman EC, Bates JE, Salley A. Pharmacologic and sensorimotor components of satiation in cigarette smoking. Pharmacol Biochem Behav 2003; 76: 243-50.

[7] Westman EC, Behm FM, Rose JE. Dissociating the nicotine and airway sensory effects of smoking. Pharmacol Biochem Behav 1996; 53: 309-15.

[8] Hajek P, Jarvis MJ, Belcher M, Sutherland G, Feyerabend C. Effect of smoke-free cigarettes on 24 h cigarette withdrawal: a double-blind placebo-controlled study. Psychopharmacology 1989; 97: 99-102.

[9] Schneider NG, Olmstead R, Nilsson F, Mody FV, Franzon M, Doan K. Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial. Addiction 1996; 91: 1293-306.

[10] Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. Arch Intern Med 1999; 159: 2033-8.

[11] Westman EC, Behm FM, Rose JE. Airway sensory replacement as a treatment for smoking cessation. Drug Dev Res 1996; 38: 257-62.

[12] Rose JE, Hickman CS. Citric acid aerosol as a potential smoking cessation aid. Chest 1987; 92: 1005-8.

[13] Levin ED, Rose JE, Behm F. Development of a citric acid aerosol as a smoking cessation aid. Drug Alcohol Depend 1990; 25: 273-9.

[14] Behm FM, Schur C, Levin ED, Tashkin DP, Rose JE. Clinical evaluation of a citric acid inhaler for smoking cessation. Drug Alcohol Depend 1993; 31: 131-8.

[15] Westman EC, Behm FM, Rose JE. Airway sensory replacement combined with nicotine replacement for smoking cessation. Chest 1995; 107: 1358-64.

[16] Shiffman SM, Jarvik ME. Smoking withdrawal symptoms in two weeks of abstinence. Psychopharmacology 1976; 50: 35-9.

[17] Levin ED, Behm F, Carnahan E, LeClair R, Shipley R, Rose JE. Clinical trials using ascorbic acid aerosol to aid smoking cessation. Drug Alcohol Depend1993; 33: 211-23.

[18] Rose JE, Behm FM. Inhalation of vapor from black pepper extract reduces smoking withdrawal symptoms. Drug Alcohol Depend 1994; 34: 225-9.

[19] Caponnetto P, Cibella F, Mancuso S, Campagna D, Arcidiacono G, Polosa R. Effect of a nicotine free inhalator as part of a smoking cessation program. Eur Respir J 2011; 38: 1005-11.

[20] Glover ED, Nilsson F, Westin A, Glover PN, Laflin MT, Persson B. Developmental history of the Glover-Nilsson smoking behavioral questionnaire. Am J Health Behav 2005; 29: 443-55.

[21] Kozlowski LT, Mehta NY, Sweeney CT, *et al.* Filter ventilation and nicotine content of tobacco in cigarettes from Canada, the United Kingdom, and the United States. Tob Control 1998; 7: 369-75.

[22] Tiffany ST, Drobes DJ. The development and initial validation of a questionnaire on smoking urges. Br J Addict 1991; 86:1467-76.

[23] Brauer LH, Behm FM, Lane JD, Westman EC, Perkins C, Rose JE. Individual differences in smoking reward from de-nicotinized cigarettes. Nicotine Tob Res 2001; 3: 101-9.

[24] Hasenfratz M, Baldinger B, Battig K. Nicotine or tar titration in cigarette smoking behavior? Psychopharmacology 1993; 112: 253-8.

[25] Butschky MF, Bailey D, Henningfield JE, Pickworth WB. Smoking without nicotine delivery decreases withdrawal in 12-hour abstinent smokers. Pharmacol Biochem Behav1995; 50: 91-6.

[26] Rose JE, Behm FM, Westman EC, *et al.* Combined effects of nicotine and mecamylamine in attenuating smoking satisfaction. Exp Clin Psychopharmacol 1994; 2: 328-44.

[27] Baldinger B, Hasenfratz M, Battig K. Switching to ultralow nicotine cigarettes: Effects of different tar yields and blocking of olfactory cues. Pharmacol Biochem Behav1995; 50: 233-9.

[28] Baldinger B, Hasenfratz M, Battig K. Effects of smoking abstinence and nicotine abstinence on heart rate, activity and cigarette craving under field conditions. Hum Psychopharmacol Clin 1995; 10: 127-36.

[29] Gross J, Lee J, Stitzer ML. Nicotine-containing *vs* de-nicotinized cigarettes: effects on craving and withdrawal. Pharmacol Biochem Behav 1997; 57: 159-65.

[30] Pickworth WB, Nelson RA, Rohrer MS, Fant RV, Henningfield JE. Pharmacodynamic effects of new de-nicotinized cigarettes. Nicotine Tob Res 1999; 1: 357-64.

[31] Breland AB, Buchhalter AR, Evans SE, Eissenberg T. Evaluating acute effects of potential reduced-exposure products for smokers: clinical laboratory methodology. Nicotine Tob Res 2002; 4(Suppl. 2): S131-40.

[32] Buchhalter AR, Schrinel L, Eissenberg T. Withdrawal-suppressing effects of a novel smoking system: comparison with own brand, not own brand, and de-nicotinized cigarettes. Nicotine Tob Res 2001; 3: 111-8.

[33] Dallery J, Houtsmuller E, Pickworth W, Stitzer M. Effects of cigarette nicotine content and smoking pace on subsequent craving and smoking. Psychopharmacology 2003; 165: 172-80.

[34] Rose JE, Behm FM. Effects of low nicotine content cigarettes on smoke intake. Nicotine Tob Res 2004; 6: 309-19.

[35] Eid NC, Fant RV, Moolchan ET, Pickworth WB. Placebo cigarettes in a spaced smoking paradigm. Pharmacol Biochem Behav 2005; 81: 158-64.

[36] Buchhalter AR, Acosta MC, Evans SE, Breland AB, Eissenberg T. Tobacco abstinence symptom suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. Addiction 2005; 100: 550-9.

[37] Juliano LM, Donny EC, Houtsmuller EJ, Stitzer ML. Experimental evidence for a causal relationship between smoking lapse and relapse. J Abnorm Psychol 2006; 115: 166-73.

[38] Donny EC, Houtsmuller E, Stitzer ML. Smoking in the absence of nicotine: behavioral, subjective and physiological effects over 11 days. Addiction 2007; 102: 324-34.

[39] Brody AL, Mandelkern MA, Olmstead RE, *et al.* Ventral striatal dopamine release in response to smoking a regular *vs* a denicotinized cigarette. Neuropsychopharmacology 2009; 34: 282-9.

[40] Cobb CO, Weaver MF, Eissenberg T. Evaluating the acute effects of oral, non-combustible potential reduced exposure products marketed to smokers. Tob Control 2010; 19: 367-73.

[41] Perkins KA, Karelitz JL, Conklin CA, Sayette MA, Giedgowd GE. Acute negative affect relief from smoking depends on the affect situation and measure but not on nicotine. Biol Psychiatry 2010; 67: 707-14.

[42] Barrett SP. The effects of nicotine, denicotinized tobacco, and nicotine-containing tobacco on cigarette craving, withdrawal, and self-administration in male and female smokers. Behav Pharmacol 2010; 21: 144-52.

[43] Lane JD, Lefebvre JC, Rose JE, Keefe FJ. Effects of cigarette smoking on perception of thermal pain. Exp Clin Psychopharmacol1995; 3:140-7.

[44] Rose JE, Salley A, Behm FM, Bates JE, Westman EC. Reinforcing effects of nicotine and non-nicotine components of cigarette smoke. Psychopharmacology 2010; 210: 1-12.

[45] Rose JE, Behm FM, Westman EC, Kukovich P. Precessation treatment with nicotine skin patch facilitates smoking cessation. Nicotine Tob Res 2006; 8: 89-101.

[46] Rezaishiraz H, Hyland A, Mahoney MC, O'Connor RJ, Cummings KM. Treating smokers before the quit date: can nicotine patches and denicotinized cigarettes reduce cravings? Nicotine Tob Res 2007; 9: 1139-46.

[47] Becker KM, Rose JE, Albino AP. A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation. Nicotine Tob Res 2008; 10: 1139-48.

[48] Hatsukami DK, Kotlyar M, Hertsgaard LA, *et al.* Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. Addiction 2010; 105: 343-55.

[49] Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. Tob Control 2010; 19: 87-8.

[50] Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiol Biomarkers Prev 2010; 19: 1945-53.

[51] Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tob Control 2010; 19: 98-103.

[52] Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. Nicotine Tob Res 2012; Available from: http://ntr.oxfordjournals.org/content/early/2012/02/05/ntr.ntr316.abstract. [cited: 7th Feb 2012].

[53] Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. Addiction 2012; Available from: http://onlinelibrary.wiley.com/doi/10.1111/j.1360-0443.2012.03791.x/abstract. [cited: 7th Feb 2012].

[54] Etter JF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. Addiction 2011; 106: 2017-28.
[55] Etter JF. Electronic cigarettes: a survey of users. BMC Public Health 2010; 10: 231.
[56] Foulds J, Veldheer S, Berg A. Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives. Int J Clin Pract 2011; 65: 1037-42.
[57] Heavner KK, Dunworth J, Bergen PL, Nissen CM, Phillips CV. Electronic cigarettes (e-cigarettes) as potential tobacco harm reduction products: results of an online survey of e-cigarette user. Available from: tobaccoharmreduction.org/wpapers/011.htm. [cited: 22nd Oct 2010].
[58] Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, Russo C. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. BMC Public Health 2011; 11: 786.
[59] Ayers JW, Ribisl KM, Brownstein JS. Tracking the rise in popularity of electronic nicotine delivery systems (electronic cigarettes) using search query surveillance. Am J Prev Med 2011; 40: 448-53.
[60] West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction 2005; 100: 299-303.

Received: January 27, 2012 Revised: March 7, 2012 Accepted: March 22, 2012