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Effects of Nicotine-Free E-Cigarettes on Urges to Smoke and Cigarette Withdrawal Symptoms: A Randomised Cross-Over Study

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Abstract

Objective: Nicotine-free electronic cigarettes (EC) alleviate cigarette withdrawal symptoms in the short-term. This is likely due to mimicking sensations of smoking, but could be a simple distraction effect. To test this, effects of EC were compared to effects of a distraction tool (a stress ball; SB) on ratings of cigarette withdrawal symptoms following overnight abstinence and following a day of abstinence.

Method: Thirty-seven smokers (≥ 18 years; at least 10 cigarettes per day, smoking within an hour of waking) participated in a randomised cross-over trial, with two conditions (EC and SB) following overnight abstinence, on two separate days. Measures were completed in the morning and again in the evening following EC and SB use throughout the day while trying to abstain from smoking. The primary outcome was changes in urge-to-smoke (11-point scale) from baseline to 10-minutes after product use, following overnight abstinence; secondary outcomes included ratings of cigarette withdrawal symptoms after product use over 1 hour in the morning, and again in the evening following abstinence over the day.

Results: EC reduced urge-to-smoke to a greater extent than SB (p=0.012) [95% CI: 0.65-1.34]. Urge-to-smoke and withdrawal symptom ratings over the hour in the morning were significantly lower with EC (p<0.001 and p=0.002, respectively), but this effect diminished by the evening.

Conclusion: Nicotine free EC alleviated urges-to-smoke acutely, over and above a distraction effect. The effect however weakened over the day.

Introduction

Over 20 years ago, Rose and colleagues proposed that smoking cessation treatment may be improved if both the nicotine and sensory and behavioural components of smoking (e.g. sensations in the mouth and throat), were addressed simultaneously [1]. If these 'sensorimotor' factors could be replaced adequately, they may help to alleviate withdrawal discomfort [2]. To this end, the team developed and evaluated inhalers and aerosols containing substances that mimic some of the airway sensations of smoking, including citric [3-6] and ascorbic acid [7], and black pepper extract [8]. The effects of these products on withdrawal symptoms and smoking cessation were modest, short-lived, and inconsistent [9].

More robust effects have been reported with de-nicotinised cigarettes (DNC) [9]. These genetically modified tobacco cigarettes contain negligible amounts of nicotine, with no central effects when smoked [10]. They thus mimic a whole range of sensorimotor elements of smoking but without nicotine. Studies have reported some modest short-term effects of DNCs in smoking cessation [11-13] but progress has been slow. DNC also still provide some of the tobacco smoke constituents which may be reinforcing such as ammonia, monoamine oxidase inhibitors and acetaldehyde [14]. This makes it difficult to establish if any effects from the DNC result from the conditioned sensorimotor aspects of smoking or from pharmacological effects of these chemicals.

Electronic cigarettes (EC) provide a new opportunity to study effects of sensorimotor replacement (SMR) on cigarette withdrawal symptoms. EC are a tobacco-free, battery operated device which emits a vapour when puffed, and can be used with or without nicotine. EC have gained considerable popularity (and controversy) since their introduction to the market in 2006, and are used by smokers predominantly to stop or reduce their smoking [15]. Much of their appeal results from their ability to provide nicotine together with sensorimotor input.

There is now some evidence that the sensorimotor input from nicotine-free EC is sufficient to alleviate urges to smoke and some withdrawal symptoms acutely [16,17]. In one study, although the nicotine EC reduced desire to smoke to a greater extent than placebo EC over the course of an hour (2.6 vs. 1.8, p=0.006), these differences were only apparent after 25 minutes. When adjusted for multiple comparisons, the difference was no longer significant [16]. In another study [17], nicotine and placebo ECs were compared to a control condition in which participants were asked to hold an EC without puffing on it. There were no differences reported between the three groups from baseline to 5 minutes, but both the nicotine and placebo EC significantly reduced desire to smoke over 20 minutes compared to the control condition.

Although these studies suggest that SMR could assist smokers who are trying to quit, they did not control for distraction. It is possible that EC alleviates urges to smoke not because it triggers conditioned reinforcement, but simply because it distracts the users from their discomfort. Distraction techniques have been traditionally recommended to smokers as a strategy to alleviate urges to smoke [18].

The objectives of the current study were to examine the effect of EC compared to a behavioural distraction tool on: (1) ratings of cigarette withdrawal symptoms following overnight abstinence; (2) ratings of cigarette withdrawal symptoms following one day of abstinence to explore the role of habituation; and (3) product ratings and preferences.

Method

Design

In this cross-over study, participants took part in two conditions with a minimum of two days in between: nicotine-free EC and stress ball (SB) which comprised the behavioural-distraction control (order counterbalanced). The SB was chosen because it provided a behavioural activity that did not involve any sensorimotor stimulation akin to smoking. No previous data exist on their effects, but they have, along with other behavioural tools such as 'Tangles', previously been a part of self-help toolkits for smokers (e.g. the NHS 'QuitKit'). 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 and EC or SB use over the day). Participants were informed that the purpose of the study was to evaluate two different non-nicotine behavioural replacements to smoking.

Participants

Forty participants consented to take part in the study and were recruited from patients attending a Smokers' Clinic in London, via advertisements in London newspapers, and through advertisements in staff bulletins at Queen Mary University of London. Participants were eligible if they were aged 18 or over, smoked at least 10 cigarettes per day (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 nicotine replacement treatment (NRT).

Measures

At baseline, participants completed a questionnaire regarding demographics, health status, and tobacco dependence [19] and smoking history.

The primary outcome was the difference between EC and SB on change in urges to smoke from baseline (prior to product use) to 10 minutes post-product use, following overnight abstinence. Secondary outcomes were to compare EC and SB on (i) urges to smoke and other withdrawal symptoms over one hour, in the morning and evening, in participants who maintained abstinence from smoking during the day; (ii) urges to smoke and other withdrawal symptoms over one day; and (iii) product satisfaction and preferences.

Withdrawal symptoms (during the one hour controlled experiments) were measured by asking participants to rate on an 11-point scale (0 ["not at all"] to 10 ["extremely"]), how they felt "right now". Three items were adapted from the Minnesota Nicotine Withdrawal Scale [MNWS; 20]: irritability, restlessness, and difficulty concentrating, as in a previous study [16]. 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 [16].

Withdrawal symptoms experienced over the course of the day were measured with the Mood and Physical Symptoms Scale [MPSS; 21]. These items were rated on a 5-point scale. The MPSS also includes two items on a 6-point scale assessing frequency and strength of urges to smoke.

Frequency of product use was assessed by asking participants to record how often they used the product each hour throughout the day. One 'use' of the SB was defined as using the SB for a period of time where it was squeezed at least 15 times, and for EC, a period of time where at least five puffs were taken. Abstinence was verified with an end-expired carbon monoxide (CO) reading of <10 ppm, using a Bedfont CO monitor.

Product perceptions were measured with a questionnaire adapted from previous work [16,22,23]. Participants responded, on 5-point scales, with regards to how satisfying their product was in comparison to smoking their usual cigarettes; how helpful it was in enabling them to keep from smoking, how pleasant it was to use, and how embarrassing it was to use; 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. Open questions asked participants to list what they liked most and least about the products. Any adverse effects experienced were listed, and rated "weak", "moderate" or "strong". At the final session, participants also 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 quitting.

Products

The EC used in this study was the Smoker's Angel Halo Electronic Cigarette, purchased from an online retailer. This EC was chosen for its ease of use; the EC used 'cartomizers' (where the cartridge and atomizer are combined), enabling easy assembly. It closely resembled a conventional cigarette in size and appearance, with a white battery and orange coloured tip. Participants were provided with two fully charged batteries and two cartomizers ('traditional' (tobacco) flavour, 0% nicotine content) for use throughout the day.

SBs were purchased from an online retailer. They were standard round squeezable balls, 70 mm in diameter.

Procedures

Participants attended the study centre in the morning following overnight abstinence and in the evening of the same day, on two separate days, with a minimum of 2 days (maximum 14 days) in-between sessions. They were instructed to smoke as normal in between the two study days. Morning sessions were scheduled to begin at 9 AM, and evening at 5 pm, though timings were flexible (up to 30 minutes either side). On one of the days participants were given the SB to use, and the other day the EC. The order of conditions was counterbalanced and determined by a computer-generated randomisation list conducted by a researcher independent to the study. Blocked randomisation (in blocks of 10) was used, and participants were

sequentially allocated (via a concealed envelope) to receive the EC or SB condition first.

At the first morning session, participants were consented and baseline measures collected. Overnight abstinence was confirmed with a CO reading (cut-off point of 15 ppm [16,23]). Six participants had readings between 16 and 18 ppm at either morning session, and one participant had an average reading of 22.5 ppm 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 to the full sample analysed. Three participants reported smoking overnight or in the morning, and were rescheduled to another day.

During each morning and evening session, participants took part in a 1-hour controlled experiment. Ratings of withdrawal symptoms and urges to smoke were completed prior to product use (baseline). Participants were then given 5 minutes to use their allocated product. When using the EC, they were asked to use the device ad-lib but to take at least 5 puffs. In the SB condition, participants were asked to squeeze the ball ad-lib, but do so at least 15 times. Participants then rated withdrawal symptoms and urges at 5, 10, 30 and 60 minutes post-product use.

Upon leaving the study centre in the morning, participants were asked to use their allocated product throughout the day, to record their product use, and to abstain from smoking their usual cigarettes. Participants returned in the evening and repeated the 1-hour experiment. They also completed the MPSS and rated product perceptions and adverse effects. Abstinence throughout the day was verified with a CO reading (<10 ppm). At the final evening session, the product preference questionnaire was also completed; participants were paid £40 towards their travel expenses, and offered smoking cessation treatment.

All study procedures were conducted by the author (DP), and ran from May 2012 until October 2012. The study was approved by the National Research Ethics Service (Ref: 11/LO/1803) in England, UK.

Statistical analyses

A sample of 40 participants was required to provide 80% probability of detecting a difference of 1.6 (SD=2.6) between products, on change in urge to smoke from baseline to 10 minutes post-product use (primary outcome) on an 11-point scale (p=0.05, two-tailed). We estimated a reduction of 2.8 for the EC condition and 1.2 for the SB condition, based on the findings in a previous study [16].
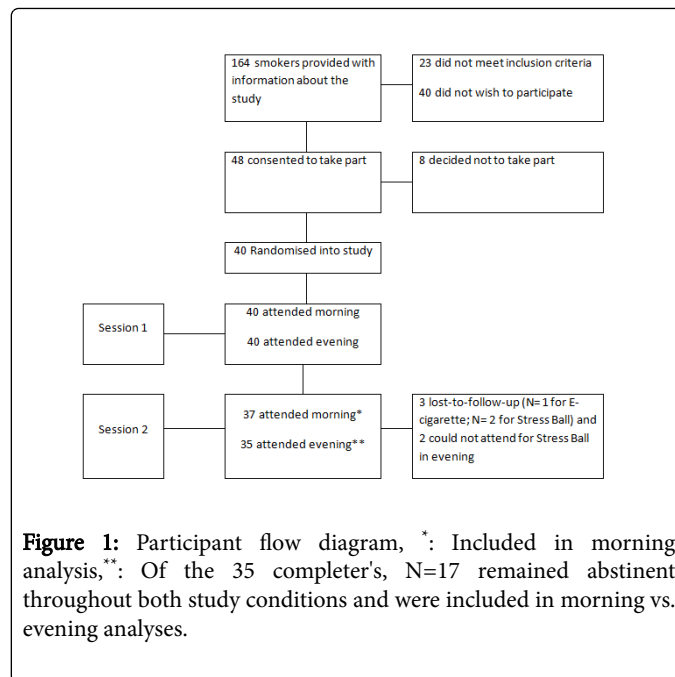
Figure 1: Participant flow diagram, *: Included in morning analysis, **: Of the 35 completer's, N=17 remained abstinent throughout both study conditions and were included in morning vs. evening analyses.

Changes in urge to smoke after overnight abstinence from baseline to 10 minutes were computed for each condition and compared using paired-samples t-test. A log transformation was used to correct for problems in distribution; all other data appeared normally distributed. Ratings of urges to smoke and composite withdrawal symptom ratings (i.e., irritability, restlessness, and difficulty concentrating, averaged) during the one-hour sessions, were entered into a repeated measures ANOVA (product x time) where time had 5 levels (baseline, 5, 10, 30 and 60 minutes). 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 baseline. All other continuous data were analysed with paired samples t-test, and categorical data with Chi-square tests. Composite MPSS and urge scores were calculated by averaging the ratings of the 5 withdrawal symptom (depressed, irritable, restless, hungry, difficulty concentrating) and the two urges-to-smoke ratings (intensity and frequency). For open questions, responses were categorised, and frequencies reported. Adverse effects were listed along with their strength. The McNemar test was used to examine differences in abstinence rates.

Analyses for the morning session were conducted on all participants as all were abstinent in the morning. Analyses assessing withdrawal symptoms over the day (MPSS scores) were conducted on both the whole sample, with abstinence entered as a co-variate, and on the subsample of participants who remained abstinent throughout both study days. Analysis of symptom ratings over the hour in the morning and evening was conducted on this sub-sample as well, to enable comparisons between the morning and evening effects. All participants were included when assessing product perceptions, user ratings and preferences. Analyses were conducted using SPSS v22.

Results

Participant characteristics

Baseline demographic and smoking characteristics are listed in Table 1. The flow of participants throughout the study is shown in Figure 1. Three participants were lost-to-follow-up and did not attend the second session at all (N=1 for EC, N=2 for SB), and two participants who attended the second morning session could not attend the second evening session (both during the SB condition) due to unforeseen circumstances. A total of 37 participants provided complete data for the morning analysis. A total of 17 participants remained abstinent over both study days and provided data for the analysis of differences between the morning and evening effects.

Demographics and baseline characteristics	N=37
Male (%)	64.9
Caucasian (%)	67.6
In full time employment (%)	56.8
With higher education (%)	59.5
Age (Mean [SD])	41.2 [15.1]
CPD* (Mean [SD])	19.5 [7.9]
FTND** (Mean [SD])	5.8 [2.2]

Table 1: Participant characteristics, *: Cigarettes per day **: Fagerstrom test of nicotine dependence.

Acute effects of EC and SB after overnight abstinence

For the primary outcome (change in urge to smoke from baseline to 10 minutes following overnight abstinence), the effect of the EC was over twice as strong as the SB: the EC reduced urge-to-smoke by 1.32 units vs. 0.62 with the SB (p=0.012).

Figure 2 shows the mean urge-to-smoke and withdrawal ratings over the hour in the morning. The repeated measures ANOVA showed a significant effect of Product (p=0.001), Time (p<0.001), and a significant Product x Time interaction for urges to smoke (p=0.009; see Table 2). Contrasts comparing each time point to baseline, revealed a significantly greater reduction in urges to smoke for the EC vs. SB at 10 minutes only (F [1,36]=15.57, p=0.032)

For composite withdrawal scores, there was also a significant main effect of Product indicating that withdrawal symptoms were significantly lower in the EC condition (p=0.002) and a significant main effect of Time, (p<0.001) with reductions from baseline evident at 5 and 10 minutes post-product use. There were no significant interactions between Product and Time (Table 2).

Session	Product	Time	Product x Time
Morning (N=37)	F (df), p value		
Urge to smoke	12.46 (1, 36) p=0.001	20.20 (3.15, 113.20) p<0.001	20.20 (2.75, 99.13) p=0.009
Composite withdrawal	11.39 (1, 36) p=0.002	10.30 (4, 77.45) p<0.001	2.23 (4, 33) p=0.087

Morning (N=17)*			
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
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 (N=17)*			
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
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

Repeated measures ANOVA analyses with Product [E-cig vs. Stress Ball] x Time [5 levels: baseline, 5, 10, 30 and 60 minutes]. Items were rated on 11-point scale: 0(not at all) to 10(extremely)

*Analyses include only those participants who abstained from smoking over both study days

Table 2: Summary of ANOVA analyses for urge-to-smoke and withdrawal ratings over 1 hour.
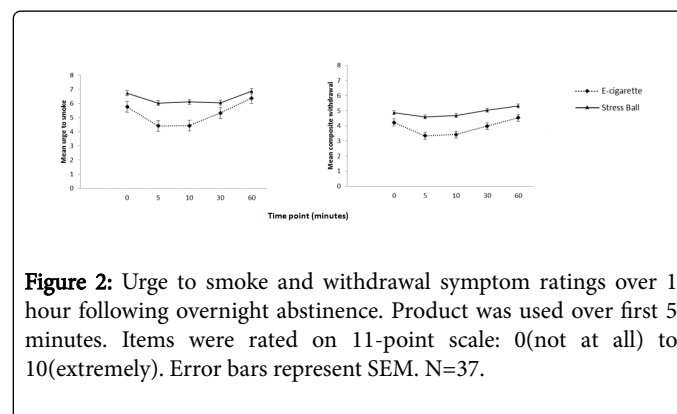
Figure 2: Urge to smoke and withdrawal symptom ratings over 1 hour following overnight abstinence. Product was used over first 5 minutes. Items were rated on 11-point scale: 0(not at all) to 10(extremely). Error bars represent SEM. N=37.

Effects of EC and SB over 1 hour in the morning and evening

Twenty-four of the 37 participants (65%) maintained abstinence during the EC condition while 21 (56%), were abstinent during SB condition (ns). To examine the effects of the products in the morning vs. evening sessions, we included participants who maintained abstinence from smoking throughout the day in both conditions (N=17). Figure 3 shows the mean urge-to-smoke and withdrawal ratings over the hour in the morning and evening, and Table 2 provides a summary of the ANOVA analyses. In this subsample, over the course of the hour in the morning, both urges to smoke (p<0.001) and withdrawal symptoms (p=0.002) were lower with EC than SB. There was also a significant main effect of time in the morning (urge to smoke p<0.001; withdrawal: p=0.010), with reductions from baseline evident at 5 and 10 minutes post-product use. There were no significant interactions between product and time. During the evening session, ratings were comparable between products. There was a significant effect of time on urge to smoke (p=0.002), where urges decreased slightly early on in both conditions, but other withdrawal symptoms remained stable over the hour.

Withdrawal symptoms during the day

Participants reported moderate levels of withdrawal discomfort over the course of the day (Table 3).

	Abstainers (N=17)				Whole sample (N=37)*			
	EC	SB	Mean difference (EC-SB)	Sig (95%CI)	EC	SB	Mean difference (EC-SB)	Sig (95%CI)
	Mean (SD)				Mean (SD)			
MPSS score**	2.52 (0.76)	2.51 (0.68)	0.01	0.933 (-0.28-0.31)	2.37 (0.78)	2.46 (0.77)	-0.09	0.149 (-0.27- 0.09)
Urge to smoke	3.26 (0.71)	3.65 (1.14)	-0.39	0.038 (-0.74- -0.02)	3.28 (0.89)	3.82 (1.68)	-0.54	0.001 (-0.81- -0.27)
Urge to smoke strength	3.18 (0.81)	3.59 (1.18)	-0.41	0.052 (-0.82-0.01)	3.19 (0.91)	3.78 (1.21)	-0.59	<0.001 (-0.87- -0.32)
Urge to smoke frequency	3.35 (1.00)	3.71 (1.21)	-0.36	0.109 (-0.80- 0.09)	3.38 (1.06)	3.86 (1.25)	-0.48	0.015 (-0.84- -0.14)

Table 3: Rating of withdrawal symptoms and urges to smoke experienced over the day, *N=2 did not attend evening session and gave responses via telephone, **Mood and Physical Symptoms Scale: 5 items (depressed, irritable, restless, hungry, poor concentration) rated on 5-point scale, Urge to smoke: Frequency and strength rated on 6-point scale.

In those who abstained, composite withdrawal scores, and individual MPSS items, were comparable between the conditions. When individual urge-to-smoke items were analysed, participants experienced the same frequency of urges to smoke in both conditions, but the strength of these urges tended to be lower with EC (p=0.052). Composite urge-to-smoke score was significantly lower in the EC condition (p=0.038). A similar pattern emerged when the whole sample was analysed with abstinence status (yes/no) included as a co-variate. However in this case, the differences between EC and SB in urge-to-smoke frequency and strength reached statistical significance (p=0.015 and <0.001, respectively).

Product perceptions, preferences, and adverse effects

Throughout the course of the day, EC were used more than SB (15.9 times [SD=1.5] vs. 10.2 times [SD=12.8] respectively, p=0.015). EC were rated as more satisfying and of more help in enabling participants to keep from smoking than SB, though satisfaction with EC compared to cigarettes was relatively low (see Table 4). EC were also seen as less embarrassing to use; participants felt more likely to use them as an aid to quitting in the future; and to recommend them to others who wanted to quit smoking. Ratings of pleasantness were similar for the two products. When participants were asked to choose between the two, the majority favoured the EC (Table 4).

N=37†	EC	SB	Sig. (p)
Product ratings	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

Product Ratings: rated on a 5-point scale

Produce preferences: participants chose between EC and SB. *N=2 and **N=3 did not choose between the two products for these items, †Two participants who did not attend the evening session gave responses via telephone

Table 4: Mean product ratings and preferences.

Seven participants reported adverse effects from EC use. These were moderate throat irritation/sore throat (N=3); EC 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). Two participants reported strong pain in their hand from squeezing the SB.

Most participants liked EC because it replaced the sensations of smoking (N=17) though the taste was the least liked aspect (N=13). For SB, the majority of participants did not like anything about the product (N=17), and lack of craving relief was the least like aspect (N=9).

Discussion

We hypothesised that nicotine-free e-cigarette (EC), which provide some of the sensorimotor stimuli of smoking, would alleviate urges to smoke and withdrawal symptoms better than a stress ball (SB), which provides a distraction without mimicking sensations of smoking. The results supported this to some extent: following overnight abstinence, EC reduced urge to smoke acutely to a greater extent than SB, but this effect diminished by the evening. EC received consistently higher ratings than SB.

Despite advantages of EC over SB in the morning and during the day, by the evening, neither product had much effect. Notably, this appeared to be due to a diminished effect of EC, as opposed to any improvement with SB. The most likely explanation is that as the relevant sensory input is not accompanied by pharmacological reinforcement, its rewarding effects extinguish. This would support recent findings that nicotine EC has a greater effect on abstinence and smoking reduction than placebo EC [24]. Additionally, studies with DNCs have reported effects on craving alleviation in abstaining smokers after one [25] and four [26] days of DNC use. This could be in part due to the potentially reinforcing chemicals still present in DNCs, or it may be because DNCs provide sensorimotor input more proximal to smoking than EC.

The EC effect detected (mean reduction of 1.32) was smaller than in the previous study which found a mean reduction in urges to smoke of 2.8 [24]. In that study however, participants were blinded to EC nicotine content, and EC was used over the hour as opposed to 5 minutes in the present study. The two studies also used different EC brands.

The artificial nature of the experimental sessions may limit generalizability, but the use of products throughout the day served to mitigate this. Due to the time of study set-up, we used a first generation EC, and as such the findings from this study may also not generalise to 2nd/3rd generation devices which offer better quality sensorimotor input in terms of taste, flavour, and amount of visible vapour. We did not formally assess the sensory properties of the EC, so it is unclear whether the sensorimotor input from this EC was adequate or not, though taste was reported as the least liked aspect of the EC. However, the purpose here was to assess the theoretical assertion that any effects of SMR are indeed due to the sensorimotor input as opposed to simple distraction. Newer models would likely provide more proximal input to smoking, but, whether or not the level of sensorimotor input would indeed have an impact is a separate empirical question which requires testing. Other limitations of the study were the relatively small sample size, and short assessment time-frame; it is possible that extinction of the EC effect was transient, as it was not assessed at a later time.
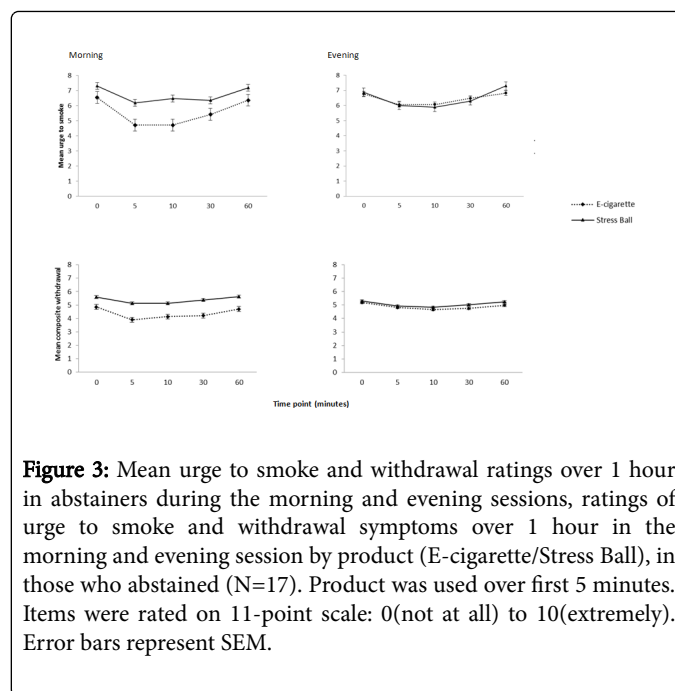
Figure 3: Mean urge to smoke and withdrawal ratings over 1 hour in abstainers during the morning and evening sessions, ratings of urge to smoke and withdrawal symptoms over 1 hour in the morning and evening session by product (E-cigarette/Stress Ball), in those who abstained (N=17). Product was used over first 5 minutes. Items were rated on 11-point scale: 0(not at all) to 10(extremely). Error bars represent SEM.

In conclusion, the experiment confirmed that SMR can acutely alleviate cigarette withdrawal symptoms above and beyond behavioural distraction. However, if effects of the EC do diminish quickly, as seen here, it is unlikely then that nicotine-free EC would have much value in smoking-cessation practice.

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