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The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition

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Abstract

Electronic cigarettes (e-cigarettes) are battery operated devices that deliver nicotine via inhaled vapour. Few studies have evaluated acute effects on craving and mood, and none have explored effects on cognition. This study aimed to explore the effects of the White Super e-cigarette on desire to smoke, nicotine withdrawal symptoms, attention and working memory. Eighty-six smokers were randomly allocated to either: 18mg nicotine e-cigarette (nicotine), 0mg e-cigarette (placebo), or just hold the e-cigarette (just hold) conditions. Participants rated their desire to smoke and withdrawal symptoms at baseline (T1), and five (T2) and twenty (T3) minutes after using the e-cigarette *ad libitum* for five minutes. A subset of participants completed the Letter Cancellation and Brown-Peterson Working Memory Tasks. After 20 minutes, compared with the just hold group, desire to smoke and some aspects of nicotine withdrawal were significantly reduced in the nicotine and placebo group; the nicotine e-cigarette was superior to placebo in males but not in females. The nicotine e-cigarette also improved working memory performance compared with placebo at the longer interference intervals. There was no effect of nicotine on Letter Cancellation performance. To conclude, the White Super e-cigarette alleviated desire to smoke and withdrawal symptoms 20 minutes after use although the nicotine content was more important for males. This study also demonstrated for the first time that the nicotine e-cigarette can enhance working memory performance. Further evaluation of the cognitive effects of the e-cigarette and its efficacy as a cessation tool is merited.

Key Words:

Electronic cigarette; nicotine; withdrawal symptoms; desire to smoke; memory; attention

1. Introduction

Electronic cigarettes (e-cigarettes) are battery-operated devices that deliver nicotine via inhaled vapour. Since no tobacco is burned, inhaling nicotine in this way potentially provides a safer alternative to smoking since it eliminates the harmful tars and carbon monoxide. E-cigarettes may therefore have a role to play in smoking cessation/ reduction. Although their efficacy in this respect has not been empirically explored, quit rates in the region of 22-49% are indicated in two recent studies (Polosa et al., 2011; Seigel, Tanwar & Wood, 2011).

Any possible effect on smoking cessation/reduction, however, is unlikely to occur unless e-cigarettes are satisfying to use, and can effectively reduce desire to smoke and withdrawal symptoms. Bullen et al. (2010) reported significant and comparable reductions in desire to smoke with the 16mg Ruyan e-cigarette and nicotine inhalator but both were less effective than regular smoking. A second study also reported reduced desire to smoke and some withdrawal symptoms although both e-cigarette brands tested failed to raise blood nicotine levels and heart rate over a 45 minute period (Vansickel, Cobb, Weaver, & Eissenberg, 2010).

That desire to smoke and withdrawal symptoms were reduced in the absence of raised blood nicotine levels is consistent with the notion that other sensorimotor factors contribute to its reinforcing effects. Several studies have demonstrated preference for smoking, reduced desire to smoke and withdrawal symptoms following the use of denicotinised tobacco (DT) (e.g. Rose, Behm, Westman & Johnson, 2010) particularly in females (Barrett, 2010).

In addition to the putative reinforcing effects of sensorimotor aspects of smoking, smokers often report that it aids concentration and cognition (McEwen, West & McRobbie, 2008; Hughes & Hatsukami, 1986) and there is empirical evidence to support this assertion (see review by Heishman,

Kleykamp & Singleton, 2010). Nevertheless, whether nicotine derived via e-cigarettes can impact on cognitive processes has not been explored.

The present study aimed to explore whether the e-cigarette can reduce desire to smoke and abstinence-related withdrawal symptoms over a twenty minute period. To determine whether the nicotine content itself rather than other sensory factors associated with smoking (e.g. visual cues, buccal sensations) are responsible for these effects, we compared the nicotine e-cigarette, placebo e-cigarette and a 'just hold' group (to control for visual and tactile aspects of handing, but not using the e-cigarette). It was hypothesised that after five minutes, desire to smoke and withdrawal symptoms would decline in both the nicotine and placebo conditions relative to the just hold condition (consistent with a sensorimotor explanation). After 20 minutes however, when nicotine reaches peak plasma levels (Bullen et al., 2010), it was predicted that the nicotine group would show a further reduction in symptoms relative to the 'just hold' and placebo groups. Given previous reports suggesting the importance of sensorimotor aspects of smoking in women (Barrett, 2010; Perkins, Donny & Caggiula, 1999) data were explored separately by gender. We also included two short cognitive tests (to tap attention/speed of processing and working memory) to explore whether nicotine derived via the e-cigarette is capable of enhancing cognitive functioning.

2. Methods

In this mixed experimental design, 86 e-cigarette naive smokers (43 female; age range: 18-52 [mean: 28.8]) were randomly allocated to either 18mg nicotine e-cigarette (nicotine), 0mg e-cigarette (placebo; nicotine and placebo conditions administered single-blind) or just hold the e-cigarette (just hold) condition. The 'White Super' electronic cigarette was used (devices and cartridges supplied by The Electronic Cigarette Company) with a new tobacco flavoured cartridge for each participant.

Following abstinence from smoking for at least one hour, participants completed The Fagerstrom Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström 1991), a single-item desire to smoke scale, and the Mood and Physical Symptoms Scale (MPSS; Hughes & Hatsukami, 1986; to assess six nicotine withdrawal symptoms: depression, irritability, anxiety, restlessness, hunger, poor concentration) at baseline (T1), five (T2) and twenty (T3) minutes after using (or just holding) the electronic cigarette *ad libitum* for five minutes. A subset of participants (N = 60; 29 females) also completed the Letter Cancellation Task and the Brown-Peterson Working Memory Task in the interval between T2 and T3.

The letter cancellation task was presented first. This provides a quick measure of attention/speed of processing and visual-spatial scanning ability (Eysenck & Keane, 2005). Participants are required to find a specific letter (e.g. 'u') and cross through each occurrence of it in a 18 X 18cm grid where it is presented amongst similarly-formed letters (e.g. 'v' and 'o'). Time taken and number of errors are recorded. In the Brown-Peterson Memory Task (Peterson & Peterson, 1959) participants are presented with a series of trigrams (consonants in sets of threes, e.g. TGH) and then asked to count backwards in threes from a specified number before recalling the trigram. The interference interval (counting backwards in serial threes) increased over six consecutive trials (3, 6, 9, 12, 15 and 18

seconds). For each trial, responses were scored as correct (all three letters correctly recalled) or incorrect (\leq two letters correctly recalled).

At the end of the testing procedure, participants were asked to indicate which cartridge they thought they had received (nicotine or placebo) before being informed of their group allocation. The study was approved by the University of East London's Ethical Committee.

2.1 Statistical analysis

The primary outcome measures of interest were change in desire to smoke and the six withdrawal symptoms between the three groups over time, thus univariate ANOVAs in SPSS were conducted on change scores from T1 to T2 and T1 to T3 (T1 minus T2 and T1 minus T3) for males and females separately. *A priori* contrasts explored the hypothesis that from T1 to T2 nicotine and placebo groups would differ from the just hold group but not from each other, and from T1 to T3, the nicotine group would differ from the just hold and placebo groups (Bullen et al., 2010). These specific contrasts between the three groups are of particular interest here although the main omnibus effect of group is reported where appropriate.

Letter cancellation time and errors were also analyzed using one-way ANOVA with Fisher's Least Significant Difference (LSD) *post-hoc* tests to clarify any group differences ($p < 0.05$).

To compare the number of participants between groups correctly recalling all three letters on the Brown-Peterson task, six 3x2 Chi Square tests were conducted (for all interference intervals) followed up by a series of 12 2x2 Chi Square tests for significant effects with a corrected alpha level of 0.004 (0.05/12) as a result of multiple tests. Since there was no *a priori* reason to suppose that

cognitive performance would be influenced by gender, letter cancellation or memory performance were not analyzed by gender.

3. Results

The three groups did not differ in age, gender, ethnicity or nicotine dependence ($p > 0.15$ in all cases). Mean FTND score was 5.2 (2.1). Guessing whether participants had received nicotine or placebo was at chance level: ($\chi^2 (2) = 1.11, p > 0.05$).

3.1 Desire to Smoke

Desire to smoke declined over time for both nicotine and placebo groups relative to the just hold group (Figure 1). This difference was statistically significant for males and females from T1 to T3 (males: just hold vs. nicotine: $p < 0.001$; just hold vs. placebo: $p < 0.05$; females: just hold vs. nicotine: $p < 0.05$; just hold vs. placebo $p < 0.01$) but not from T1 to T2 (males: $F (2,40) < 1, p > 0.05$; females: $F (2,40) = 1.44, p > 0.05$). The decline in desire to smoke was also significantly greater in the nicotine vs. placebo group for males ($p < 0.05$) but not females ($p > 0.05$; see Figure 1).

3.2 Mood and Physical Symptoms Scale (MPSS)

From T1 to T2 (see Table 2), overall main effects of group were only apparent for anxiety (females: $F (2, 40) = 3.66, p < 0.05$; males: $F (2, 38) = 3.05, p = 0.06$). Differences were significant for nicotine vs. just hold and placebo vs. just hold for males ($p < 0.05$) and for placebo vs. just hold for females ($p = 0.01$).

From T1 to T3 there were overall significant group differences for males in change in MPSS: anxiety ($F(2, 40) = 6.35, p < 0.01$), poor concentration ($F(2, 40) = 4.23, p < 0.05$), irritability ($F(2, 40) = 4.44, p < 0.05$) and restlessness ($F(2, 40) = 4.45, p < 0.05$). In all cases, the decline in symptoms in the nicotine group was significantly lower than the just hold (all $ps < 0.01$) and placebo (all $ps < 0.05$) groups.

The pattern of change in withdrawal symptoms from T1 to T3 for females indicated overall group differences for depression ($F(2, 40) = 4.80, p < 0.05$) and a trend for poor concentration ($F(2, 40) = 2.98, p = 0.06$). This reflected a greater reduction in symptoms in both the nicotine and placebo groups relative to the just hold group (all $p < 0.05$).

3.3 Letter Cancellation Task

Whilst the nicotine group were fastest to complete this task (mean = 63.70, SD = 13.87), followed by the just hold (mean = 64.95, SD = 13.58) and placebo group (mean = 71.05, SD = 13.93) these differences were not significant ($F(2, 57) = 2.00, p = 0.14$). There was a significant group difference in the number of errors made ($F(2, 57) = 3.34, p < 0.05$) reflecting worse performance in the just hold (mean = 1.25, SD = 1.48) vs. placebo group (mean = 0.25, SD = 0.44).

3.4 Brown-Peterson Memory Test

The nicotine group performed consistently better across all trials and retained better memory performance at the longer time intervals with significant group differences at 6 seconds ($\chi^2(2) = 7.06, p < 0.05$), 12 seconds ($\chi^2(2) = 6.06, p < 0.05$), 15 seconds ($\chi^2(2) = 11.31, p < 0.01$) and 18 seconds ($\chi^2(2) = 12.35, p < 0.01$). Significantly more individuals in the nicotine group achieved correct recall compared with placebo at the 15 and 18 second interval ($\chi^2(1) = 10.42, p < 0.004$; $\chi^2(1) = 8.12, p < 0.004$ respectively), and with the just hold group at the 18 second interval ($\chi^2(1) = 10.00, p < 0.004$).

4. Discussion

Desire to smoke and some aspects of nicotine withdrawal were significantly reduced twenty (but not five) minutes after e-cigarette use; the nicotine e-cigarette was superior to placebo in this respect in males but not in females. Nicotine derived via use of the electronic cigarette also improved working memory performance particularly at the longer interference intervals.

The desire to smoke findings are consistent with Bullen et al. (2010) who reported that nicotine blood concentrations reached a peak level of 1.3ng/ml in 20 minutes. In relation to withdrawal symptoms, for males, the reduction in MPSS ratings from T1 to T3 was significantly greater in the nicotine group for anxiety, poor concentration, irritability and restlessness. By contrast, there were no significant reductions in MPSS scores with nicotine in females. Females in both the nicotine and placebo groups did however, report improvements in depression and concentration from T1 to T3 relative to the just hold group, although this difference partly reflects an increased level of symptom reporting in the just hold group. One limitation of the present study was that participants were only 1-2 hours abstinent; reflected in the low MPSS scores. This low symptom reporting at baseline (T1) would however, militate against finding an effect of e-cigarette use/nicotine on symptoms measured here due to floor-effects. That significant findings still emerged (for males) is therefore all the more striking and suggests that a longer duration of abstinence may reveal more robust effects which may extend to females.

The distinct and consistent findings for males and females across symptom reporting resonates with the emerging literature on sex differences in smoking reinforcement (Barrett, 2010; Perkins et al., 1999) and the observation that, relative to females, males are more likely to succeed in quitting

using NRT (Perkins & Scott, 2008). Thus one might tentatively conclude that the nicotine content may be more important for males and the sensorimotor aspects of smoking more important for females. Cessation studies using the e-cigarette have yet to be completed but together these findings raise the intriguing possibility that females may be just as responsive to the placebo e-cigarette for quitting.

Performance on the letter cancellation task was not significantly influenced by e-cigarette use or the nicotine content specifically. By contrast, nicotine was associated with superior working memory performance. Recall was consistently higher in the nicotine group with significant differences emerging relative to placebo and just hold groups at the longer interference periods (15 and 18 seconds). The Brown-Peterson task has, however, been criticised for lack of ecological validity and the categorical nature of scoring which lends itself to non-parametric testing. Although this finding is consistent with a recent meta-analysis in which a significant positive effect of nicotine on working memory reaction time was observed (Heishman, Kleykamp and Singleton, 2010), it is clearly in need of replication.

4.1 Conclusions

Our findings suggest that the electronic cigarette can reduce desire to smoke and nicotine withdrawal symptoms twenty minutes after use and that the nicotine content may be more important for males. This is also the first study to demonstrate that the nicotine e-cigarette can improve working memory performance. Taken together these findings suggest that the electronic cigarette may aid smoking cessation and highlights the need for further research regarding the importance of the nicotine content and effects on a wider repertoire of cognitive functioning.

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Table 1: Mean (SD) change scores¹ for MPSS variables from T1 to T2 and T1 to T3 for the three groups for males and females

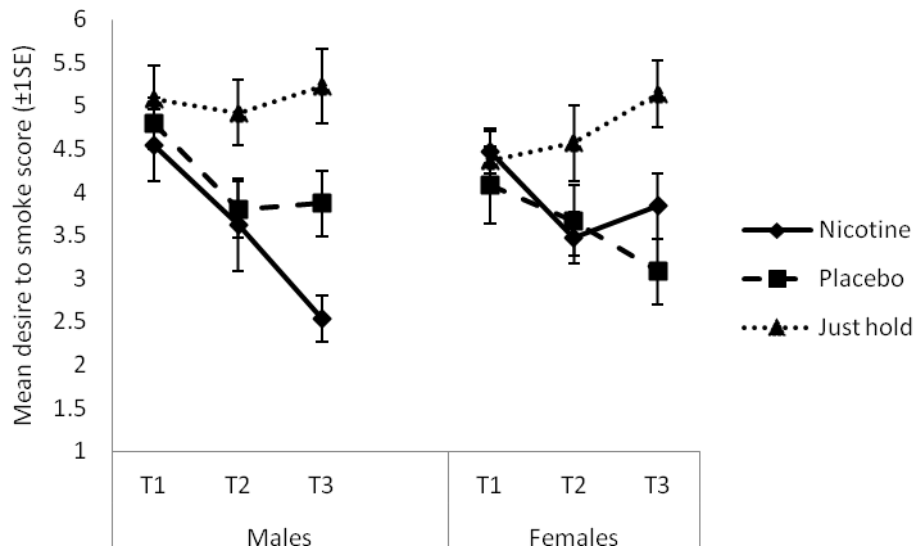
MPS	Nicotine		Placebo		Just Hold	
	T1-T2	T1-T3	T1-T2	T1-T3	T1-T2	T1-T3
<i>Males</i>						
Anxiety	0.62 (1.04) *	0.62 (0.96) **#	0.13 (0.52) *	0.67 (0.46)	-0.15 (0.80)	-0.31 (0.48)
Poor concentration	0.08 (1.85)	0.69 (1.18) **#	0.07 (0.80)	0.07 (0.70)	0.08 (0.64)	-0.23 (0.44)
Depression	0.15 (0.38)	0.08 (0.28)	0.13 (0.35)	0.13 (0.35)	-0.08 (0.28)	-0.08 (0.28)
Hunger	-0.13 (1.32)	-0.08 (0.76)	0.33 (0.62)	-0.07 (0.59)	0.46 (1.05)	0.31 (0.75)
Irritability	-0.08 (1.50)	0.62 (0.77) **#	0.27 (0.88)	0.33 (0.90)	0.08 (0.49)	-0.23 (0.44)
Restlessness	-0.08 (1.44)	0.62 (0.77) **#	0.13 (0.52)	0 (0.76)	0 (1.35)	-0.23 (0.73)
<i>Females</i>						
Anxiety	0.12 (0.60)	0.06 (0.83)	0.42 (0.79) *	0.33 (0.78)	-0.36 (0.84)	-0.14 (0.66)
Poor concentration	0.29 (0.92)	0.24 (1.09) *	-0.17 (0.72)	0.25 (0.45) *	-0.14 (0.66)	-0.50 (1.02)
Depression	0.12 (0.33)	0.12 (0.49) *	0.17 (0.58)	0.42 (0.67) *	-0.07 (0.47)	-0.29 (0.61)
Hunger	-0.18 (0.53)	-0.18 (0.63)	-0.17 (1.19)	-0.08 (0.79)	-0.14 (0.53)	-0.29 (0.73)
Irritability	0.06 (0.65)	0.06 (0.90)	-0.08 (1.38)	0.17 (0.72)	-0.07 (0.47)	-0.07 (0.62)
Restlessness	0.29 (0.99)	0.12 (1.36)	0 (1.48)	0.25 (0.97)	0.14 (0.66)	-0.36 (1.15)

¹ A positive score reflects a decrease in symptom reporting over time whilst a negative score reflects an increase

* Indicates significant difference from Just Hold (p < 0.05)

** Indicates significant difference from Just Hold (p < 0.01)

Indicates significant difference from placebo (p < 0.05)



Legend for Figure:

Figure 1: Mean ($\pm 1SE$) desire to smoke scores in males and females for the nicotine e-cigarette, placebo e-cigarette and just hold groups over the three time points.