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ARTICLE AVAILABLE ONLINE
Journal of **Smoking Cessation**

Nicotine Absorption From Seven Current Nicotine Replacement Products and a New Wide-Bore Nicotine Delivery Device

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This preliminary laboratory study investigated nicotine absorption rates of seven current nicotine replacement therapy (NRT) products and a new wide-bore nicotine delivery device (the 'Nicotine Cannon'). The nicotine products (Cannon, inhalator, nasal spray, microtab, 2 mg and 4 mg gum and 2 mg and 4 mg lozenge) were used for ten minutes by two non-nicotine tolerant subjects. Blood was taken at frequent intervals for the next 60 minutes and plasma nicotine concentrations assessed. Of current NRT products investigated the 4 mg lozenge performed best with the highest blood nicotine levels at each time point, the 2 mg gum delivered the lowest concentrations at each time point. The nicotine nasal spray delivered nicotine the fastest of all the products. The Cannon delivered the highest blood nicotine concentration (mean 8.95 ng/ml) of all products one minute after device use had stopped, and the highest concentration (11 ng/ml) five minutes after termination of use. The Cannon showed it could deliver nicotine relatively rapidly in a manner that was readily tolerated by users.

Keywords: nicotine absorption, NRT, Cannon

Tobacco use represents a considerable health hazard, but many smokers are unable to stop smoking without help. Among the many hurdles that smokers trying to quit have to overcome is the discomfort associated with tobacco withdrawal and the urges to smoke; in fact, in smokers attempting to quit, the experience of severe urges to smoke is predictive of relapse (Doherty, Kinnunen, Militello, & Garvey, 1995; West, Hajek, & Belcher, 1989). It has been observed that pure nicotine in the doses that smokers receive it is relatively safe, while the other constituents of tobacco smoke (tar and noxious gases) are primarily responsible for the health risks from smoking (Royal College of Physicians, 2000). Hence, pure nicotine delivery devices are used as an aid to smoking cessation and as a means of reducing withdrawal discomfort, and might potentially be used as a safer alternative to smoking. 'Nicotine replacement therapy' (NRT) refers to a group of medications that deliver therapeutic nicotine and are available as aids to smoking cessation that significantly increase abstinence rates (Silagy, Lancaster, Stead, Mant, & Fowler, 2004). A review in the United Kingdom by the National Institute of Health and Clinical Excellence (NICE) concluded that NRT products are among the most cost-effective life-saving interventions available to the healthcare system (NICE, 2000). NRT products are approved prescription medications for smoking cessation in many countries and, in some, are also available over the counter (OTC) and on general sale.

However, despite the success and cost-effectiveness of NRT, their efficacy remains relatively limited (Silagy et al., 2004) and there is a need for further improvements. There are many different forms of pure nicotine delivery available to smokers wanting to stop; these commonly include the nicotine transdermal patch, nicotine chewing gum, nicotine lozenge, nicotine nasal spray and nicotine sublingual tablet. Other forms of nicotine delivery have been developed but are not

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widely used; for example, the biphasic buccal adhesive tablet (Park & Munday, 2002) and oral-transmucosal nicotine (Muramoto, Ranger-Moore, & Leischow, 2003). All NRT products have strengths and weaknesses as delivery systems, but one major disadvantage they all share is that they deliver nicotine slowly relative to cigarettes. Nicotine from cigarette smoke is absorbed via the lungs and so reaches the brain within a few seconds of each puff (Royal College of Physicians, 2000). The slow rate of administration of nicotine from NRT, compared with that from cigarettes (Hukkanen, Jacob, & Benowitz, 2005) requires that individuals abstaining from smoking with the aid of NRT must use the products regularly throughout the day to maintain nicotine blood plasma levels. This is counterintuitive to smokers, who can respond to urges to smoke by having a cigarette, thus experiencing an almost instant reduction in these urges. Nicotine delivery devices that maximise peak nicotine blood plasma levels within the shortest possible time may increase medication compliance and improve abstinence rates.

Blood nicotine levels of 15–30 ng/ml have been measured within 8 minutes of smoking a cigarette (Armitage, Dollery, George, Houseman, Lewis, & Turner 1975; Benowitz, Porchet, Sheiner, & Jacob, 1988; Henningfield, Stapleton, Benowitz, Grayson, & London, 1993; Lunell, Molander, Ekberg, & Wahren, 2000; Rose, Behm, Westman, & Coleman, 1999; Russell, Jarvis, Iyer, & Feyerabend, 1980). A study of 190 treatment-seeking smokers found that the mean baseline blood nicotine level was 19.3 ng/ml; with a mean nicotine 'boost' of 10.9 ng/ml within three minutes of smoking a single cigarette (Patterson et al., 2003). A review of the pharmacokinetics and metabolism of nicotine (Hukkanen et al., 2005) did not allow for any direct comparisons to be made of nicotine absorption from different NRT products because the studies reviewed were independent of each other and used different subjects. The studies reviewed generally also suffered the limitation of varied length of abstinence for subjects prior to experimentation; plus heterogeneity in subjects' cigarette consumption, levels of dependence, age and ethnicity.

To our knowledge, no study has compared the nicotine absorption rates of current NRT products using the same procedures on the same non-nicotine tolerant individuals. It was also hypothesised that a new device (the 'Nicotine Cannon'), which aims to enable the user to ingest pure nicotine rapidly, would be more effective in delivering nicotine. If this were found to be the case, it would merit further study of this device with a view potentially to adding it to the range of products available for smokers.

Methods

Seven current NRT products and the Cannon were tested for rates of nicotine absorption up to 60 minutes after use. The Nicorette® inhalator, nasal spray and microtab (McNeill Healthcare UK, 2007) were tested alongside the NiQuitin® 2 mg and 4 mg lozenge (GlaxoSmithKline, 2005) and the Nicotinell® 2 mg and 4 mg gum (Novartis, 2007). The various forms of nicotine transdermal patch were not tested, as with these products peak blood plasma levels are generally not reached for 3 or 4 hours, or more (Hukkanen et al., 2005). The Cannon is a nicotine inhalation device consisting of a tube of approximately 3 cm in diameter and 4 cm in length capable of holding securely five removable nicotine cartridges, of the type used in the Nicorette® inhalator, and allowing air to be drawn through those cartridges so that nicotine vapour enters the mouth and upper airways. The dimensions of the device are important insofar as it needs to be wide enough to allow inhaled nicotine to pass into the upper airways. In this experiment, we tested the Cannon with one and with all five cartridges activated; one cartridge to compare it directly with the Nicorette® inhalator and five to see what the maximum nicotine absorption could be achieved with the device.

Two non-nicotine tolerant males tested the products with a minimum of 10 days in between laboratory tests. Subject 1 (first author, AMc) was 37 years of age, 175 cm tall and weighed 68 kg; subject 2 (second author, RW) was 46 years old, 180 cm tall and weighed 73 kg. Subject 1 had experimented with cigarette smoking during adolescence but had not smoked for 20 years; subject 2 had been a regular smoker but had also not smoked for 20 years. Approval for this study was sought from St George's University London Committee on Ethics.

This preliminary study took place in a laboratory setting with minimal external stimulus. Both subjects self-administered each NRT product according to the manufacturers' instructions for the same length of time (10 minutes). In the case of the Cannon and the inhalator the subjects inhaled as often as was comfortable (i.e., for the inhalator this exceeded the manufacturer's recommended dose). On one occasion (Cannon I) only one of the possible five nicotine cartridges was pierced, on another (Cannon II) all five cartridges were activated. For the Cannon and inhalator a tally was kept of inhalations (the number of inhalations for Cannon I was repeated for Cannon II), for the nasal spray a dose in each nostril was delivered once and the gum, microtab and lozenge were weighed before and after use.

A cannula was inserted into the subjects' median cubital vein and fixed to the arm. Blood was taken for measurement of nicotine at: baseline; halfway through administration (5 minutes); and at 1, 5, 10, 15, 30 and 60 minutes after administration of nicotine had ceased. The cannula was flushed with heparin to prevent clotting after each sample was taken and again with sterile water prior to the next sample. Ten millilitres (10 mls) of blood was collected in a test tube containing heparin at each time point. The blood tube was inverted four times and cen-

Table 1

NRT Product Usage (10 Minutes of Use)

	Subject 1	Subject 2	Mean
Nicorette inhalator			
Dose:	55 puffs	26 puffs	40.5 puffs
Cannon I (× 1)			
Dose:	44 puffs	38 puffs	41 puffs
Cannon II (× 5)			
Dose:	44 puffs	38 puffs	41 puffs
NiQuitin 2 mg lozenge			
Dose:	1 lozenge	1 lozenge	1 lozenge
Weight before use:	1.214g	1.197g	0.4405g
Weight after use:	0.53g	1.0g	
Amount used:	0.684g	0.197g	
NiQuitin 4 mg lozenge			
Dose:	1 lozenge	1 lozenge	1 lozenge
Weight before use:	1.2g	1.2g	0.62g
Weight after use:	0.66g	0.5g	
Amount used:	0.54g	0.7g	
Nicotinell 2 mg gum			
Dose:	1 piece	1 piece	1 piece
Weight before use:	0.99g	1.011g	0.0555g
Weight after use:	0.94g	0.95g	
Amount used:	0.05g	0.061g	
Nicotinell 4 mg gum			
Dose:	1 piece	1 piece	1 piece
Weight before use:	1.0g	1.0g	0.045g
Weight after use:	0.95g	0.96g	
Amount used:	0.05g	0.04g	
Nicorette nasal spray			
Dose	2 sprays	2 sprays	2 sprays

trifuged within 30 minutes of collection. Plasma was separated and placed into a labelled, sterile, plastic vial. All plasma samples were labelled and bagged separately before freezing, then shipped for analysis in insulated packaging. At all times blood and plasma samples remained clear of rooms that contained tobacco smoke and from contact with anyone who smoked or had touched a nicotine delivery device. Serum samples were analysed and measured for nicotine using capillary gas chromatography with a neurophysiologic detection limit of 0.1 ng/ml (Feyerabend & Russell, 1990). Individual and mean blood plasma nicotine levels are reported.

In addition, the subjects completed a 10-point rating scale on the presence of any of the following symptoms: nausea, throat irritation, dizziness, feeling unwell, pleasant feelings and agitation. These self-report ratings were made at the same intervals that blood was taken and were marked between 1 (*none*) and 10 (*extreme*).

In another laboratory test, five cartridges were used in the Cannon (Cannon III) but blood was taken at baseline and then 2, 4, 6, 8 and 10 minutes after start of administration and 1, 5 and 10 minutes after administration had stopped. This part of the experiment was conducted differently from the other parts to investigate in more detail the absorption rate of the Cannon.

Results

Subject 1 puffed more frequently than subject 2 on the inhalator and Cannon I and II, especially the inhalator. The consumptions of the oral products were more similar. Table 1 shows the mean product usage on each occasion and for each subject.

Of the current NRT products investigated the 4 mg lozenge performed the best with the highest blood nicotine levels at each time point, the 2 mg gum delivered the lowest concentrations at each time point. The Cannon II (using all five nicotine cartridges) delivered the highest blood nicotine concentrations (mean 8.95 ng/ml) of all the products one minute after the devices had stopped being used, and the highest level of all (mean 11 ng/ml) at five minutes postproduct use. The Cannon I yielded lower blood nicotine concentrations 5 minutes after start of product use than the 4 mg lozenge and the nasal spray, but higher than all the other products. It also yielded higher blood nicotine levels than all the other devices between 1 and 5 minutes after cessation of product use. The Cannon I (using just one nicotine cartridge) also consistently resulted in higher blood nicotine levels than the other products, notably the inhalator. Table 2 shows the mean blood nicotine levels for each

Table 2

Mean Blood Nicotine Levels (ng/ml)

	Time since baseline							
	Base-line	5 mins	11 mins	15 mins	20 mins	25 mins	40 mins	70 mins
Nicorette inhalator	0.15	0.6	2.25	2.75	2.6	2.5	2.2	1.95
Cannon I (× 1)	0.1	1.0	2.85	4.45	4.05	3.35	2.7	1.85
Cannon II (× 5)	0.1	0.75	8.95	11.0	7.4	6.85	5.4	3.9
NiQuitin 4 mg lozenge	0.1	1.45	6.65	7.3	7.3	6.1	5.3*	4.5
Nicotinell 4 mg gum	0.1	0.4	2.5	2.95	2.7	2.4	2.35	1.95
Nicorette nasal spray	0.15	3.25	3.3	3.5	3.25	3.05	2.65	1.95
NiQuitin 2 mg lozenge	0.15	0.7	1.5	2.0	2.15	2.2	1.95	1.7
Nicotinell 2 mg gum	0.2	0.1	1.25	0.8	1.85	1.6	1.7	1.0
Nicorette microtab	0.15	0.65	1.8	2.25	2.25	2.35	2.85	2.45

Table 3

Blood Nicotine Levels (ng/ml): Subject 1

	Time since baseline							
	Baseline	5 mins	11 mins	15 mins	20 mins	25 mins	40 mins	70 mins
Nicorette inhalator	0.1	1.0	2.9	3.1	2.7	2.0	1.6	1.1
Cannon I (× 1)	0.1†	1.4	5.5	5.5	4.3	3.9	2.8	1.8
Cannon II (× 5)	0.1†	1.2	11.3	12.5	6.7	5.8	4.4	2.9
NiQuitin 4 mg lozenge	0.1†	2.1	7.0	7.7	8.5	6.7	6.6	4.1
Nicotinell 4 mg gum	0.1†	0.6	3.8	4.0	3.1	2.3	1.9	1.3
Nicorette nasal spray	0.1	3.9	2.9	2.5	2.5	2.1	2.0	1.5
NiQuitin 2 mg lozenge	0.1	1.2	1.9	1.8	2.3	2.3	1.4	0.9
Nicotinell 2 mg gum	0.1	0.1	1.0	0.1*	1.5	1.5	1.8	0.8
Nicorette microtab	0.1†	0.7	1.8	2.8	2.3	2.2	2.7	1.9

Note: * sample haemolysed, so for calculation of mean the midpoint between previous and subsequent sample was used
† baseline sample < 0.01

product and Figure 1 represents these mean blood nicotine levels in graph form.

Tables 3 and 4 show the blood nicotine levels for subjects 1 and 2 respectively. In terms of product efficacy, the same general conclusions can be drawn from these individual blood nicotine levels as from the mean blood nicotine levels shown in Table 2. In terms of individual differences, it appears as though subject 1 was able to self-administer more nicotine from the inhalator and Cannon (I and II) than subject 2; while subject 2 had higher blood nicotine levels during and after using the nasal spray. Subject 1 achieved higher blood nicotine levels earlier than subject 2 with the inhalator and Cannon (I and II), but then subject 1's levels declined faster than those of subject 2. Blood nicotine levels across the time points for the other products were generally fairly well matched between subjects.

Subject symptom ratings for each product showed that throat irritation was the most common side effect experienced. There was only a small mean increase from baseline (< 2.0 rating points) in throat irritation for the inhalator, 2 mg lozenge and 2 mg gum; and this did not persist for more than 5 minutes after product use had ceased. Moderate increases from baseline (2.0 to < 3.0 rating points) in throat irritation were recorded for the 4 mg lozenge, 4 mg gum, nasal spray and Cannon I; and again these did not persist much after product use ceased. The microtab and Cannon II produced slightly

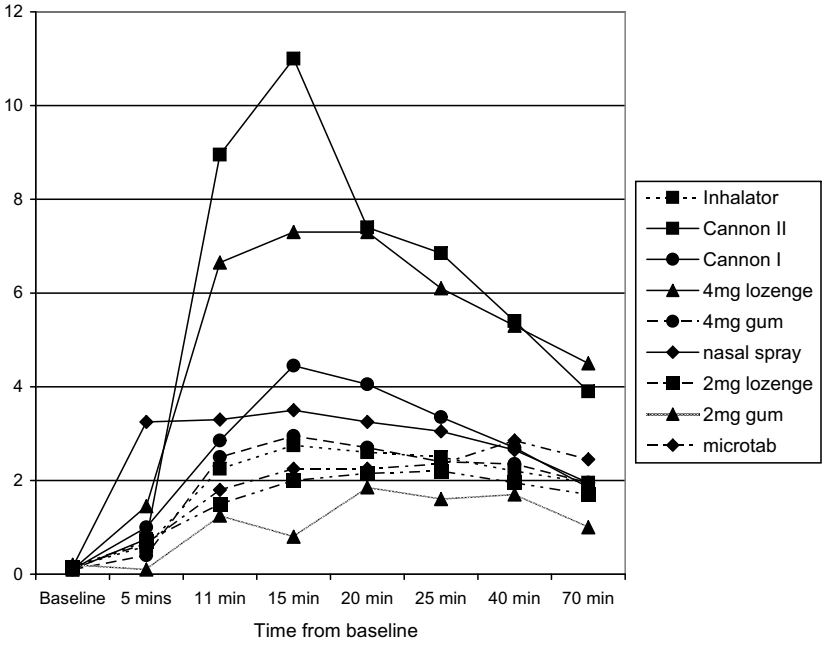

Figure 1

Mean blood nicotine levels (ng/ml).

Table 4

Blood Nicotine Levels (ng/ml): Subject 2

	Time since baseline							
	Baseline	5 mins	11 mins	15 mins	20 mins	25 mins	40 mins	70 mins
Nicorette inhalator	0.2	1.1	1.6	2.4	2.5	3.0	2.8	2.8
Cannon I (× 1)	0.1†	0.6	2.0	3.4	3.8	2.8	2.6	1.9
Cannon II (× 5)	0.1	2.0	6.6	8.5	8.1	7.9	6.4	5.1
NiQuitin 4 mg lozenge	0.1†	0.8	6.3	7.0	6.1	5.5	0.8*	4.9
Nicotinell 4 mg gum	0.1†	0.2	1.2	1.9	2.3	2.5	2.8	2.6
Nicorette nasal spray	0.2	2.6	3.7	4.5	4.1	4.0	3.3	2.4
NiQuitin 2 mg lozenge	0.2	0.2	1.1	2.0	2.0	2.1	2.5	2.5
Nicotinell 2 mg gum	0.3	0.1	1.4	1.5	2.2	1.7	1.6	1.2
Nicorette microtab	0.2	0.6	1.8	1.7	2.2	2.5	3.0	3.0

Note: * sample haemolysed, so for calculation of mean the mid-point between previous and subsequent sample was used
† baseline sample < 0.01

larger mean increases from baseline (3.0 to 4.5 rating points) of ratings of throat irritation than the other products; although for both, these effects did not remain for more than 10 minutes after product use ceased. Dizziness was also experienced by the subjects, although not for all products (i.e., 2 mg gum and microtab), and tended to still be present 15 minutes after product use stopped. Higher ratings for dizziness were recorded for Cannon I, Cannon II, 4 mg lozenge and nasal spray. The 4 mg lozenge was the only product to induce significant feelings of nausea. Subjects also rated the products for pleasant feeling. These feelings could persist for 15 minutes after product use had stopped and were greatest in Cannon I, Cannon II and nasal spray.

Table 5 and Figure 2 show the individual and mean blood nicotine levels for Cannon III (five nicotine cartridges were used) when blood was taken every 2 minutes during product use and three times to 10 minutes after use. In the 10-minute period of product use there were a mean of 53.5 puffs taken (57 for subject 1 and 50 for subject 2).

Discussion

Of current NRT products the 4 mg lozenge performed best with the highest blood nicotine levels at each time point, the 2 mg gum delivered the lowest results. The Cannon delivered higher mean blood nicotine levels than all products 1 minute after device use had stopped, and the highest mean level overall at 5 minutes post-product use; the hypothesis appears to have been at least partly proven. The nicotine nasal spray delivered nicotine the fastest of all the products.

The Cannon II produced higher mean blood nicotine levels than all the existing NRT products at each time point post-product use. The fact that the Cannon I (with one active nicotine cartridge) also produced higher mean blood nicotine levels than all the NRT products except for the 4 mg lozenge and, at 1 and 60 minutes post-product use, the nicotine nasal spray, suggests that the wide bore contributed to the improved nicotine delivery. Importantly, the Cannon I resulted in significantly higher mean blood nicotine levels than the nicotine inhalator at all time points, pre- and post-product use, except for 60 minutes after product use had stopped. The use of the inhalator was more intensive than the manufacturers recommend and thus the mean blood nicotine levels reported are likely to be higher than found in general use; however, the mean number of puffs on the inhalator and the Cannon (I and II) were almost identical. Subject 2 used the inhalator less than subject 1, but it is not known whether the volume of each puff was similar. Subject 1 achieved higher peak blood nicotine levels than subject 2 for the inhalator, Cannon I and Cannon II. Administration technique,

Table 5

Individual and Mean Blood Nicotine Levels (ng/ml) for the Cannon III

	During product use Time since baseline						After product use Time since baseline		
	Base-line	2 mins	4 mins	6 mins	8 mins	10 mins	11 min	15 mins	20 mins
Subject 1	0.1	0.2	1.4	3.8	6.2	7.5	14.7	13.4	11.6
Subject 2	0.1†	0.6	1.2	1.9	4.3	6.3	7.7	9.7	10.6
Mean	.1	.4	1.3	2.85	5.25	6.9	11.2	11.55	11.2

Note: † baseline sample < 0.01

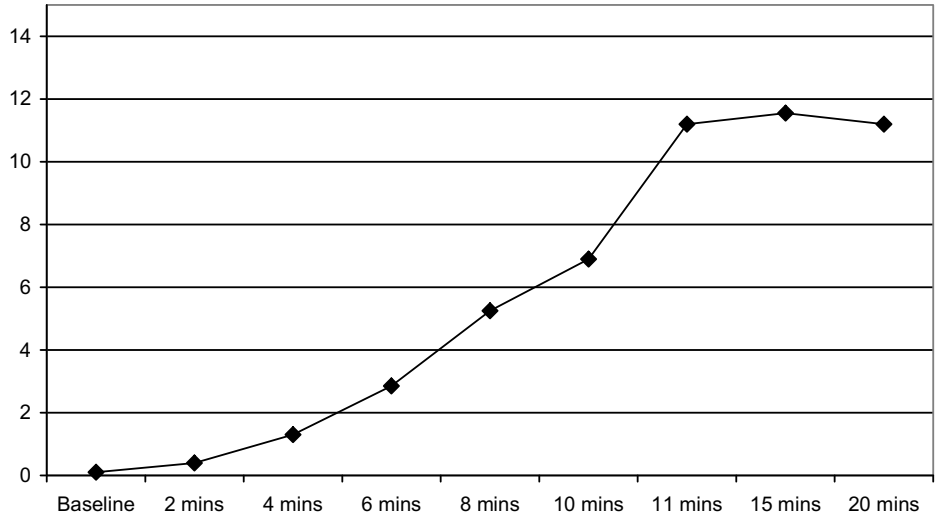

Figure 2

Mean blood nicotine levels (ng / ml) for the Cannon III.

which was not examined, could explain these differences, as it could for the higher levels achieved by subject 2 with the nasal spray. All of the other NRT products resulted in comparable nicotine absorption rates and levels, apart from the 2 mg gum, which resulted in the lowest mean blood nicotine levels at each time point.

Nicotine from the nasal spray was most rapidly absorbed (as judged by mean blood nicotine levels halfway, 5 minutes, into product use); although the levels did not rise much above this. The 4 mg lozenge, perhaps surprisingly, also produced relatively high mean blood levels 5 minutes into use and the levels continued to rise to 10 minutes after the end of product use, to more than double that of the nasal spray. The Cannon resulted in significantly lower blood nicotine levels in the first 5 minutes of use than the 4 mg lozenge and the nasal spray; although slightly higher levels compared with the other products. This perhaps suggests that the inhaled nicotine vapour was not reaching the upper respiratory tract as theorised, and that the high levels of blood nicotine produced by use of the Cannon were as a result of a large volume of nicotine vapour being deposited in the mouth. The mean blood nicotine levels from use of the Cannon III also suggest that this might be the case, tracing as they do a steady rise and peaking post-product use.

The Cannon I resulted in higher mean blood nicotine levels after 5 minutes of use than the Cannon II, surprising given the differences in dosage (one and five nicotine cartridges respectively), although this was the only time point at which this occurred. It is possible that with only one nicotine cartridge, puffing on the Cannon I was less irritant than the Cannon II and allowed for deeper inhalations in the first few minutes of use. It is also possible that use of the Cannon II on a previous date had inured the subjects to irritancy of the products, allowing for more intensive use of Cannon I. Certainly, the nicotine devices that resulted in the highest mean blood nicotine levels (Cannon I and II, 4 mg lozenge and nasal spray) also resulted in the highest mean ratings of aversive side effects; although in none of these cases were the symptoms severe enough to reduce, let alone cease, use of the products. These same devices also produced the highest mean ratings of a 'pleasant feeling'; except for the 4 mg lozenge, which was also alone in producing significant feelings of nausea.

Both the subjective self-ratings of symptoms associated with product use, and the mean nicotine blood levels reported, should be treated with some caution because the subjects used in this study were non-nicotine tolerant. The use of such subjects was felt to be important to reduce any physiological bias and to avoid using subjects in varying states of nicotine withdrawal; although this clearly limits the generalisability of the findings. Likewise does the fact there were only two subjects and clearly there would be merit in repeating this study with a larger number of subjects. Differences in product use, specifically with the inhalator and the 2 mg lozenge by these two subjects, clearly requires further investigation; such investigation should also consider examining puffing technique and measuring puff volume of the inhalator and Cannon and not just puff rate. A crossover design might be indicated in any future similar research as it is possible that subjects could, if not develop tolerance to nicotine, become accustomed to the unpleasant side effects of product use such that they use later products more intensively than earlier ones in the study timetable. In addition to repeating this laboratory study with an improved methodology and more subjects, it would also be worth considering using

smokers who abstain for 24 hours so as to assess the impact upon withdrawal symptoms.

Conclusion

This study is the first of its kind to compare the nicotine absorption rates of current NRT products using the same procedures on the same subjects. Of existing NRT products investigated, the 4 mg lozenge performed best, the 2 mg gum delivered the lowest blood nicotine levels. New nicotine products that result in relatively rapid and high blood nicotine levels could lead to greater medication compliance and improved abstinence rates. In this preliminary study, the Cannon showed it could deliver high doses of nicotine relatively rapidly in a manner that was readily tolerated by users and points the way to important future research.

Acknowledgments

We would like to thank Margaret Reuben for her assistance with this study and ABS Laboratories Ltd (www.abslabs.com) for conducting the assays. Andy McEwen and Robert West had the original idea for the study and were responsible for study design, collecting data, data analysis, and writing the paper. Robert West is guarantor for the study. Maria Gaiger was responsible for collecting the data and writing the paper.

This study was self-funded.

Competing Interests

Robert West and Andy McEwen have received research and travel funding from, and undertaken consultancy for, manufacturers of smoking cessation medications. Robert West and Andy McEwen have a commercial interest in the development of the nicotine Cannon.

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