

LETTERS

Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration

Electronic nicotine delivery devices (E-cigarettes) are marketed to deliver nicotine without tobacco toxicants and are sold in shopping malls and over the internet despite no published safety or efficacy data.^{1,2} These unregulated products consist of a battery, heater and cartridge containing a solution of nicotine, propylene glycol and other chemicals.³ Puffing activates the heater and the solution is vaporised and inhaled. Cartridges can be refilled using drops of solution sold in bottles labelled as containing over 500 mg nicotine, approximately 10 times the lethal dose. Some smokers emphasise the products' potential as a cessation aid,¹ while some public health advocates highlight possible health risks and uncertain effects.^{1,4} Because there are no published studies examining the products' nicotine delivery or subjective and cardiovascular effect profile, this study examined how two brands of electronic nicotine delivery devices (E-cigarettes) influence plasma nicotine levels, heart rate and cigarette craving in cigarette smokers, and compared these effects to those produced by smokers' usual brand of cigarettes.

METHODS

Using previously described methods,⁵ smokers in this institutional review board-approved clinical laboratory study ($n=16$; all naïve to electronic nicotine delivery devices (E-cigarettes): 5 women; 8 non-white; mean age=29.8 years, $SD=10.7$; mean cigarettes/day=18.5, $SD=2.2$) each provided informed consent and participated in 4 Latin-square ordered conditions (each separated by 48 h) that differed by product: own brand cigarettes, sham smoking (puffing an unlit cigarette), 'NPRO' (NJOY, Scottsdale, Arizona, USA) with a 16 mg nicotine cartridge, or 'Hydro' (Crown Seven, Scottsdale, Arizona, USA) with a 16 mg nicotine cartridge. Cartridge flavour (menthol or regular) was chosen to match participant's preferred cigarette flavour. A new cartridge (within its expiration date) and a fully charged battery were used for each session. Conditions were preceded by >12 h tobacco/nicotine abstinence (verified with expired air carbon monoxide <10 ppm) and began with forearm vein catheter insertion and continuous heart rate recording followed by subjective measures and blood sampling. Participants were instructed to puff normally and then puffed ad libitum 10 times (30-s inter-puff interval) from the product of the day (bout 1). At 5, 15, 30 and 45 min after the first puff, subjective measures were completed and blood sampled. At time +60 min assessments

were repeated, product was administered (bout 2), and identical subsequent assessments completed. Plasma nicotine levels were assayed and heart rate data were averaged as reported previously.⁵ Data were analysed using a condition \times bout \times time within-subject analysis of variance; The Tukey honestly significant difference test was used to explore mean differences ($p<0.05$).

RESULTS

For plasma nicotine and 'craving for a cigarette/nicotine', significant condition \times bout ($F(3, 45)>12.4$; $p<0.001$) and condition \times time ($F(12,180)>11.8$; $p<0.001$) interactions were observed (figure 1). Relative to before bout 1, own brand cigarettes increased plasma nicotine and decreased craving significantly at most post-administration timepoints ($ps<0.05$). Hydro and NPRO failed to increase nicotine levels significantly and NPRO decreased craving significantly 5 min after bout 2 only ($p<0.05$). Mean plasma nicotine

levels in the sham condition never were greater than 2.0. After bout 1, Own brand plasma nicotine level was significantly greater than either Hydro or NPRO at 5 (own mean=16.8 ng/ml, $SEM=3.4$; Hydro mean=2.5 ng/ml, $SEM=0.2$; NPRO mean=3.5 ng/ml, $SEM=0.5$), 15 (own mean=11.2 ng/ml, $SEM=1.6$; Hydro mean=2.3 ng/ml, $SEM=0.2$; NPRO mean=2.8 ng/ml, $SEM=0.3$) and 30 min (own mean=8.7 ng/ml, $SEM=1.2$; Hydro mean=2.2 ng/ml, $SEM=0.1$; NPRO mean=2.6 ng/ml, $SEM=0.2$), and also for bout 2 at 5 (own mean=20.0 ng/ml, $SEM=3.3$; Hydro mean=2.5 ng/ml, $SEM=0.3$; NPRO mean=3.0 ng/ml, $SEM=0.3$), 15 (own mean=15.4 ng/ml, $SEM=2.0$; Hydro mean=2.3 ng/ml, $SEM=0.2$; NPRO mean=3.1 ng/ml, $SEM=0.4$) and 30 min (own mean=12.9 ng/ml, $SEM=1.7$; Hydro mean=2.3 ng/ml, $SEM=0.1$; NPRO mean=2.9 ng/ml, $SEM=0.3$; all $ps<0.05$). For heart rate, a significant condition \times bout \times time interaction was observed ($F(12,180)=2.3$; $p<0.05$). Relative to before bout 1, significant increases

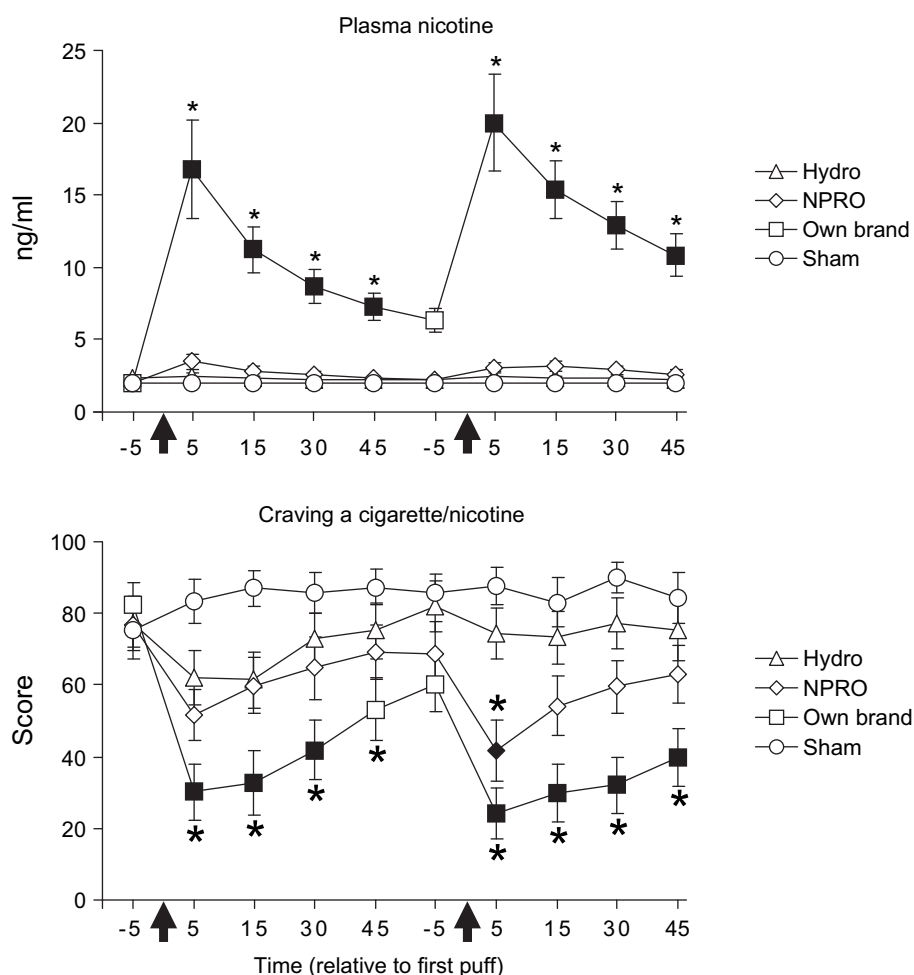


Figure 1 Mean (± 1 SEM) plasma nicotine (top panel; assay's limit of quantitation=2 ng/ml) and response to a visual analogue scale item assessing 'craving for a cigarette/nicotine' (bottom panel; 0–100 scale) from 16 cigarette smoking participants who each abstained from tobacco/nicotine for at least 12 h before completing each of the study's 4 conditions. Arrows indicate timing of product administration (each administration consisted of 10 puffs with a 30-s inter-puff interval). Filled symbols indicate a significant difference from the first assessment timepoint; asterisks (*) indicate a significant difference from sham smoking at each timepoint ($ps<0.05$; Tukey honestly significant difference test).

in heart rate were observed 5 and 15 min after bouts 1 and 2 for own brand only ($p < 0.05$).

DISCUSSION

Relative to a tobacco cigarette, 10 puffs from either of these electronic nicotine delivery devices (E-cigarettes) with a 16 mg nicotine cartridge delivered little to no nicotine and suppressed craving less effectively (see Bullen *et al.*).⁶ Importantly, these results were from two specific products tested under acute conditions in which puff number was controlled. Variability in product design may influence vapour content⁷ and chronic use and/or more intensive puffing (ie, more puffs, greater puff volume) may influence nicotine delivery. Given these and other factors, there is an ongoing need to evaluate electronic nicotine delivery devices (E-cigarettes). These evaluations should be conducted in a manner that takes into account variability in design (including cartridge nicotine content), examines the effects of user behaviour over time and compares these products to existing methods of delivering therapeutic nicotine safely and effectively. Taken together, the well known lethality of nicotine, variability in cartridge/vapour content,⁷ and the results reported here all support the notion that electronic nicotine delivery devices (E-cigarettes) and their nicotine-containing solution should be evaluated, regulated, labelled and packaged in a manner consistent with cartridge content and product effect. At the least, consumers should be aware that, unlike several regulated nicotine products

(eg, gum,⁸ patch⁹), these putative drug delivery systems do not deliver nicotine effectively after acute administration.

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