Nicotine absorption from e-cigarettes over 12 months

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Abstract

Background: Research indicates that, over time, exclusive e-cigarette users (vapers) gradually reduce the nicotine concentration in their e-liquid and transition to more sophisticated devices. Alongside this, consumption of e-liquid increases and constant cotinine levels are maintained. *Aims:* We aimed to confirm these observations in 27 experienced vapers tested at baseline and 12 months later, by measuring nicotine absorption (via salivary levels of the nicotine metabolite cotinine; ng/ml), nicotine concentrations in e-liquid (mg/mL), volume of e-liquid consumed (mL per day), device types and flavours used, both at baseline and 12 months. *Results:* Vapers reduced both their nicotine concentrations in e-liquid over 12 months (from 13.83 mg/mL at baseline to 9.91 at follow up) but significantly increased their e-liquid consumption (from 4.44 to 6.84 mL). No significant changes in salivary cotinine concentrations (370.88 ng/mL at baseline and 415.78 ng/mL at follow up) were observed. There was an increase in sub-ohming (using an atomiser coil with resistance of < 1 ohm with increased power) at 12 months, and in the use of fruit flavoured e-liquids. *Conclusions:* Our sample of experienced vapers reduced the concentration of nicotine in their e-liquid over time, but maintained their nicotine intake possibly through self-titration via more intensive puffing. Findings suggest there may be little benefit in reducing nicotine e-liquid concentration since this appears to result in higher e-liquid consumption which may incur both a financial and health cost. Gaining an understanding of underlying reasons for lowering e-liquid concentration would be a useful line of empirical enquiry.

Keywords: e-cigarettes, cotinine, nicotine absorption, vapers, nicotine concentrations, titration

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treatments. Lynne Dawkins has provided consultancy for the pharmaceutical industry (2015, 2017) and acted as an expert witness for an e-cigarette patent infringement case (2015).

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Highlights:

- Vapers reduced the nicotine in their e-liquid but maintained stable cotinine levels over 12 months
- This was accompanied by an increase in the amount of e-liquid consumed
- Findings suggest that vapers self-titrate when lowering their nicotine e-liquid concentration

1. Introduction

Electronic cigarettes (E-cigarettes,) are increasingly being recognised as a less harmful alternative to smoking and are documented as an effective tool in supporting those wishing to quit or reduce smoking (Brown et al, 2014; Zhu et al 2017; Hartmann-Boyce et al 2016). E-cigarettes come in a variety of shapes and sizes, with a choice of e-liquids, flavours and nicotine strengths (ranging from 0 to 20 mg/ml in the EU). E-cigarette users (vapers) may opt for, or switch to, lower nicotine e-liquids in the belief that it is healthier, and/or due to the upper limit (20mg/ml) imposed on the sale of e-liquids by the EU Tobacco Products Directive (TPD) in May 2016. Alternatively, this behaviour may be driven by technology advancement characterised by a recent trend to use lower electrical resistance atomisers which may not be compatible with higher nicotine concentrations. Indeed, research suggests that over time, vapers gradually reduce the nicotine concentration in their e-liquid (Lechner et al., 2015; Polosa et al, 2015) but at the same time move on to using more sophisticated vaping devices (Yingst et al., 2015), typically with higher power, multiple atomiser configuration and lower (< 1 ohm) atomiser resistance (known as sub-ohming). However, although vapers may perceive a reduction in nicotine concentration e-liquid as a move to reducing nicotine intake, this may not necessarily be the case. Etter (2015), for example reported that over an 8-month period, although exclusive vapers decreased the concentration of nicotine in their e-liquid, the amount of liquid consumed increased and salivary cotinine (a metabolite of nicotine) levels remained stable. As has shown to be the case with tobacco smoking (Ashton, Stepney, Thompson, & Rawbone, 1979; Ashton, Watson, Marsh, & Sadler, 1970; Kassel et al., 2007; Russell, 1980; Sutton, Russell, Iyer, Feyerabend, & Saloojee, 1982), it is likely that vapers self-titrated, by adjusting their puffing patterns to maintain their desired level of nicotine as we have shown previously (Dawkins et al, 2016).

We aimed to replicate Etter's (2015) study and to confirm these observations, over a slightly longer period (12 months), to determine whether exclusive vapers do indeed maintain their levels of nicotine intake even if nicotine e-liquid concentrations are reduced. We measured levels of the nicotine metabolite, cotinine, in saliva and collected self-report data on the concentration of nicotine e-liquid used (in mg/mL) and volume (in mL) of e-liquid consumed at baseline and follow up (12 month). In

addition to Etter's (2015) work, we also assessed what changes were made to e-cigarette devices (if any) and whether reported flavours changed over the 12-month period.

2. Methods:

Using a within-participants prospective design, with a baseline and a 12 month follow up point (between June 2015 and March 2017), 32 exclusive electronic cigarette users (i.e. did not also smoke or use nicotine in any other form) were recruited via social media (e.g. Twitter, Facebook) or were known to us from participation in other research studies. Participants were asked questions via email, concerning general demographic information, their e-cigarette use (e.g. what device they are currently using, strength of e-liquid (mg/ml), flavours) and provided a saliva sample (via post using a Salivette©) at the two-time points: baseline and after 12 months.

Saliva samples were frozen at -20 ^{o}C on receipt and subsequently sent to ABS Laboratories (Welwyn Garden City, UK) for cotinine analysis by gas chromatography. Participants who failed to respond following three reminders at the 12 months follow up were considered drop outs. Participants were excluded if they were smokers, non-English speaking, unable to communicate via email and under the age of 18. The University of East London's ethics committee approved the study.

2.1. Data analysis

To establish whether there was a significant change over time in cotinine levels, volume of liquid consumed (mL), and nicotine e-liquid concentration (mg/mL) paired-sample t-tests were conducted on data for both time points (baseline and 12 months follow up). Two participants failed to return cotinine saliva samples and 4 participants did not indicate daily e-liquid consumption (mL) at either one of the two timepoints. Data is therefore presented on all complete participant data. Bayesian analyses (Dienes, 2014) were conducted on all non-significant findings to establish the Bayes Factor (BF) to determine the strength of the 'no effect' (West, 2015).

Participants reported vaping a large range of flavours and reported details on individual device characteristics, these were subsequently categorised into 5

common categories of flavours (tobacco, mint/menthol, fruit, dessert/bakery and beverage) and tank type. Tank types consisted of 2nd generation devices (small pen-like open tank systems), 3rd generation (larger open tank systems usually with variable wattage/voltage) and 3rd generation devices with sub-ohm atomisers. Given the small sample size, and small numbers per cell, changes in data for these categorical variables (flavours and device type) across the two-time points have been presented and interpreted based on the descriptive data (n and %) only.

3. Results:

Of the 32 recruited at baseline, 3 reverted back to smoking, 1 withdrew, and 1 did not respond at 12 months follow up (84% follow up rate). Data is therefore presented on those participants who completed both the baseline and 12-month follow (n=27). Seventy percent of participants were male (n=19), the mean age was 43.81 (SD=9.19) years, 85% (n=23) were white British and 74% (n=20) in paid employment.

Vapers reported using an e-cigarette on average for 37.57 (SD=25.97) months prior to baseline assessment. At the 12-month follow up, 33% (n = 9) reported some level of sub-ohming, with 26% (n = 7) reporting daily sub-ohming. An additional question was included at the 12-month follow up to establish the PG/VG ratio of participants' e-liquid. Of the 17 who responded to this additional question 65% (n = 11) reported vaping 50/50 PG/VG e-liquid, 12%(n = 2) vaped predominantly PG based and 24% (n = 4) vaped predominantly VG based e-liquid.

Table 1 displays changes over time in usage patterns. Paired samples t-test indicated a significant reduction in the strength of e-liquid (mg/mL consumed over the 12 month period [$t(26) = 2.32$, $p = 0.03$ 95% *CI* [0.45,7.38] and a significant increase in daily e-liquid consumption (mL), [t(22) = -2.51, p = 0.02] 95% CI[-4.38,2.51]. Cotinine levels increased slightly over the 12 month period but this change was not statistically significant [t(24)=-1.21, p=0.24], [CI -121.76- 31.96]. The BF of 1 indicates that there is sufficient evidence to support no statistical difference between the two-time points.

Most vapers reported using a 3rd generation device and using a variety of flavours at both time points (baseline and 12 months; see table 1). There was an increase in

the number of reports of sub-ohming and use of fruit flavoured e-liquids after 12 months relative to baseline.

Table 1: E-cigarette usage patterns at baseline and after 12 months

	Baseline		**12 months**		
	Mean	**SD**	**Mean**	**SD**	***p***
Saliva Cotinine	370.88	230.90	415.78	242.50	0.240
Nicotine e-liquid concentration (mg/mL)	13.83	8.53	9.91	6.48	0.020
Daily liquid consumption (mL)	4.44	2.86	6.84	6.45	0.028
	N	**%**	**N**	**%**	
Device Type					
2nd Generation	1	3.7	2	7.4	
3rd Generation	17	63.0	13	48.1	
3rd Generation & Sub-ohming	8	29.6	11	44.4	
Frequency of flavours*:					
Tobacco	7	17.5	4	9	
Mint/Menthol	9	22.5	8	18.6	
Fruit	14	35.0	22	51.2	
Dessert/Bakery	5	12.5	5	11.6	
Beverages	0	0	2	4.7	
Others	5	12.5	2	4.7	
Total	40		43		

*participants could report more than one flavour so % is based on total flavours reported

Discussion:

In this prospective study of 27 vapers followed up over 12 months, self-reported nicotine concentrations in e-liquid declined significantly over time whilst volume of e-liquid consumed significantly increased. There was no change (and even a slight increase over time) in salivary cotinine levels. Consistent with Etter (2015), it therefore appears that whilst vapers reduce the nicotine concentration of their e-liquid, this has no effect on their nicotine intake since levels of nicotine absorption remain stable. This could possibly occur through a self-titration mechanism (e.g. increasing the volume of liquid consumed by altering puffing patterns in response to a change in nicotine exposure). These findings are in line with our previous work on compensatory puffing; in 11 experienced vapers tested in the lab, liquid consumption and puff number were higher, and puff duration longer, when using a low (6 mg/mL) compared with a high (24 mg/mL) nicotine concentration e-liquid (Dawkins et al, 2016).

In the present study, we have also documented changes in device types and e-liquid flavours consumed by vapers over a 12-month period. Reflecting current trends (as implied in EC online discussion forums), vapers in our sample reported moving to sub-ohming over time (44% at baseline v 30% at 12 months). We observed an increase in reports of the use of fruit flavoured e-liquids (35% to 51%) and a decrease in tobacco flavoured e-liquids (18% to 9%); a change which is consistent with national trends in e-cigarette flavours (ASH, 2017). Recent studies suggest that device type, PG/VG ratio , and flavours play a role in nicotine delivery (Farsalinos et al 2014; Kosmider at al 2018, St Helen et al 2017; Spindle et al. 2018) . Thus, changes to flavourings and device types including the subsequent increase in device power, may also contribute to more effective nicotine delivery helping to offset the effect of reducing nicotine concentration in the e-liquid. Changes in e-liquid flavours may also influence puffing topography due to palatability and varying pH, which may in turn affect nicotine absorption (St.Helen, et al, 2017).

There are several limitations of the current study. We acknowledge that the current study consists of a small size, however a strength is that we have followed all 27 vapers up over a 12 months period, with a low dropout rate from the initial sample (14%). All participants were experienced users (exclusive vapers who had been

using e-cigarettes on average 38 months) prior to commencing the study and were known to the researchers (but were not aware of the full aims of the study at baseline; these were only divulged at 12 months). In addition, at 12-month follow up users were vaping on average 6.84 mL of e-liquid per day, higher than most UK daily vapers at that time (≤ 4mls; ASH, 2017). Therefore, these findings may not be representative of the general population of current vapers. Additionally, device type may also be influential; we were only able to adopt a broad categorisation of device types (2nd generation, 3rd generation and 3rd generation sub-ohming) based on self-reported data, thus we haven't considered any changes in individual product type, e-cigarette manufacturer and atomiser resistance over the 12 months, which all could influence changes in nicotine delivery. Whilst our participants were all exclusive e-cigarette users, we have no record of former smoking status or when participants last used any other form of nicotine replacement therapy prior to providing the saliva sample, thus cotinine levels could be contaminated by other sources of nicotine. Finally, our sample solely relies on volunteers and data on their e-cigarette use was collated via questionnaires, thus aside saliva cotinine data we are reliant on self-report data, consistent with Etter (2015).

The current study has demonstrated that a reduction in nicotine e-liquid concentration (mg/mL) does not translate to a reduction in nicotine absorption, possibly because vapers engage in some form of compensatory puffing and changes in device characteristics resulting in the consumption of greater e-liquid volume. Therefore, any perceived health or addiction-reducing benefits may not be borne out. In fact, reducing nicotine e-liquid concentration may actually increase exposure to potentially harmful chemicals in e-cigarette aerosol albeit at much lower levels than those in tobacco cigarettes (Kosmider et al, 2017). These findings have implications for public health messaging regarding potential effects of reducing nicotine e-liquid concentration, and for policy makers regarding regulations around the nicotine concentrations of e-liquids.

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