Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users

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ABSTRACT

Introduction Electronic cigarettes' (e-cigarettes) viability as a public health strategy to end smoking will likely be determined by their ability to mimic the pharmacokinetic profile of a cigarette while also exposing users to significantly lower levels of harmful/potentially harmful constituents (HPHCs). The present study examined the nicotine delivery profile of third- (G3) versus second-generation (G2) e-cigarette devices and their users' exposure to nicotine and select HPHCs compared with cigarette smokers.

Methods 30 participants (10 smokers, 9 G2 and 11 G3 users) completed baseline questionnaires and provided exhaled carbon monoxide (eCO), saliva and urine samples. Following a 12-hour nicotine abstinence, G2 and G3 users completed a 2-hour vaping session (ie, 5 min, 10-puff bout followed by ad libitum puffing for 115 min). Blood samples, subjective effects, device characteristics and e-liquid consumption were assessed.

Results Smokers, G2 and G3 users had similar baseline levels of cotinine, but smokers had 4 and 7 times higher levels of eCO ($p<0.0001$) and total 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol (i.e., NNAL, $p<0.01$), respectively, than G2 or G3 users. Compared with G2s, G3 devices delivered significantly higher power to the atomiser, but G3 users vaped e-cigarette liquids with significantly lower nicotine concentrations. During the vaping session, G3 users achieved significantly higher plasma nicotine concentrations than G2 users following the first 10 puffs (17.5 vs 7.3 ng/mL, respectively) and at 25 and 40 min of ad libitum use. G3 users consumed significantly more e-liquid than G2 users. Vaping urges/withdrawal were reduced following 10 puffs, with no significant differences between device groups.

Discussion Under normal use conditions, both G2 and G3 devices deliver cigarette-like amounts of nicotine, but G3 devices matched the amount and speed of nicotine delivery of a conventional cigarette. Compared with cigarettes, G2 and G3 e-cigarettes resulted in significantly lower levels of exposure to a potent lung carcinogen and cardiovascular toxicant. These findings have significant implications for understanding the addiction potential of these devices and their viability/suitability as aids to smoking cessation.

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INTRODUCTION

While not harmless, electronic cigarettes (e-cigarettes) have demonstrated a much more favourable toxicological profile than combustible cigarettes—the worldwide leading cause of preventable death.[1 2] Their viability as a public health strategy to end the use of combustible cigarettes will likely be determined by their ability to decrease smokers' exposure to levels of harmful constituents as well as their ability to deliver nicotine efficiently and serve as a sufficient replacement for smoking.

Since their market emergence, e-cigarettes have evolved into devices with more efficient nicotine delivery.[3] First-generation devices (G1; ie, cig-a-likes) were found to have inefficient nicotine delivery, resulting in few smokers successfully achieving smoking abstinence.[3–8] Second-generation devices (G2; ie, eGO tank-style systems) were found to have more efficient nicotine delivery, resulting in a larger proportion, though not a majority of smokers, achieving smoking abstinence.[6 9 10] To date, no studies have systematically investigated the nicotine delivery profile of the latest third-generation devices (G3; ie, mechanical mods, rebuildable drip tanks, rebuildable atomisers, advanced personal vaporisers); however, they are often used by e-cigarette aficionados who report enhanced nicotine delivery beyond second-generation devices.[11] If e-cigarettes are to be a viable method of smoking cessation for a majority of smokers, it will likely be necessary that they achieve a similar amount and speed of nicotine delivery as a combustible cigarette (~15 ng/mL in 10–12 puffs).[4 5 12] To date, the results from several studies investigating the ability of second-generation devices to achieve cigarette-like levels of nicotine delivery have been mixed.[9 13–15] Moreover, these studies may have limited generalisability, as participants were often provided a standard e-cigarette and nicotine concentrations, did not use their own devices or e-liquid, and were not allowed to vape as they would normally (ad libitum).[13 14]

There are also concerns that newer e-cigarette products which deliver higher levels of nicotine[7] may deliver higher levels of harmful constituents.[8 9] Harmful tobacco-related constituents like N-Nitrosonornicotine ketone (NNK), often considered the most potent tobacco product ingredient responsible for lung cancer,[16] have been detected in e-cigarette aerosol,[17 18] but there has been little systematic exploration of how older versus newer

e-cigarette designs may also influence users' uptake of these types of harmful constituents. Two studies have examined the uptake of constituents among e-cigarette users beyond nicotine/cotinine;[17 19] however, none have examined uptake by early versus new designs. Additionally, most users in these studies appeared to be using a first-generation or second-generation e-cigarette, with few using a third-generation device.

The current study examined a sample of exclusive cigarette smokers, and exclusive vapers using G2 and G3 devices. The purpose of the present study was threefold: (1) to examine the device and e-liquid characteristics of G2 and G3 users; (2) to assess the uptake of a potent lung carcinogen (total NNAL), a cardiovascular toxicant (carbon monoxide) and nicotine (salivary cotinine); and (3) to examine and compare the nicotine delivery profile of G2 and G3 e-cigarette devices under naturalistic use conditions.

METHODS

Participants

Recruited via internet advertisements, flyers and word-of-mouth, 20 current G2 (n=9) and G3 (n=11) e-cigarette users and 10 smokers completed study procedures. All participants (1) were ≥18 years old; (2) denied currently breast feeding, pregnant or planning to become pregnant during the time of their participation in the study; (3) denied any recent history of cardiac event; and (4) denied use of marijuana within the past 30 days. Specific eligibility criteria for exclusive e-cigarette users included (1) denying use of any other tobacco/nicotine product ≥3 months and (2) using the same style of e-cigarette device for ≥3 months, and (3) using a G2 device (specified as entry-level tank systems/eGo style tank system without modifications to the tank, atomiser or battery) or a G3 device (specified as an advanced device such as mechanical mods, rebuildable drip tanks, rebuildable atomisers or advanced personal vaporisers). Specific eligibility criteria for smokers included (1) smoking cigarettes ≥3 months and (2) no other tobacco/nicotine product for≥3 months.

Procedures

The study design consisted of two phases, a baseline and pharmacokinetic (PK) assessment phase (standardised and ad libitum vaping session). To provide some control over daily fluctuations in exposure to tobacco-related harmful/potentially harmful constituents (HPHCs) for the baseline phase and to facilitate adherence to abstinence for the PK assessment phase, all sessions were conducted in the morning hours (~8:00–11:00), near the participant's typical waking time.

Baseline phase

Participants visited the research laboratory and completed self-report measures assessing smoking and e-cigarette history, current use of all nicotine and tobacco products, and demographic information. For e-cigarette users, information regarding the nicotine concentration of their e-liquid and specifications of their e-cigarette device (eg, number of atomiser/heating coils) was also collected. Voltage and resistance metres were used to objectively measure volts and ohms of the e-cigarette device.

Saliva and urine samples were collected for analysis of salivary cotinine (metabolite of nicotine) and total urinary NNAL (a metabolite of the lung carcinogen NNK). Analyses of NNAL and cotinine were carried out according to validated methods[11] and participants' use of medications or drugs that may have affected these biomarkers were examined (eg, dexamethasone), with none reported. Exhaled carbon monoxide (eCO; a cardiovascular toxicant) was also assessed using a Bedfont Smokerlyzer (Bedfont Scientific).

Participation in the baseline phase lasted ~45 min and participants were compensated $20 for their time. G2 and G3 e-cigarette users attended a second study visit (PK assessment) within the next week and were asked to abstain from nicotine-containing products 12 hours prior to the visit.

Standardised and ad libitum vaping session (PK assessment phase)

Confirmation of abstinence from combustible tobacco use was verified by eCO (≤10 ppm). E-cigarette users used their own device and e-liquid with their preferred flavour and nicotine concentration for all study procedures. Specifications for personal e-cigarette devices and e-liquids used during this phase were collected.

A registered nurse placed a venous catheter for blood collection. Consistent with previous studies assessing cigarette and e-cigarette nicotine delivery,[5 9 13 14] for the first 5 min of the session, participants completed a standardised puffing segment. A research assistant with a stopwatch instructed participants to take a puff every 30 s, resulting in 10 puffs during the first 5 min. Immediately following the standardised segment, participants were instructed to vape ad libitum for the next 115 min (2 hours total session time). Venous blood samples were obtained at baseline and 5 min (immediately after the directed puffing segment), then at 10, 25, 40, 60, 80, 100 and 120 min. Time was measured continuously, starting with the first puff of the standardised puffing segment. Plasma nicotine levels were analysed by liquid chromatography-tandem mass spectrometry.[20]

Participants completed a vaping-adapted version of the Brief Questionnaire of Smoking Urges (QSU-brief)[21] at baseline, and at 5, 60 and 120 min postbaseline. The QSU-brief is a 10-item self-report measure with items rated from 1 (strongly disagree) to 7 (strongly agree). Items have been shown to load on two factors—'desire to smoke' and 'anticipated relief from withdrawal'. Vaping adaptation included changing words such as 'cigarette' and 'smoke' to 'vape' and 'vaping'. Participants were compensated $60 for completing this phase. All procedures were approved by the university's Institutional Review Board.

Data analytic plan

Data were analysed using SAS V.9.4 (SAS Institute). Descriptive analyses were conducted for participants' demographics, smoking and vaping history and use, e-cigarette device and e-liquid use characteristics. For biomarker values determined to be below the limit of detection (LOD), one-half of the LOD was used. NNAL data had a skewed distribution and therefore were transformed using a natural logarithm to normalise the data used for inferential statistics but are summarised in the text using the raw values. An analysis of covariance with Tukey adjusted post hoc comparisons was used to compare the exposure to constituents between groups, accounting for sex and age. Independent samples t-tests were also used to examine differences in e-cigarette device and e-liquid use characteristics. Repeated measures analysis of variance methods were used to compare the mean plasma nicotine concentrations, urges and cravings between G2 and G3 users. This was achieved by introducing an interaction term between the e-cigarette generation and time and testing the difference in least-square means at each time point using a Tukey adjustment for multiple comparisons. A fourth root transformation of the plasma nicotine concentrations and a square root transformation of urges and cravings

was used to normalise the distribution and stabilise the variance of the residuals. A two-sided α level of 0.05 was used.

RESULTS

Participants characteristics

Participant characteristics are presented in table 1. The mean age of the study participants (n=30) was 33.8 years (SD=10.9) and 63% were male. Forty-three per cent of the sample identified as white, 10% as black/African-American and the remaining 47% reported multirace/ethnicity.

Smoking and vaping history and current use

All EC users were former cigarette smokers. G2 users reported vaping for an average of 2.2 years (range 1–3 years) while G3 users reported vaping for an average of 3.0 years (range 1–8 years). Smokers reported smoking 18.4 cigarettes/day (SD=9.2) for an average of 19.2 years (SD=12.1). Compared with G2 users, G3 users reported consuming a significantly higher amount of e-liquid per week (G2: 22.0 mL, SD=13.7 vs 54.8 mL, SD=25.0; t (18)=4.71, p<0.0001). All but one of the G3 users (91%) reported using the 'dripping' technique to supply e-liquid to their atomiser; none of the G2 users reported dripping.

E-cigarette device characteristics

Mean (SD) voltage applied to the atomiser was not significantly different between G2 and G3 devices (G2: 4.1 (0.5) volts vs G3: 4.0 (0.4) volts, p=0.74), but resistance of the atomiser was significantly higher in G2 compared with G3 devices (G2: 2.0 (0.3) Ω vs G3: 0.4 (0.2) Ω, p<0.00001), resulting in significantly higher vaping power in G3 devices (G2: 8.6 (1.9) watts vs G3: 71.6 (50.0) watts, p=0.001). Number of atomiser coils was not significantly different between G2 and G3 devices (G2: 1.8 (0.5) vs G3: 1.6 (0.7), p=0.73).

Exposure to harmful and potentially harmful constituents at baseline

Average eCO levels (ppm) were significantly higher in smokers (M=13.9, SD=11.1) than in G2 (M=2.3, SD=1.0, p<0.0001) or G3 users (M=3.4, SD=1.2, p<0.0001). No significant differences were found between G2 and G3 users (p>0.05). Average urinary total NNAL levels (pmol/mL) were also significantly higher in smokers (M=1.47, SD=0.82) than in G2 (M=0.17, SD=0.19, p=0.0035) or G3 users (M=0.21, SD=0.47, p=0.0005), but no significant differences were found between G2 and G3 users (p>0.05). Total NNAL was below the LOD (0.015 pmol/mL) in six EC users (30%), but among seven others (35%), they were higher than expected—0.099, 0.521, 0.326, 0.341, 0.169, 1.446, 0.2510. No differences emerged between smokers, G2 or G3 users in terms of nicotine uptake (p>0.05), with mean cotinine levels of 331.1 (SD=179.3), 316.6 (SD=235.8) and 430.5 (SD=225.4), respectively.

E-liquid concentration and consumption during PK assessment phase

Participants using G2 devices had significantly higher nicotine concentration in their e-liquid compared with G3 users (G2: 22.3 (7.5) mg/mL vs G3: 4.1 (2.9) mg/mL; p<0.00001), but G3 users consumed a significantly greater amount of e-liquid by weight (G2: 0.5 (0.3) mg vs G3: 4.7 (2.3) mg, p=0.0003). Using label nicotine concentrations and actual e-liquid consumption during the laboratory session, nicotine mass aerosolised was estimated ((nicotine concentration×mass e-liquid consumed)/(e-liquid density)=nicotine mass (mg)); no significant difference

Table 1 Demographic characteristics of study participants, and smoking/vaping history and use

	Smokers (n=10) *M (SD) or per cent*	2nd Generation (n=9) *M (SD), per cent, [range]*	3rd Generation (n=11) *M (SD), per cent, [range]*	p Value
Age (years)	36.4 (13.0)	35.1 (12.1)	30.8 (7.9)	NS
Male (%)	60%	45%	81%	NS
Non-Hispanic white (%)	40%	44%	55%	NS
Age started smoking (years)	15.2 (3.6)	14.6 (3.2)	15.7 (3.5)	NS
Cigs per day (current/previous*)	18.4 (9.2)	15.8 (6.8)*	17.3 (11.4)*	NS
Former smoker (%)	–	100%	100%	–
Years vaping	–	2.2 (0.83)	3.0 (2.24)	NS
Self-reported e-liquid consumption/week (mL)	–	22.0 (13.7)	54.8 (25.0)	<0.0001
E-liquid nicotine concentration (mg/mL)	–	22.3 (7.5) [11–36]	4.1 (2.9) [1.5–6]	<0.00001
E-cig voltage (V)	–	4.1 (0.5) [3.4–4.7]	4.0 (0.4) [3.4–4.7]	NS
E-cig resistance (Ω)	–	2.0 (0.3) [1.6–2.6]	0.4 (0.2) [0.1–0.6]	<0.001
E-cig power (W)	–	8.6 (1.9) [6.6–12.6]	71.6 (50.0) [18.6–162.4]	0.001
Number of heating coils	–	1.8 (0.5) [1–2]	1.6 (0.7) [1–3]	NS
eCO (ppm)	13.9 (11.1)	2.3 (1.0)	3.4 (1.2)	<0.0001
NNAL (pmol/mL)†	1.47 (0.82)	0.17 (0.19)	0.21 (0.47)	<0.01
Cotinine (ng/mL)	331.1 (179.3)	316.6 (235.8)	430.5 (225.4)	NS

*Previous level of cigarettes smoked per day for G2 and G3 users.
†Total NNAL was below the LOD (0.015 pmol/mL) in 6 EC users (30%).
E-cig, electronic cigarette; eCO, exhaled carbon monoxide; LOD, limit of detection.

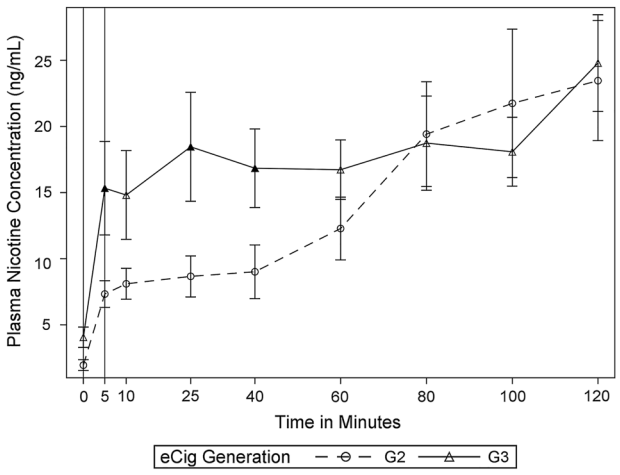

Figure 1 Plasma nicotine levels over time by type of e-cigarette device. Note: mean (±SEM) plasma nicotine concentrations over time for second-generation and third-generation devices. Filled symbols indicate a significant difference (p<0.05) at that time point between G2 and G3 e-cigarettes. Reference lines at 0 and 5 min indicate 5 min, 10-puff standardised puffing segment. E-cig, electronic cigarette.

was found between G2 and G3 users (G3: 12.0 (6.9) mg vs G2: 9.0 (4.2) mg, p=0.33).

Plasma nicotine concentrations during PK assessment phase

Figure 1 depicts the mean plasma nicotine concentrations over time for G2 and G3 devices. Significant differences (p<0.05) emerged between users of G2 and G3 devices immediately after the 10th puff (5 min; G2: 7.3 (2.8) vs G3: 17.5 (12.9)), and after 25 min (G2: 8.6 (4.4) vs G3: 18.5 (13.0)), and 40 min (G2: 9.0 (5.4) vs G3: 19.7 (13.0)) of ad libitum vaping. No significant differences were seen at 10 (G2: 8.1 (3.5) vs G3: 17.5 (13.5), p=0.051), 60 (G2: 12.3 (7.1) vs G3: 18.9 (10.0), p=0.08), 80 (G2: 19.4 (8.8) vs G3: 18.7 (10.1), p=0.55), 100 (G2: 21.8 (13 0.7) vs G3: 18.1 (7.8), p=0.77) or 120 min (G2: 23.5 (12.8) vs G3: 24.8 (11.6), p=0.37) of ad libitum vaping.

Vaping urges/craving (QSU-brief) during PK assessment phase

Mean values for QSU-brief desire and relief factors over time for G2 and G3 users are depicted in figure 2A,B, respectively. Significant within-participant reduction was observed in both subscales of desire and anticipated relief for G2 and G3 groups following the initial directed puffing segment. No between-group differences were seen except for baseline levels of anticipated relief (p<0.05).

DISCUSSION

The findings suggest that while baseline cotinine concentration levels among exclusive smokers, G2 and G3 users are similar, which may have implications for addiction and their viability as a substitute for smoking, G2 and G3 users had significantly lower levels of exposure to a potent lung carcinogen and a cardiovascular toxicant. In fact, in 30% of the EC users sampled, total NNAL levels were below the LOD. However, seven of the EC users had higher levels of NNAL than would be expected given previous studies examining NNAL in non-tobacco/nicotine users and even those exposed to secondhand smoke.[22] These elevated levels most likely suggest misreporting of complete combustible tobacco abstinence over the previous 3 months, but contamination of e-cigarette liquids with NNK at

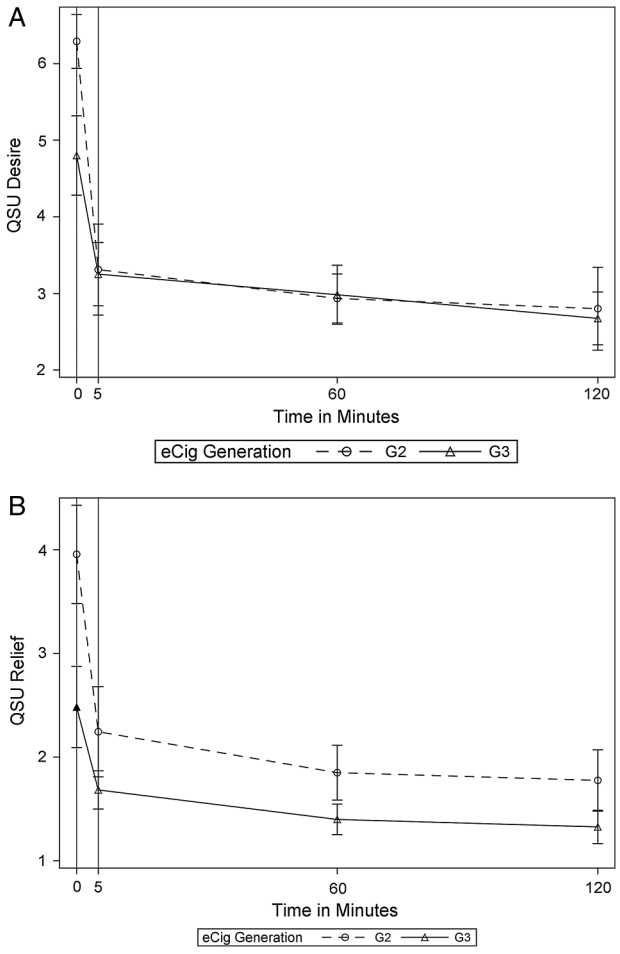

Figure 2 (A) QSU factor (desire) over time by type of e-cigarette device. Filled symbols indicate a significant difference (p<0.05) at that time point between G2 and G3 e-cigarettes. Reference lines at 0 and 5 min indicate 5 min, 10-puff standardised puffing segment. (B) QSU factor (relief) over time by type of e-cigarette device. Filled symbols indicate a significant difference (p<0.05) at that time point between G2 and G3 e-cigarettes. Reference lines at 0 and 5 min indicate 5 min, 10-puff standardised puffing segment. E-cig, electronic cigarette; QSU, Questionnaire of Smoking Urges.

levels not previously not seen in the literature[18] or interindividual differences in NNK metabolism could also be contributing. The total NNAL levels of smokers in this study were consistent with previous research.[17]

Moreover, the findings demonstrate that the evolution of e-cigarettes has led to a third-generation of high-powered devices that when used by experienced vapers mimics the PK profile of combustible cigarettes. This finding has significant implications as public health officials and regulators, such as the US Food and Drug Administration (FDA), continue to make regulatory decisions that may impact the availability of these newer generation devices. Some contend that the FDA's new regulation of e-cigarettes would essentially ban all newer generation e-cigarette devices brought to market after 2007, as they will be subject to onerous regulations as 'new tobacco products' under section 910(a)[1] of the Family Smoking Prevention and Tobacco Control Act.[23] As a result, for some period of time, this would potentially leave only devices with poor nicotine delivery and less viability as smoking cessation aids on the market (ie, cig-a-likes). In consideration of the present findings, regulators should examine the cost-benefit of this regulation.

Interestingly, the users of G3 devices achieved cigarette-like nicotine delivery while vaping e-cigarette liquid with very low nicotine concentrations, especially when compared with G2 users. The low concentration of nicotine appears to be overcome by an eightfold power (wattage) increase compared with G2 devices; device power is known to increase e-cigarette nicotine yield.[12] Thus, these results may be the first published evidence that relatively high-powered e-cigarettes paired with relatively low nicotine concentration liquids are capable of maintaining cigarette-like nicotine exposure. This observation has implications for regulators seeking to limit e-cigarette nicotine delivery via control of liquid nicotine concentration exclusively. Low concentration nicotine liquid paired with high-powered devices may have the same dependence potential as other tobacco products. Thus, controlling e-cigarette nicotine delivery requires, at the least, control over liquid nicotine concentration and device power.

As the results of this study imply, user behaviour is also relevant. G3 users reported consuming approximately twice the amount e-cigarette liquid per week as did G2 users and this increased e-cigarette liquid consumption was also observed during the vaping session. There may be both positive and negative implications of improved nicotine delivery accompanied by increased consumption of e-liquid. Though currently unanswered, G3 e-cigarettes may be more effective smoking cessation devices due to their cigarette-like nicotine delivery profile. However, they may potentially expose users to higher levels of HPHCs due to higher volumes of e-cigarette liquid consumption, specifically consumption of non-nicotine compounds, which are believed to be responsible for e-cigarette HPHCs.[1 18 24] In light of this possibility and recent research demonstrating that G2 users reduce their puff topography (and likely their e-cigarette liquid consumption) with increased nicotine concentrations,[14] setting a 'floor' as opposed to a 'ceiling', on the nicotine concentrations allowed in e-cigarette liquid may be a viable strategy to provide users the nicotine levels needed to reduce the craving and urge to smoke while also reducing their exposure to HPHCs. However, due to concerns of potential nicotine poisonings, regulators in the European Union have taken the opposite strategy. Through the Tobacco Products Directive, officials set a ceiling on the allowable nicotine concentration for e-cigarette liquid at 20 mg/mL.[25 26] It may be important for future e-cigarette liquid regulations to consider both the implications for nicotine concentrations that are too high and too low.

Also of note, after ~60 min of ad libitum use, both G2 and G3 users achieved comparable levels of plasma nicotine that were sustained (~20–24 ng/mL) for the remaining hour. This finding is consistent with baseline cotinine concentrations and replicates previous studies, demonstrating that G2 devices are able to deliver cigarette-like nicotine levels, but at a much slower rate than combustible cigarettes.[9] Moreover, use of G2 and G3 devices resulted in similar levels of craving and withdrawal reduction, suggesting that for some users, G2 devices could be a sufficient replacement for smoking.

Finally, as G3 devices closely mimic the nicotine delivery of combustible cigarettes, there may be cause for concern that they may lead to nicotine dependence among youth who are experimenting with e-cigarettes at an increasing rate or make achieving nicotine abstinence for e-cigarette users difficult.[27] However, to the best of our knowledge, the available published surveillance research has not examined the types of e-cigarette devices that youth are using and if they are using e-cigarette liquid with nicotine, making it difficult to gauge the extent to which this may be a problem. Moreover, unlike current reports of e-cigarette ingredients, cigarettes are known to contain other constituents, such as monoamine oxidase inhibitors, demonstrated in animal studies to significantly augment the reinforcing effects of nicotine.[28]

Despite these important and novel findings, the study has several notable limitations. First, the study used a small convenience sample who may not be representative of all vapers or smokers. Second, measures of cotinine, CO and total NNAL levels were gathered at one time point; thus, we are unable to determine how exposure to constituents changes over time. Third, several eligibility criteria and outcome variables were self-reported and participants may have been dishonest about their exclusivity to a product or past use of combustible products. Fourth, although multiple types of G2 and G3 products were represented, the sample size is small and more research is needed to further establish toxicological exposure and nicotine delivery as a result of generation of product used. Fifth, this study examined a limited, although very important, number of harmful constituents of tobacco exposure. Future research should expand on this study by examining exposure to other harmful constituents found in tobacco smoke and e-cigarette aerosol, especially those influenced by greater heating (eg, aldehydes and carbonyls). Finally, participants were limited to samples of exclusive users of e-cigarettes or combustible cigarettes and results cannot be generalised to dual users of e-cigarettes and combustible cigarettes/other tobacco products.

The present study is the first to systematically examine the nicotine delivery profile of G3 devices and to examine differential exposure to HPHCs based on generation of e-cigarette device. Moreover, it is the first study to demonstrate that an e-cigarette under natural use conditions can match the nicotine delivery profile of a combustible cigarette. This finding has significant implications in terms of our understanding of the addiction potential of these devices and their viability as an aid to smoking cessation. However, additional research is needed to examine the relationship between quantity and strength of e-liquid consumed and the uptake of HPHCs.

What this paper adds

- The study is the first to systematically examine the nicotine delivery profile of G3 devices and to examine differential exposure to harmful/potentially harmful constituents (HPHCs) based on generation of electronic cigarette (e-cigarette) device.
- G3 devices are able to mimic the nicotine delivery profile and craving reduction capability of a conventional cigarette, even with users vaping low nicotine concentration e-cigarette liquid, which may have implications for their addiction potential and viability as smoking cessation aids.
- G3 users consumed significantly higher amounts of e-liquid than G2 users, which have implications for their exposure to HPHCs not examined in the current study.

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