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Electronic cigarettes: abuse liability, topography and subjective effects

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ABSTRACT

Objective To review the available evidence evaluating the abuse liability, topography, subjective effects, craving and withdrawal suppression associated with e-cigarette use in order to identify information gaps and provide recommendations for future research.

Methods Literature searches were conducted between October 2012 and January 2014 using five electronic databases. Studies were included in this review if they were peer-reviewed scientific journal articles evaluating clinical laboratory studies, national surveys or content analyses.

Results A total of 15 peer-reviewed articles regarding behavioural use and effects of e-cigarettes published between 2010 and 2014 were included in this review. Abuse liability studies are limited in their generalisability. Topography (consumption behaviour) studies found that, compared with traditional cigarettes, e-cigarette average puff duration was significantly longer, and e-cigarette use required stronger suction. Data on e-cigarette subjective effects (such as anxiety, restlessness, concentration, alertness and satisfaction) and withdrawal suppression are limited and inconsistent. In general, study data should be interpreted with caution, given limitations associated with comparisons of novel and usual products, as well as the possible effects associated with subjects' previous experience/inexperience with e-cigarettes.

Conclusions Currently, very limited information is available on abuse liability, topography and subjective effects of e-cigarettes. Opportunities to examine extended e-cigarette use in a variety of settings with experienced e-cigarette users would help to more fully assess topography as well as behavioural and subjective outcomes. In addition, assessment of 'real-world' use, including amount and timing of use and responses to use, would clarify behavioural profiles and potential adverse health effects.

INTRODUCTION

Electronic cigarettes (e-cigarettes), a type of electronic nicotine delivery system, are often packaged to look and feel like traditional (ie, combusted) cigarettes, also known as ciga-like e-cigarettes. While earlier studies used first-generation devices,[1 2] newer generations of e-cigarettes contain tanks and/or have variable voltage options that allow users to customise their experience by increasing available dosages.[3] First marketed in China in 2004,[4] these novel cigarette-like products have been introduced to the market and have been used by smokers because of perceptions that they are less harmful/less toxic than traditional cigarettes,[5–8] less expensive than regular cigarettes,[8 9] aid in tobacco craving/withdrawal symptom relief,[5 10] aid in smoking reduction/cessation,[8 11 12] aid in relapse prevention[5 10] and can be smoked everywhere without disturbing people with secondhand smoke.[8 10 13] Although e-cigarette design characteristics vary,[14 15] the common feature is an electrically powered heating element that aerosolises a liquid containing nicotine, humectants (typically propylene glycol and/or vegetable glycerin) and flavourings.[16 17] The smoker inhales an aerosol that contains nicotine into his or her lungs and exhales the aerosol into the environment.[14] Initial results with novice users suggest that e-cigarettes delivered very little nicotine,[1 2] though more recent studies with experienced users suggest that, under certain conditions, these products can deliver nicotine levels that approximate those of a traditional cigarette.[5 18]

Despite limited research on safety and in the absence of regulation, e-cigarettes are gaining substantial popularity in the USA. The U.S. Court of Appeals ruled that e-cigarettes that do not make therapeutic claims can be regulated as a tobacco product,[19 20] and the U.S. Food and Drug Administration (FDA) intends to assert jurisdiction over them in the future.[21] The purpose of this review is to (1) describe the state of knowledge regarding the abuse liability, topography, subjective effects, craving and withdrawal suppression associated with e-cigarette use; (2) identify information gaps and deficiencies; and (3) provide recommendations for future research that could inform the development of potential e-cigarette regulation.

METHODS

Systematic literature searches were conducted between October 2012 and January 2014 to identify research related to e-cigarettes and abuse liability (the degree to which a psychoactive drug has properties that may facilitate addiction), topography (how a person smokes, including puff number and puff volume) and subjective effects (individual ratings of smoking effects). Five reference databases (Web of Knowledge, PubMed, SciFinder, Embase and EBSCOhost) were searched using a set of relevant search terms used singly or in combination. Search terms included the following: "electronic nicotine devices" OR "electronic nicotine device" OR "electronic nicotine delivery systems" OR "electronic nicotine delivery system" OR "electronic cigarettes" OR "electronic cigarette" OR "e-cigarettes" OR "e-cigarette" OR "e-cig" OR "e-cigs" OR "Potential Reduced Exposure Product" OR "vaping" OR "topography" OR "puff topography" OR "puff profile" OR "nicotine delivery profile" OR "abuse liability" OR "subjective effects" OR "abstinence suppression"

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OR "craving" OR "withdrawal." The search date range was unrestricted.

To be considered for inclusion, published articles had to (1) be written in English; (2) be publicly available; (3) be published in a peer-reviewed journal; and (4) deal partly or exclusively with abuse liability, topography and/or subjective effects. The validity and strength of each study was determined based on a qualitative assessment of research design. Meaningful study limitations are noted in the analysis.

RESULTS

A total of 15 peer-reviewed articles regarding behavioural use and effects of e-cigarettes were identified. (See tables 1 and 2 for key features of each study.)

Abuse liability

Two articles addressed the abuse liability of e-cigarettes. Vansickel *et al*[22] examined the abuse liability of an e-cigarette in a clinical laboratory setting using a multiple-choice procedure (MCP). Twenty adult traditional cigarette smokers with no experience using e-cigarettes completed four within-subject sessions. The first was an e-cigarette ("Vapor King" KR808 model, a cigarette-like disposable product) sampling session that involved six 10-puff bouts (30 s interpuff interval), with each bout separated by 30 min. Participants were randomised into the remaining three sessions and, using the MCP, made choices between 10 e-cigarette puffs and varying amounts of money, 10 e-cigarette puffs and a varying number of own brand cigarette puffs, and 10 own brand puffs and varying amounts of money. The MCP was completed six times at 30 min intervals, and one choice was reinforced randomly at each trial. The choice session outcome measure was the cross-over value on the MCP (values ranged from $0.01 to $5.12). Subjective and behavioural outcomes, including tobacco abstinence symptom suppression and increased product acceptability ratings, were reported. e-cigarette use resulted in a significant increase in plasma nicotine from a preadministration level of 2.2 to 7.4 ng/mL 5 min after the final 10-puff bout, although both the magnitude of the increase in plasma nicotine concentration and the slope of its rise were lower than that observed with a traditional cigarette. A slower rate of nicotine delivery has implications for abuse liability, as the rapidity with which a psychoactive drug (ie, nicotine) is delivered to the brain is related directly to its potential for abuse and dependence.[23] On the MCP, participants chose to receive 10 e-cigarette puffs over an average of $1.06 or three own brand puffs and chose 10 own brand puffs over an average of $1.50. Choice of puffs over money decreased as monetary values increased, regardless of choice condition. A strength of the study is that clinical laboratory methods have demonstrable internal and predictive validity and have been used successfully to determine the abuse potential and consequences of drug use for decades.[24] Although the authors suggest that e-cigarettes may have a lower abuse potential than cigarettes, it may be inappropriate to make direct comparisons between a usual product (own brand) and a novel product (e-cigarette). Furthermore, experience has been shown to be a factor in smoking behaviour and nicotine exposure[5 18]; this study included only naïve users. Therefore, findings may not be generalisable to real-world use and thus should be interpreted with caution.

Farsalinos *et al*[25] examined nicotine dependence in 111 subjects (93 males) who had completely substituted traditional smoking with e-cigarette use for at least 1 month (mean use 8 months). Subjects were included in the analysis irrespective of type of e-cigarette or nicotine level used. At the time of analysis, cartridge nicotine levels per per cent of overall use were 0–5 mg/mL (12%), 6–10 mg/mL (27%), 11–15 mg/mL (31%), 16–20 mg/mL (29%) and >20 mg/mL (2%). Subjects were asked about past dependence on traditional cigarettes ("How soon after waking up did you smoke your first cigarette?") and current dependence on e-cigarettes ("How soon after waking up do you smoke your first e-cigarette?"). The answers were scored with three points assigned to "within 5 min", two points to "between 6 and 30 min", one point to "between 31 and 60 min" and zero point to "more than 60 min". Median dependence scores were 2 for both cigarettes (range 2–3) and e-cigarettes (range 1–2). Subjects were also asked, "How would you rate your past dependence on smoking?" and "How would you rate your current dependence on e-cigarettes?" which were scored on a 100-point visual analogue scale (VAS). The median dependence scores were 59 (range 49–66) for e-cigarettes and 83 (range 77–89) for cigarettes, demonstrating lower dependence for e-cigarettes. Generalisability may be limited since this study included a convenience sample and was limited to mostly males.

In summary, findings from two studies suggest that e-cigarettes may have a lower abuse potential than traditional cigarettes.

Topography

Five articles included measures of topography (table 1). Etter and Bullen[26] conducted an online survey of 3587 participants (70% former tobacco smokers; mean duration e-cigarette use=3 months) to determine e-cigarette use. They found that daily use of e-cigarettes was 120 puffs per day (five refills per day; averaging 24 puffs per refill and 18 mg/mL). While this dose is less than smoking machine studies in which three refills were exhausted for a total of 170–300 puffs,[14] this dose suggests more intense naturalistic setting puffing than has been reported in laboratory studies where smoking has been limited to 10 puffs.[2 27]

Hua *et al*,[28] used data from randomly selected videos to analyse and compare ad libitum puff and exhalation duration for individuals using e-cigarettes (n=64) and traditional cigarettes (n=9) in YouTube videos. e-cigarette users showed a large variation in puff duration (range 1.9–8.3 s), with average puff duration significantly longer (4.3 s, SD ±1.5) than puff duration for the traditional cigarettes (2.4 s, SD ±0.8). The values for average duration of exhalation did not differ significantly between e-cigarette users (1.7 s, SD 1.1) and traditional cigarette smokers (1.6 s, SD 0.7), although it was unknown whether the e-cigarette users were naïve or experienced users. According to the authors, longer puff duration may help e-cigarette users compensate for the poor delivery of nicotine. Data were limited to observational data (puff and exhalation duration only) from YouTube videos and may not be as accurate as data obtained through the use of validated topography machine measures.[29]

Farsalinos *et al*[3] examined e-cigarette puff topography using a second-generation e-cigarette device in 45 experienced e-cigarette users and 35 traditional cigarette smokers (naïve to e-cigarettes who also smoked own brand cigarettes in addition to e-cigarettes for comparison) in a randomised cross-over design in which users were video-recorded. The results of the study revealed significant differences in the topography associated with cigarette and e-cigarette use, indicating that e-cigarettes are not smoked like traditional cigarettes. For traditional cigarettes, puff duration was the time interval between the frame at which the mouth was closed (with the cigarette filter-tip inside the mouth) until the frame at which the cigarette

Table 1 Topography in e-cigarette users

Reference	Study characteristics Study product/sample Size	Traditional cigarette	*Use duration e-cigarette*	Use duration traditional cigarette	Results e-cigarette topography	Traditional cigarette topography	Other topography measures
Etter and Bullen[26]	Varied brands	N/A	*Mean=3 months*	N/A	*120 puffs/day*	N/A	N/A
Hua *et al*[28]	Preferred e-cigarette, flavour, nicotine concentration/ 64-e-cigarette users; 9 traditional cigarette users	Preferred traditional cigarette flavour, nicotine concentration	Ad libitum	Ad libitum	Puff duration 4.3 s, SD ±1.5; exhalation duration 1.7 s, SD 1.1	Puff duration 2.4 s, SD ±0.8; exhalation duration 1.6 s, SD 0.7	Observational data; e-cigarette users showed large variation in puff duration
Farsalinos *et al*[3]	eGo-T battery, Epsilon atomiser, Nobacco 9 mg/ mL nicotine/45 e-cigarette users; 35 traditional cigarette users	2 cigarette cigarettes (brand not identified)	Ad libitum for 20 min for experienced users; ad libitum for 10 min for naïve users	2 cigarette cigarettes ad libitum, 00.7 mg nicotine	E-cigarette user puff duration 4.2±0.7, inhalation 1.3±0.4 s; puff number=43; traditional cigarette users using e-cigarettes puff duration 2.3±0.5, inhalation 2.1±0.4 s	Puff duration 2.1±0.4 and inhalation 2.1±0.4 s	Observational data; nicotine absorption was not measured
Trtchounian *et al*[14]	Liberty Stix, Crown Seven Hydro Kit, NJOY, Smoking Everywhere Gold	Merit Ultra Lights, Marlboro Ultra Lights, Marlboro Lights, Marlboro Reds, Camel unfiltered, Camel Lights, Camel filtered, Pall Mall unfiltered	First 10 puffs of an e-cigarette	7–11 puffs; puffs were 2.2 s long every minute; 3 series	Average vacuums ranged from 25±3 mm H_2O to 153±12 mmH_2O	Average vacuums ranged from 30 mm H_2O±3 to 80 mm H_2O±5	Machine yield data from non-standardized, non-validated topography equipment
Trtchounian *et al*[14]	Liberty Stix, Crown Seven Hydro Kit, NJOY, Smoking Everywhere Gold, VapCigs	N/A	Vacuum and aerosol density measured until each cartridge was exhausted, 3 series	N/A	Average vacuums ranged from 34±6 mm H_2O to 174±23 mmH_2O; puffs ranged from 177±15 to 313±115.	N/A	Machine yield data from non-standardized, non-validated topography equipment
Williams and Talbot[30]*	Liberty Stix #1, Liberty Stix #2, VapCigs, Crown Seven Hydro Imperial, Smoking Everywhere Platinum	N/A	First 10 puffs of an e-cigarette	N/A	Pressure drop, flow rate and aerosol density remained constant for a given e-cigarette but varied among brands. Liberty Stix had the lowest pressure drop (20 mm H_2O) and Liberty Stix #2 had the highest pressure drop (150 mm H_2O)	N/A	Machine yield data from non-standardized, non-validated topography equipment
Williams and Talbot[30]*	VapCigs #2, Crown Seven Hydro Imperial, Smoking Everywhere Platinum	N/A	Aerosol density measured until each cartridge was exhausted, 3 series	N/A	Puffs ranged from 160±6 to 400±10.	N/A	Machine yield data from non-standardized, non-validated topography equipment
Williams and Talbot[30]*	Liberty Stix #1, Liberty Stix #2	N/A	11 puffs, 3 series	N/A	Aerosol density remained similar for the first e-cigarette so performed quite uniformly from trial to trial. In contrast, pressure dropped significantly during trial 3 for the second cigarette with a drop in aerosol density	N/A	Pressure drop was consistent for Liberty Stix #1 so performed uniformly; Liberty Stix #2 did not perform uniformly; machine yield data from non-standardized, non-validated topography equipment

*One Liberty Stix and one VapCigs e-cigarette from prior study (Trtchounian *et al*[14]) were included in this study. The original purchases are designated Liberty Stix #1 and VapCigs #1; the purchases used only in this study are designated Liberty Stix #2 and VapCigs #2.

Table 2 Subjective effects in e-cigarette users

Reference	Study characteristics Product experience of participants	Study product	Labelled nicotine content	Sample size	Use duration	Results Subjective effects
Bullen *et al*[1]	Naïve users	Ruyan V8	16 or 0 mg	8	5 min ad libitum	16 mg e-cigarette significantly reduced desire to smoke 10 min after last puff
Dawkins *et al*[31]	Naïve users; single session of short duration after only 1 h tobacco abstinence	White super	18 or 0 mg	86	5 min ad libitum	Desire to smoke, anxiety, poor concentration, irritability, restlessness were significantly reduced (males) and depression, concentration (females) improved 20 min after e-cigarette use
Dawkins *et al*[32]	Experienced users; wide variety of products; survey	Preferred e-cigarette, flavour, nicotine concentration	0–36 mg, custom mg	1347	Estimated 235.72 (SD 339.13) puffs/ daily	Reduction in craving to smoke
Dawkins and Corcoran[33]	Experienced users; no control group with non-nicotine e-cigarette users; no manipulation of nicotine concentrations; descriptive study	SKYCIG	18 mg/mL	14	10 puffs within 5 min; 1 h ad libitum	Reduction in urge to smoke 5 and 60 min after e-cigarette use
Dawkins *et al*[34]	Naïve users	Tornado	0–18 mg/mL	20	Ad libitum for 60 min	Desire to smoke and anxiety decreased in the 18 mg e-cigarette
Eissenberg[27]	Naïve users; NJOY NPRO and Crown 7 hydro failed to increase nicotine levels significantly	NJOY NPRO or Crown 7 Hydro	16 mg	16	2 series of 10 puffs, 30 s interpuff interval, 1 h between series	NJOY NPRO decreased craving significantly 5 min after Series 2 only
Vansickel *et al*[2]	Naïve users; NJOY NPRO and Crown 7 hydro failed to increase nicotine levels significantly	NJOY NPRO or Crown 7 Hydro	18 mg (NPRO), 16 mg (Hydro)	32	2 series of 10 puffs, 30 s interpuff interval, 1 h between series	Abstinence symptom suppression on craving a traditional cigarette and urge to smoke
Vansickel and Eissenberg[18]	Experienced users; no control group with non-nicotine e-cigarette users; no manipulation of nicotine concentrations	Preferred e-cigarette, flavour, nicotine concentration	9–24 mg/mL	8	10 puffs, 30 s interpuff interval; 1 h ad libitum; 2 h rest period	Some VAS ratings and positive direct effects of e-cigarette administration increased significantly following the 10-puff period, peaked following the ad libitum period, and decreased after the rest period

VAS, visual analogue scale.

was removed from the mouth; for e-cigarette use, puff duration was defined as the interval between the frame when the LED light was activated (with the mouthpiece inside the mouth) until the frame when the e-cigarette was removed from the mouth. The interval from that frame until the frame just before visible smoke was exhaled was defined as inhalation time. e-cigarette user puff duration (4.2±0.7 s), inhalation (1.3±0.4 s) and puff number (43 puffs) were different from traditional cigarette smokers using e-cigarettes, who had shorter puff durations (2.4 ±0.5 s) and longer inhalation (2.0±0.4 s).[i] The differences observed when comparing e-cigarette use topography between experienced and novice users confirmed previous assumptions that experienced e-cigarette users use the device more intensively, with longer puffs and lower inhalation time, than inexperienced users.[9]

Trtchounian *et al*[14] conducted two studies that examined the smoking characteristics of traditional cigarettes and e-cigarettes. In both studies, which used specially designed topography equipment, researchers examined the vacuum required to produce smoke (in the case of traditional cigarettes) or aerosol (in the case of e-cigarettes) and compared the density of the smoke/aerosol over time. In the first study, a comparison was made for three series between traditional cigarettes being smoked completely (7–11 puffs; puffs were 2.2 s long at a frequency of one puff every minute) and the first 10 puffs of an e-cigarette. Higher vacuums (more suction) were required to smoke e-cigarettes than traditional cigarettes, and vacuum and aerosol density varied across e-cigarette brands. In the second study, the same brand e-cigarettes were subjected to three identical smoke-out experiments in which vacuum and aerosol density were measured until each cartridge was exhausted. The average vacuums for e-cigarettes ranged from 34±6 mm H_2O to 174±23 mm H_2O. As cartridges were considered exhausted when consecutive increases in pump speed failed to produce aerosol, aerosol density data were used to estimate the average maximum puff number for each brand of e-cigarettes. Total puffs ranged from 177±15 to 313±115. Interestingly, the two e-cigarettes produced almost the same average number of puffs even though one had a reservoir of e-liquid that was three times smaller than the other, indicating that puff number is influenced by factors in addition to reservoir size.

[i]The results presented in the abstract did not match those presented in the body of the article. The results described here are from the body of the article.

Williams and Talbot[30] examined characteristics of multiple e-cigarettes in three different studies. In the first study, five e-cigarettes were compared during the first 10 puffs. Pressure drop, flow rate and aerosol density remained relatively constant for a given e-cigarette but varied among brands; however, the two Liberty Stix e-cigarettes, which appeared identical and were the same model, had very different pressure drops, with one having a pressure drop of 20 mm H_2O and the second having a pressure drop of 150 mm H_2O. In the second study, three e-cigarettes were subjected to three identical 'smoke-out' experiments in which aerosol density was measured until each cartridge was exhausted. Puffs ranged from 160±6 to 400±10. In the third study, two different e-cigarettes (same model purchased at different times) were used for 11 puffs in three trials. Aerosol density remained similar for the first e-cigarette, which thus performed quite uniformly from trial to trial. In contrast, pressure dropped significantly during trial 3 for the second cigarette. Thus, investigators identified performance variability in these products. The authors attributed the variability in performance to the atomiser and not the battery. For all studies, e-cigarettes required stronger vacuums to smoke than traditional cigarettes. The amount of aerosol produced by e-cigarettes decreased during smoking, which necessitated increasing puff strength to produce a comparable amount of aerosol. Increasing puff strength may result in increased exposure or alter the deposition of chemicals into the lungs. The decreased efficiency of aerosol production during e-cigarette smoking makes nicotine dosing progressively less uniform over time. One limitation of these studies is use of a non-standardised, non-validated smoking box, which limits the ability to replicate the methodology. Taken together, these studies indicate that the smoking parameters usually used for standard machine-smoking of traditional cigarettes may need to be altered when testing e-cigarettes.

In summary, topography studies found that, compared with traditional cigarettes, e-cigarette average puff duration was significantly longer, and e-cigarette use required stronger suction.

Subjective effects

Eight articles included measures of subjective effects, craving and withdrawal associated with e-cigarette use (table 2). Bullen *et al*[1] evaluated smoking desire and withdrawal symptom suppression in smokers (n=40) naïve to e-cigarettes in a single-blind repeated measures cross-over trial where participants were randomised to use an inhalator, 0 or 16 mg e-cigarette, or own brand cigarette on four separate study days. Following overnight abstinence, significant reductions in desire to smoke were reported after 1 h with the 16 mg e-cigarette; however, reductions were not as great as those seen following traditional cigarette smoking. The e-cigarette was reported to be well-tolerated and acceptable to most users. A limitation of the study was the use of a single short-duration session, which may not generalise to a real-world setting and may not identify any delayed or long-term adverse effects. In addition, experience changes how an e-cigarette is smoked,[5 18] so the current data may not generalise to experienced users.

Dawkins *et al*[31] examined desire to smoke and withdrawal symptom suppression associated with e-cigarettes in a mixed experimental design study involving e-cigarette-naïve subjects. Following an hour of abstinence, males' (n=43) desire to smoke and some aspects of nicotine withdrawal (anxiety, poor concentration, irritability and restlessness) were significantly reduced 20 (but not five) min after e-cigarette use. Females (n=43) in both the nicotine and placebo groups reported improvements only in depression and concentration 20 min after e-cigarette use, suggesting that they may not be as sensitive to nicotine as males. Since the study participants were only nicotine abstinent for 1 h, a longer duration of abstinence could reveal more robust effects and gender differences. Another study limitation includes the use of a single session of short duration, which may not generalise to a real-world setting with greater opportunity to use the product. Since participants were e-cigarette naïve, a behavioural use profile could be different after multiple uses of the product.[5 18]

In another study, Dawkins *et al*[32] characterised the subjective effects of e-cigarette use in e-cigarette users (n=1347) in a 9-month online survey. On average, participants reported daily use of 3.36 mL e-liquid (SD 3.53) and 235.72 (SD 339.13) puffs daily. Users reported that e-cigarette use was extremely satisfying and had reduced tobacco craving and urge to smoke. A significantly higher proportion of former smokers (95%) reported a reduction in craving for traditional cigarettes as compared with current smokers (70%). One limitation of this study is the wide variety of products used, which differed in product specifications (eg, voltages, sizes) and strengths of nicotine (0–36 mg, mix own strength).

Dawkins and Corcoran[33] examined the subjective effects of acute administration of an e-cigarette in a clinical laboratory study involving regular e-cigarette users (n=14; 13 women; e-cigarette use of 4.73±3.76) months) who had been overnight abstinent and then used an e-cigarette for 10 puffs, followed by a 60 min break, then ad libitum smoking, for a total of 2.5 h. Urge to smoke, irritability, restlessness and poor concentration were significantly decreased at the end of the 10-puff period and the 60 min ad libitum period. This study used experienced e-cigarette users, increasing the likelihood that use behaviour was stable. However, there was no control group with non-nicotine e-cigarettes for comparison, nor was there any experimenter manipulation of nicotine concentrations.

Dawkins *et al*[34] examined the subjective effects of acute administration of an 18 mg or 0 mg cigarette-like disposable e-cigarette after overnight abstinence in two counterbalanced sessions in a clinical laboratory study involving regular e-cigarette users (n=20). At the end of the 60 min ad libitum smoking period, urge to smoke and anxiety were significantly decreased with the 18 mg e-cigarette. This finding of a significant reduction in desire to smoke is consistent with previous studies;[2 31] however, this study used experienced e-cigarette users, increasing the likelihood that use behaviour was stable. A strength of the design was the use of non-nicotine e-cigarettes for comparison.

Eissenberg[27] examined craving suppression and subjective effects after acute administration of e-cigarettes in smokers who were naïve to e-cigarettes (n=16) in a four Latin-square order condition study (own brand cigarettes, sham smoking, 16 mg 'NPRO', 16 mg 'Hydro'). After overnight tobacco abstinence, participants were instructed to take 10 puffs ad libitum, twice, with a 60 min interval, in the experimental condition. Both e-cigarette brands tested failed to increase nicotine plasma levels significantly and suppressed craving less effectively than traditional cigarettes. The participants had their puff numbers controlled, a condition that would not be present outside of the laboratory. Chronic use and/or more intensive puffing would likely influence nicotine delivery and, subsequently, craving suppression. A comparison of data from a novel product (e-cigarette) with a usual product (smokers' own brand of cigarette) may not be an appropriate reflection of real-world behaviour.

Vansickel *et al*,[2] using methods described in Eissenberg,[27] performed a clinical laboratory study examining subjective effects in smokers who were naïve to e-cigarettes (n=32) and reported reduced desire to smoke and suppression of some withdrawal symptoms; however, both e-cigarette brands tested failed to raise blood nicotine levels and heart rate over a 45 min period. While suppression of some withdrawal symptoms was reported, limitations of this study include the brief e-cigarette exposure period and inclusion of e-cigarette-naïve participants who may be representative of cigarette smokers sampling an e-cigarette for the first time, but not of a more experienced e-cigarette user population. As previously discussed, since experience has been shown to be a factor in smoking behaviour and nicotine exposure, these results are limited to only naïve users.[5 18]

Vansickel and Eissenberg[18] conducted a clinical laboratory study to examine subjective effects after acute (one 5 h session) administration of an e-cigarette in experienced e-cigarette users (n=8) who had been using e-cigarettes for 11.5 (±5.4) months. VAS ratings (anxious, restlessness, Questionnaire on Smoking Urges (QSU) Factor 1 intention to smoke) and positive direct effects of e-cigarette administration (indicated by responses to the following prompts: "feel awake", "calm you down", "concentrate", "pleasant", "satisfying", "reduce your hunger for food", "taste good") increased significantly following the 10-puff period, peaked following the ad libitum period and decreased after the rest period. This study used experienced e-cigarette users only; there was no control group with non-nicotine e-cigarettes for comparison, nor was there any experimenter manipulation of nicotine concentrations.

In summary, data on subjective effects and withdrawal suppression of e-cigarettes are limited, with some studies citing withdrawal suppression[1] and others finding insufficient withdrawal suppression as compared with traditional cigarettes.[27] Potential gender differences in withdrawal suppression were also noted.[31]

DISCUSSION

e-cigarettes are a relatively new and diverse line of products in the US market, and information related to possible abuse liability, topography and subjective effects is scarce. e-cigarettes are highly variable in design, performance and nicotine delivery. Studies with naïve users used first-generation devices that are now obsolete, and, with rapidly evolving technology, future studies should use the latest-designed devices. Puff durations of electronic cigarettes are longer than those associated with traditional cigarettes.[9 14 25 31]

Limited data on subjective effects and withdrawal suppression of e-cigarettes exist; some studies report withdrawal suppression,[1] while others report that withdrawal suppression is insufficient compared with traditional cigarettes.[27] Gender differences in withdrawal suppression are possible.[31] The authors of one abuse liability study suggested that e-cigarettes appear to have lower potential for abuse than traditional cigarettes.[24]

However, for e-cigarette studies that compared experienced cigarette smokers' behaviour and subjective effects with those of inexperienced e-cigarette users, two major caveats significantly limit the ability to draw conclusions. The first is that a usual product (usual brand cigarette) may be an inappropriate comparator for evaluating responses to a novel product (e-cigarette) since product novelty itself is known to produce different behaviours.[23] The second is that subjects with no previous experience using e-cigarettes likely interact with the product differently than experienced users, which affects use behaviour and nicotine exposure. Therefore, it is unknown how e-cigarettes compare to traditional cigarettes with regard to abuse potential since experienced smokers of traditional cigarettes were studied and usual traditional cigarettes were compared with novel e-cigarettes.

Currently, no published experimental topography studies with validated devices[29] or methodology exist, but a video content analysis[28] revealed that e-cigarette users exhibit longer puff durations than traditional cigarette smokers. This finding was also supported in an observational study.[9] Indeed, higher vacuums were required to smoke e-cigarettes than traditional brand cigarettes in two smoking machine studies.[14 31] Extended opportunities to use e-cigarettes in a variety of settings with non-naïve users would help to assess topography as well as behavioural and subjective outcomes. In addition, assessment of 'real-world' use, including amount and timing of use and responses to use, would be beneficial to understanding potential adverse health effects and behavioural profiles. In conclusion, critical information gaps exist, including a need for information based on e-cigarette variability, a need for information about real-world use and a need for information about e-cigarette use by experienced users.

What this paper adds

- This is the first review to investigate abuse liability, topography and subjective effects in e-cigarettes.
- Topography studies found that, compared with traditional cigarettes, e-cigarette average puff duration was significantly longer, and e-cigarette use required stronger suction. Data on e-cigarette subjective effects and withdrawal suppression are limited and inconsistent. Abuse liability studies are limited in their generalisability.
- Study data should be interpreted with caution, given limitations associated with comparisons of novel and usual products as well as the possible effects associated with subjects' previous experience/inexperience with e-cigarettes.

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